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CYTOLOGICAL ANALYSIS OF THYROGLOSSAL DUCT CYSTS

CITOLOŠKA ANALIZA CISTA TIROGLOSNOG KANALA

Gostimir MIKAČ[1,2] and Momčilo BIUKOVIĆ[1]

Summary

Introduction. Thyroglossal duct cysts are regarded as congenital anomalies. They arise from the residual segments of thyroglossal duct. A cancer with the incidence rate from 1% to 1.5% may develop in thyroglossal duct cysts. Approximately 30% of patients asked to be examined due to inflammatory cysts. This study was aimed at determining the cytological characteristics of thyroglossal duct cyst smear, such as cell specificity, cellularity and the content of the extracellular matrix. **Material and Methods.** Thyroglossal duct cyst smears were analyzed in 28 adult patients who had undergone the fine-needle aspiration cytology in the period from 2004 to 2014. Three patients underwent the surgery following the Sistrunk procedure. The rest of the patients are in the process of monitoring. The monitoring process lasts from 1 to 10 years. **Results.** As many as 27 out of 28 smears contained macrophages, 9 contained stratified squamous epithelial cells and only 4 smears contained follicular cells. Granulocytes were present in 4 smears. Two smears had scarce cellularity, 21 had moderate and 5 high cellularity. Malignant cells were not observed. In 19 smears, extracellular matrix consisted of cholesterol crystals. **Conclusion.** Thyroglossal duct cysts have no specific cytological features. Macrophages are the dominant cell population. Cholesterol crystals and stratified squamous epithelial cells enable differentiation of thyroglossal duct cysts from thyroid gland cystic nodules. Fine-needle aspiration cytology is necessary when assessing the cellular composition of thyroglossal duct cysts in order to promptly detect the possible presence of malignant cells and to conduct a surgical treatment.

Key words: Thyroglossal Cyst; Cytological Techniques; Carcinoma, Papillary; Biopsy, Fine-Needle; Ultrasonography; Congenital Abnormalities

Sažetak

Uvod. U cisti tiroglosnog kanala može nastati karcinom, sa incidencijom 1−1,5%. Oko 30% bolesnika javi se na pregled zbog inflamacije ciste. Smatra se da su ciste tiroidnog kanala kongenitalne anomalije. Nastaju iz rezidualnog segmenta tiroglosnog kanala. Cilj rada bio je određivanje citoloških karakteristika razmaza ciste, ćelijske specifičnosti, celularnosti i sadržaja ekstracelularnog matriksa. **Materijal i metode**. Analizirani su razmazi cista 28 odraslih pacijenata, punktiranih u periodu 2004−2014. godine. Tri pacijenta su podvrgnuta operaciji prema *Sistrunk* protokolu. Ostali pacijenti su u procesu praćenja. Praćenje neoperisanih traje 1−10 godina. **Rezultati**. Čak 27 razmaza sadrži makrofage, 9 sadrži orožale pločaste epitelne ćelije, a u 4 razmaza nalaze se folikularne ćelije. Dva razmaza su bila oskudne celularnosti, 21 umerene i 5 visoke celularnosti. Maligne ćelije nisu uočene. U 19 razmaza, ekstracelularni matriks je sadržao kristale holesterola. Histološke dijagnoze za troje operisanih bolesnika su bile ciste tiroglosnog kanala benignih karakteristika. **Zaključak**. Ciste tireoglosnog kanala nemaju specifičnu citološku sliku. Dominirajuća ćelijska populacija su makrofagi. Citološka analiza je neophodna u proceni celularnog sastava ciste kako bi se eventualno prisustvo malignih ćelija pravovremeno uočilo i bilo podvrgnuto operativnom lečenju.

Ključne reči: cista tiroglosnog kanala; citološke tehnike; papilarni karcinom; aspiraciona biopsija tankom iglom; ultrasonografija; kongenitalne anomalije

Introduction

Thyroglossal duct is an endodermal diverticulum whose origin, foramen caecum, is located between the bases for the development of tongue, that is, in front of the copula, to be more specific. The duct grows into the mesenchyme and grows distally. As early as the 7th week of embryonic development, thyroglossal duct is separated from the pharynx and it atrophies, except for its anterior, distal part which develops into a thyroid gland [1]. Thyroglossal duct atrophy occurs prior to the formation of the hyoid bone. In cases when there are remaining parts of the duct, the development of the hyoid bone can affect the final position of the duct or its residuals. Residual segments of thyroglossal duct are the basis for the development of cysts that can occur at any height from the base of the tongue to the sternum [1, 2].

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Abbreviations
TDC – thyroglossal duct cyst
MR – magnetic resonance

They are located in the median or close midline of the neck and hence they are commonly referred to as medial cysts of the neck. They are noticeable at all ages and can reach the size of 1-5 cm. Furthermore, they are asymptomatic, except in the case of inflammation when they become painful and hard. In the adult population, thyroglossal duct cysts (TDC) have a prevalence of 7%. Malignant TDC incidence rate ranges from 0.7 to 1.5% [3, 4]. In the case of malignancies, it is most frequently the case of papillary carcinoma, and very rarely the case of the squamous epithelium carcinoma [5].

Although the cancer rarely occurs according to statistical data, the literature data warn us to be very careful when diagnosing each case [6]. TDC is presented as an oval tumor mass which should not be confused for an ectopic thyroid gland. Before making the final decision on treatment, ultrasound or scintigraphy should verify the size and morphology of the thyroid gland. TDC should be distinguished from branchiogenic cysts developed close to the midline, solitary cysts in the thyroid gland, hemangioma, cystic lymphangioma and cystic degenerated lymph nodes [7].

Comparative analysis of diagnostic procedures and treatments of TDC in children and adults did not show significant differences [8]. However, studies proving the existence of papillary carcinoma refer to adult patients, between the ages of 21 and 68 years [5]. The treatment of TDC is surgical, according to the Sistrunk Protocol [9]. Unfortunately, there are cases of cysts regrowth after the surgical treatment [10, 11].

Although the initial diagnosis of TDC can be set by clinical examination, most authors agree that its confirmation implies the usage of ultrasonography and cytological analysis, and in special cases, the magnetic resonance (MR) imaging [12]. So far, a relatively small number of studies have been published regarding the TDC cytology [13]. In most cases, cytological analysis of the cystic content enables us to differentiate benign from malignant lesions [5, 14]. In doing so, the positive, subjective effects of evacuation of cyst content should not be ignored.

This study was aimed at determining the cytological characteristics of cyst content, cell specificity, cellularity and the content of the extracellular matrix as well as the significance of cytological analysis in the detection of papillary carcinoma of a thyroglossal duct cysts.

Material and Methods

Cytological findings of 28 adult patients with TDC were analyzed. All patients were treated at the Center for Thyroid Gland in Banja Luka from 2004-2014. A soft tissue oval tumefaction of the anterior side of the neck was present on clinical examination. The patients underwent ultrasonography and fine-needle aspiration cytology (FNAC). Ultrasonography included the examination of the thyroid gland as well. The patients were between the ages of 16 and 64 years, the average age being 29.2 years. There were 17 women and 10 men (the ratio being 1.7: 1.0)

In addition to the size of the cyst, ultrasonography established the localization and echo-structure of the content. The localization refers to the position of cysts in relation to the median line of the anterior side of the neck, and in relation to the hyoid bone according to the height. In accordance with usual regulations, the content of the cyst was classified into three categories: anechoic, homogeneous hypoechoic and heteroehogenic content. Aspiration puncture was performed with a fine needle (23G), with the adjusted dose of 10 ml. The prepared smear was air-dried and then stained according to the May Grunwald – Giemsa procedure. The analysis was done with a wide field-of-view microscope, Axioscope, while the pictures were taken with a digital camera Canon EOS-450D.

The cell type, cellularity and content of the extracellular matrix were analyzed. According to the type, the following were described: follicular cells, squamous epithelium, macrophages, erytrophages, lymphocytes, granulocytes, and erythrocytes. Cellularity was expressed with semi-quantitative method as A (low), B (moderate) and C (high), where cellularity A represented the total number of cells less than 10 in 10 consecutive visual fields; cellularity B represented 10-100 cells in 10 consecutive visual field and cellularity C represented more than 100 cells in 10 consecutive fields. Granulocytes and erythrocytes were not included in the semi-quantitative analysis.

The extracellular matrix or substrate was descriptively shown as dense-opaque, translucent and scarce. The presence of cholesterol crystals or cellular debris in the matrix was noted. There was no evidence of malignity in the study period. Three patients underwent surgical treatment according to the Sistrunk protocol. Other patients refused surgical treatment because they did not feel any functional disorders or esthetic deficiency.

Results

All cysts were ultrasonographically identified in the medial or close midline. Most of them, i.e. 25 cysts were placed distally from the hyoid bone. The cyst was adjacent to the hyoid bone in only three cases: one directly above it, and in two cases closely below it. The size of cysts varied from 1.5 to 6.0 cm in diameter. The cysts were of anechoic, homogeneous hypoechoic and heteroehogenic structure in 14, 8 and 6 cases, respectively. The thyroid gland was properly developed, without pathological changes in 23 patients. Smaller nodules of benign characteristics were observed in the thyroid gland in 4 patients. One patient had agenesis of the left lobe. The amount of aspirated content ranged from 0.5 - 7 ml. According to the layout, the content was mostly densely-brown or clear-yellowish.

Table 1. Cytologycal profile of 28 smears
Tabela 1. *Citološki sadržaj 28 razmaza*

Cell type/*Tip ćelija*	Cellularity/*Celularnost*			Σ 28
	A (N=2)	B (N=21)	C (N=5)	
Without cells/*Acelularno*	1			1
Follicular cells/*Folikularne ćelije*		2	2	4
Squamous epithelial cells/*Pločaste epitelne ćelije*		7	2	9
Macrophages/*Makrofagi*	1	21	5	27
Erythrophagocites/*Eritrofagi*			1	1
Granulocytes/*Granulociti*		4		4
Erythrocytes/*Eritrociti*			1	1

A - low/*niska*, B - moderate/*umerena*, C - hypercellular/*hipercelularnost*

Cytological analysis indicated significant differences in relation to the type of cells presented in the analyzed content. In one case, the content of the cyst was acellular! Follicular cells were detected in 5 cysts, squamous epithelial cells in 4, macrophages in 27, erytrophages in 1, granulocytes in 4, and older red cells in 1 cyst. In terms of cellularity, semiquantitative method indicated that low cellularity (A) was present in 2 smears, moderate cellularity (B) in 21 smears, and the remaining 5 smears were hypercellular (C) **(Table 1).**

In group A, one smear consisted of only a few macrophages and transparent, pinkish colored matrix. In another smear, there were no cells, and the matrix was extremely dense, dark purple with numerous cholesterol crystals **(Figure 1).**

Group B consisted of 21 smears of moderate cellularity. Macrophages, few squamous epithelial cells, cholesterol crystals and amorphous extracellular mass were observed in 17 smears **(Figure 2).** In 4 cases, macrophages, numerous granulocytes and detritus were observed.

In the third, C group, there were 5 cystic nodes. Four cysts contained a higher number of macrophages, single or in small clusters of follicular cells, dense colloid and a slight amount of cholesterol crystal **(Figure 3).**

Apart from the classic macrophages, the remaining, fifth cyst consisted of erythrophages, individual follicular cells and many old and partially destroyed red blood cells. In the extracellular matrix, there were cholesterol crystals in as many as 19 smears. The proportion between the smear density and the amount of cholesterol crystals was not observed.

Cytological analysis did not show any changes that would unequivocally imply the presence of carcinoma. Histological diagnosis was established only in three cases. Two out of five patients with hypercellular content and a patient from the first group underwent the surgical treatment primarily due to esthetic reasons. In all three cases, TDC of benign characteristics was determined pathohistologically. All other patients are controlled periodically. The monitoring period varies from 1 - 10 years. During this period, "recharging" of the cyst did not occur in 8 patients after the initial evacuation of the content. In the same period, punctures had to be repeated in four patients because of a slight enlargement of the cyst. It should be mentioned that the time interval before repeated punctures was 1-2 years.

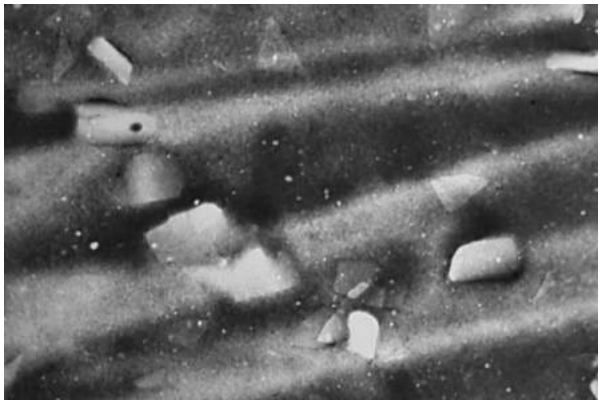

Figure 1. Cholesterol crystals, acellular content (MGG; 200x enlargement)
Slika 1. *Kristali holesterola, acelularan sadržaj (MGG; uvećanje 200 x)*

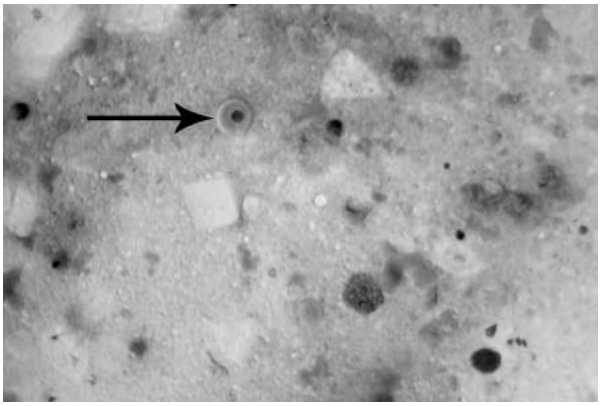

Figure 2. Squamous epithelial cells (arrow) and macrophages (MGG; 200x enlargement)
Slika 2. *Pločasti epitel (strelica) i makrofagi (MGG; uvećanje 200 x)*

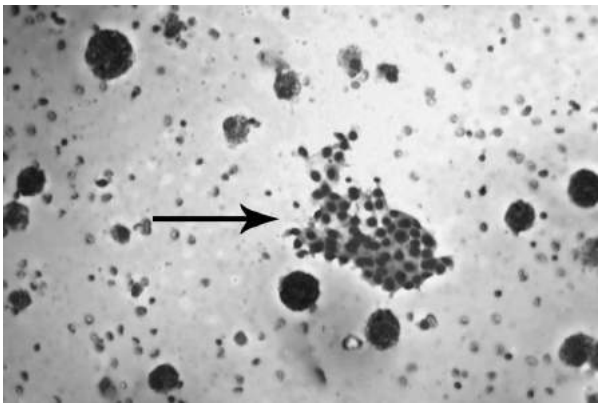

Figure 3. Follicular cells (arrow) and macrophages (MGG; 200x enlargement)
Slika 3. *Folikularne ćelije (strelica) i makrofagi (MGG; uvećanje 200 x)*

No important difference in relation to earlier cytological picture was observed in the smears of repeated punctures.

Discussion

Clinically, TDC can often be confused with the low-lying branchiogenic cyst, anterior cyst of thyroid gland or lymphoepithelial cyst [13].

Thyroglossal duct cyst is typically located in the median line of the anterior side of the neck, below the hyoid bone. Although results vary, studies show that 40% of TDC lie outside the midline i.e. laterally to the supposed medial line in adult population. When it comes to the height, over 82% of TDC are located at the infrahyoid muscles, and only 5% at the suprahyoid ones [12].

In everyday work, ultrasonography has the priority in determining the position and size of TDC over the more expensive techniques such as computed tomography CT/MR. In this analysis, ultrasonography determined the size, position and echogenicity of the cysts. There were no significant difference in comparison with the data in the above cited studies [2, 12].

Cytological examination of stained smears showed different characteristics in terms of types of the cells present as well as in terms of their number. Distribution and density of the extracellular matrix and the presence of cholesterol crystals showed significant differences. Although they are not numerous, previous studies have shown that in most TDC there are macrophages, and that all other cell types are sporadic [13]. In this analysis, as many as 27 out of 28 smears contained macrophages; whereas mature, stratified squamous cells and follicular cells were found in 9 and 4 smears, respectively. In some cases, TDC clinically look like an anterior cyst of the thyroid gland. The difference in cytological imaging of the TDC smear and a cyst in the thyroid gland is not always clear. Cysts of the thyroid gland usually contain neither stratified nor squamous epithelial cells nor cholesterol crystals [7]. The presence of any of these parameters with the clear absence of follicular cells refers to TDC. Otherwise, TDC smear in which only phagocytes and follicular cells are seen cannot be cytologically distinguished from colloidal-cystic nodules of the thyroid gland.

A greater number of granulocytes which indicated the inflammatory process were observed in 4 smears, although there was neither pain nor redness in the clinical picture. After additionally conducted analysis of erythrocyte sedimentation rate (ESR), white blood cells (WBCs) and C-reactive protein (CRP), an adequate antibiotic therapy was administered. According to the literature, up to 30% of patients come to the first check-up with signs of intracystic infection [15]. A big difference was noticeable in terms of cellularity, i.e. the number of cells in the smear. The smear of one cyst was completely acellular! Purple colloid and cholesterol crystals were visible. In contrast, five smears were described as hypercellular. Although it was expected, the turn in terms of atypia was not noticed. Two out of five were treated surgically, and the histological diagnosis was: TDC.

No malignant cells were detected in any smear. According to previous studies, cytological analysis of TDC cancer showed about 60-66% accuracy [5, 16]. Diagnostic criteria for papillary carcinoma in TDC did not differ from the criteria for the same kind of cancer in the cystic nodule of the thyroid gland. This in itself justifies the request of the majority of authors to make cytological analysis of the TDC aspirates an obligatory diagnostic procedure. None of 28 patients belonged to pediatric population. Although some authors claim they have not noticed significant differences in behavior of children and adult patients with TDC, they are united in opinion that the cytological analysis is a useful diagnostic method, regardless of age [8, 17]. In contrast, Lee et al. stated that in children under 10 years of age, cytological analysis showed a diagnostic sensitivity of 70% and a positive predictive value of 41% so it is not recommended as a routine procedure in the stated age [18].

Comparing cytological findings of this analysis with the similar ones reported in literature, containing a larger number of histological diagnoses, we can assume that none of our patients suffered from the cancer in TDC. This is supported by the fact that there were no elements of tumor growth related to TDC in the process of clinical monitoring, which was 10 years long for some patients. Nevertheless, we believe that surgical treatment of TDC is justified and definite.

Conclusion

Cytological analysis shows that thyroglossal duct cysts do not have a uniformed cytological picture. Most thyroglossal duct cysts contain phagocytes and cholesterol crystals. Although cellularity of the smear was different, no difference in clinical status of thyroglossal duct cysts was observed during the specified period.

Thyroglossal duct cysts that do not contain cholesterol crystals and squamous cells in the smear are not cytologically different from colloidal-cystic nodules of the thyroid gland. The presence of granulocytes in the thyroglossal duct cyst smears requires an additional processing and antibiotics, in spite of the absence of any elements of inflammation in the clinical picture.

Despite the fact that typical characteristics of papillary carcinoma were not detected in the analyzed smears, we believe that cytological analysis is of great importance in its detection.

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PLASMA ENDOTHELIN-1 LEVELS AND ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

ODNOS PLAZMATSKE KONCENTRACIJE ENDOTELINA-1 I ALBUMINURIJE KOD BOLESNIKA SA TIPOM 2 ŠEĆERNE BOLESTI

Radmila ŽERAVICA[1,2], Branislava ILINČIĆ[1,3], Velibor ČABARKAPA[1,2], Vladimir SAKAČ[3,4], Veljko CRNOBRNJA[1,2] and Zoran STOŠIĆ[1,2]

Summary

Introduction. Microalbuminuria is a very important independent risk factor for the progression of renal diseases as well as diseases of the cardiovascular system. Pathophysiological mechanisms that lead to the development of microalbuminuria in patients with diabetes are complex and they are a result of numerous factors. In the past decade, endothelin-1, the most potent vasoconstrictor peptide, was identified as an important factor that significantly contributes to the functional and structural renal changes. The objective of this study was to investigate the relationship between plasma concentration of endothelin-1 and urinary albumin excretion in patients with type 2 diabetes mellitus. **Material and Methods.** There were 76 patients with type 2 diabetes who were divided into those having normoalbuminuria (n=33), microalbuminuria (n=29), and macroalbuminuria (n=14), and 30 healthy controls. Plasma levels of endothelin-1 were measured by enzyme-linked immunosorbent assay. **Results**. There were significant differences in plasma concentration of endothelin-1 among groups ($p<0.01$). The correlation between endothelin-1, albuminuria, proteinuria and glomerular filtration rate was significant. In multiple regression analyses the plasma concentration of endothelin-1 was independently and significantly associated with albuminuria ($\beta=0.01$, $p=0.009$), proteinuria ($\beta=0.02$, $p<0.001$) and glomerular filtration rate ($\beta=-0.01$, $p=0.0006$). **Conclusion.** Higher plasma concentrations of endothelin-1 are independently associated with the levels of urinary excretion of albumin which may corroborate the hypothesis of a potential role of this peptide in the development of microalbuminuria in diabetic nephropathy.

Key words: Diabetes Mellitus, Type 2; Albuminuria; Proteinuria; Glomerular Filtration Rate; Endothelin-1; Diabetic Nephropathies; Risk Factors; Enzyme-Linked Immunosorbent Assay

Sažetak

Uvod. Mikroalbuminurija predstavlja veoma značajan nezavisni faktor rizika za progresiju bubrežnih bolesti kao i bolesti kardiovaskularnog sistema. Patofiziološki mehanizmi koji dovode do razvoja mikroalbuminurije kod bolesnika sa dijabetesom kompleksni su i rezultat su delovanja brojnih faktora. Poslednjih godina izdvojio se endotelin-1, kao najpotentniji vazokonstriktorni peptid koji značajno doprinosi funkcionalnim i strukturnim bubrežnim promenama. Cilj ove studije bio je da se ispita odnos plazmatske koncentracije endotelina-1 i urinarne ekskrecije albumina kod pacijenata sa tipom 2 šećerne bolesti. **Materijal i metode.** Izmerene su plazmatske koncentracije endotelina-1 sendvič-imunometrijskom metodom (ELISA) kod ukupno 76 bolesnika sa tipom 2 šećerne bolesti, koji su podeljeni u grupe na osnovu različitog stepena albuminurije: na grupu sa normoalbuminurijom (n = 33), mikroalbuminurijom (n = 29) i makroalbuminurijom (n = 14). **Rezultati.** Postojala je statistički značajna razlika u vrednostima plazmatske koncentracije endotelina-1 između ispitivanih grupa ($p < 0,01$). Takođe postojala je značajnija korelacija između endotelina-1 i albuminurije, proteinurije kao i izmerene vrednosti jačine glomerulske filtracije. U multiploj regresionoj analizi, plazmatska koncentracija endotelina nezavisno je povezana sa albuminurijom ($\beta = 0,01$, $p = 0,009$), proteinurijom ($\beta = 0,02$, $P < 0,001$) i jačinom glomerulske filtracije ($\beta = -0,01$, $p = 0,0006$). **Zaključak.** Povišene vrednosti plazmatske koncentracije endotelina-1 u korelaciji su sa stepenom urinarne ekskrecije albumina što može ukazati na potencijalnu ulogu ovog peptida u razvoju mikroalbuminurije kod dijabetesne nefropatije.

Ključne reči: dijabetes melitus tip 2; albuminurija; proteinurija; glomerularna filtracija; endotelin-1; dijabetesna nefropatija; faktori rizika; imunometrijska metoda

Introduction

Microalbuminuria occurs in about 25% of patients with type 2 diabetes and it is an important independent risk factor for the progression of kidney disease as well as diseases of the cardiovascular system [1].

Increased urinary excretion of protein in patients with type 1 diabetes is indicative of the development of diabetic nephropathy; whereas, microalbuminuria as well as hypertension is already present at the time of

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Abbreviations

ETA – endothelin type A
ETB – endothelin type B
ET-1 – endothelin-1
BMI – body mass index
GFR – glomerular filtartion rate
UEA – urinary albumin excretion
DM – diabetes mellitus

diagnosis of diabetes in most patients with type 2 diabetes. This is most likely the result of a generalized disorder of vascular endothelium. The development of this complication of diabetes is accompanied with the progressive increase in proteinuria and blood pressure, which contributes to the progression of nephropathy [2, 3]. Pathophysiological mechanisms that lead to the development of microalbuminuria in diabetic patients are complex and they are a result of the action of a numerous of hemodynamic and metabolic factors. Nowadays, it is believed that hemodynamic factors, such as systemic hypertension, glomerular hypertension and glomerular hyperfiltration, as well as ultrastructural changes at the level of the glomeruli such as thickening of the glomerular basement membrane and loss of negatively charged proteoglycans, are important factors in the development of albuminuria in diabetic nephropathy [4–6].

In the past decade, endothelin-1 (ET-1) was identified as an important factor among vasoactive factors contributing to the onset and progression of proteinuria. ET-1 is a potent vasoconstrictor peptide, derived from the production of a vascular endothelium, from big ET-1 and its splitting under the action of endothelial-converting enzyme inhibitors [6, 7]. ET-1 is produced as a result of activation of the endothelin type A (ETA) receptors and endothelin type B (ETB) receptors [7, 8]. ETA receptors are predominantly localized in the vascular smooth muscle cells and mediate vasoconstriction of large and small blood vessels, while ETB receptors located on endothelial cells mediate vasodilatation through the production of nitric oxide (NO) and prostacyclin [7–9].

Endothelin-1 is a vasoactive peptide which has an important role in the regulation of renal function and blood pressure. The pathophysiological processes, in which ET-1 participates, have been identified. These processes consist of the mechanisms of vasoconstriction, increased vascular permeability, and inflammatory and oxidative effects of ET-1 [9–12].

Previous studies have indicated the presence of elevated concentrations of plasma ET-1 levels in patients with diabetes; however, the connection between ET-1 and albuminuria is not yet entirely clear; therefore, the objective of this study was to examine the relationship between plasma levels of ET-1, a marker of endothelial dysfunction and potent vasoactive factors and urinary albumin excretion in patients with type 2 diabetes.

Material and Methods

This cross-sectional study was conducted in the Clinical Center of Vojvodina in the period from June 2012 to July 2013. Of 106 respondents included in the study, 76 were the patients with type 2 diabetes (secondary insulin-dependent), who were treated at the Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Vojvodina in Novi Sad and 30 were healthy controls matched by sex and age. The excluding criteria were: glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2, any cardiovascular incident having happened 6 months before the inclusion into the study, malignancy, liver disease, acute inflammatory or infectious processes, and no change in concomitant therapy and supplementation, levels of physical activity, body weight changes, diet and smoking habits in the last 6 months.

The clinical evaluation of patients consisted of a detailed history taken, physical examination, measurement of body weight and height, as well as the calculation of body mass index (BMI), and blood pressure measurement. Laboratory evaluation was performed in the morning, after 12-hour fasting and a 30-minute resting period. Blood samples and 24-hour urine were taken on the same day when the measurement of glomerular filtartion rate (GFR) was done, with prior verbal explanation to the respondents along with the attached written instructions on the methodology of collecting 24-hour urine. All analysis were done immediately after sampling, with the exception of ET-1 (samples were frozen for no longer than one month prior to the determination of ET-1).

The diabetic patients were divided into groups according to their values of urinary albumin excretion (UAE): the first group included the respondents with diabetes mellitus (DM) and the normoalbuminuria (UAE less than 30 mg/24 h), the second group of diabetic patients with microalbuminuria (UAE between 30–299 mg/24 h) and the third group of diabetic patients with macroalbuminuria (UAE ≥300 mg/24 h).

Determination of Urinary Albumin Excretion - Albuminuria

Albuminuria was determined from a sample of 24-hour urine, by sandwich immunometric assay, with the use of commercial Nyco Card tests (Oslo, Norway) on Nyco Card reader, the upper reference limit being 30 mg/24 h. The diagnosis of persistent micro or macroalbuminuria could be made in case of positive finding in at least two of three urine samples at intervals of three to six months.

Proteinuria was determined from a sample of 24-hour urine, by modified staining method on biochemical analyzer ADVIA 1800 by means of commercial Siemens kits (Siemens Health Care Diagnostics, Tarrytown, USA), the upper reference limit being 140 mg/24 h.

ET-1 measurements

The level of plasma endothelin-1 was determined by ELISA method by means of a commercial company sets (R&D Systems, USA) on the biochemical analyzer RYTO. The assay is based on the direct sandwich technique with monoclonal antibodies directed to the ET-1. The results were expressed as pg/mL.

GFR measurement

Assessment of GFR was determined by using a single-spaced model with the isotopic clearance of ^{99m}Tc-labeled diethylene- triamine-penta acetic acid (^{99m}Tc-DTPA), using a single injection at a dose of 37 MBq and measurements of two blood samples, taken after 180 and 240 minutes. The values were normalized to a standard body surface and adjusted according to the age of patients [13, 14].

Serum concentration of creatinin, urea and uric acid were determined by standard biochemical methods on the biochemical analyzer Olympus AU400. Furthermore, in all respondents serum concentrations of glucose were measured by the glucose oxidase method, the reference range being 4.0 – 5.9 mmol/L and glycated hemoglobin A1c (HbA1c) by the immune-inhibitory test (Beckman-Coulter, Ireland), the reference range being 4.7–6.0%.

Statistical Analysis

A statistical analysis was performed using SPSS version 12.0 (StatSosftinc, Tulsa, OK, USA) for Windows. Descriptive statistics, including median, arithmetic mean and standard deviation (SD) were used to describe the studied parameters. The distribution of numeric variables was tested by means of Kolmogorov-Smirnov test. Differences in distributions of individual parameters between the study groups were analyzed with the parametric (t-test, ANOVA) and nonparametric tests (Mann-Whitney test, Kruskal–Wallis test, chi-square test). Pearson and Spearman coefficients of linear correlation were used to determine the correlation between the variables. Multiple regression analysis was performed to estimate the independent contribution of plasma ET-1 concentration to albuminuria. A difference was considered significant if the p-value was less than 0.05.

Results

A total of 76 patients with type 2 DM (43 female and 33 male) were evaluated according to the level of urinary albumin excretion and classified into the following groups: diabetic patients with normoalbuminuria (n=33), microalbuminuria (n=29) and macroalbuminuria (n=14).

The main characteristics of the study respondents are shown in **Table 1**.

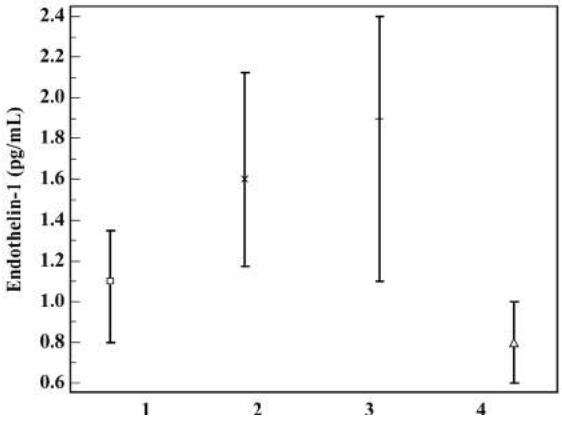
There was a statistically significant difference in the median value of ET-1 between two groups (p

Table 1. Clinical and laboratory characteristic of the respondents
Tabela 1. *Kliničke i laboratorijske karakteristike ispitivanih grupa*

	Normo/*Grupa sa normo* (n = 33)	Micro/*Mikro* (n = 29)	Macroalbuminuria *Makroalbuminurija* (n = 14)	p
Number (f/m)/*Broj (ž/m)*	18/15	12/17	8/6	p>0.05
Age (year)/*Starosno doba (godine)*	59 (39-75)	60 (46-77)	59 (52-75)	p>0.05
BMI (kg/m^2)/*ITM (kg/m^2)*	28.9 (±4.5)	27.4 (±4.2)	29.4 (±3.2)	p>0.05
Duration of diabetes (year) *Trajanje dijabetesa (godine)*	10 (3-27)	13 (3-26)	12.5 (9-30)	p>0.05
Insulin therapy (year) *Trajanje insulinske terapije (godine)*	4 (1-12)	5 (1-25)	6 (2-7)	p>0.05
Fasting glucose (mmol/L)/*Glikemija (mmol/L)*	8.7 (4.5-13)	8.6 (4.6-16)	8.8 (5-17)	p>0.05
HbA1c/*HbA1c (%)*	7.7 (5.6-9.1)	7.7 (5.8-9)	8.0 (7.2-9)	p>0.05
Systolic BP (mmHg)/*Sistolni KP (mmHg)*	140 (110-180)	130 (110-180)	140 (120-190)	p>0.05
Diastolic BP (mmHg)/*Dijastolni KP (mmHg)*	83 (±11)	81 (±6)	84 (±10)	p>0.05
HT (n)/*Prisustvo HT (n)*	27/33	21/29	14/14	p>0.05
Duration of HT (year)/*Trajanje HT (godine)*	5 (1-20)	5 (1-30)	6 (3-20)	p>0.05
ACE inhibition use (n) *Upotreba ACE inhibitora (n)*	16/27	14/29	13/14	p>0.05
mGFR/*mJGF (mL/min/1,73 m^2)*	98 (±12)	94 (±18)	71 (±11)	Pab<0.05
Creatinine/*Kreatinin (µmol/L)*	73 (±12)	74 (±13)	81 (±10)	p>0.05
Urea/*Urea (mmol/L)*	5.4 (3.8-7)	5.6 (4-8.9)	6 (4.4-10)	p>0.05
Uric Acid/*Mokraćna kiselina (µmol/L)*	291 (±77)	299 (±91)	360 (±65)	Pab<0.05
UAE (mg/24 h)/*UEA (mg/24 h)*	10 (7-18.5)	50 (30-127)	340 (300-860)	P<0.05
Proteinuria (g/24 h)/*Proteinurija (g/24 h)*	109 (45-149)	196 (40-501)	400(235-800)	p<0.05

BP – blood pressure, ACE- angiotensin-converting enzyme, HT-hypertension, HbA1c - glycated hemoglobin, a - p<0.05 – compared macro to normoalbuminuria group; b - p<0.05–compared macro to microalbuminuria group

ITM − indeks telesne mase, KP − krvni pritisak, inhibitori ACE – angiotenzin-konvertujućeg enzima, HT − hipertenzija, HbA1c − glikozilirani hemoglobin, UEA − urinarna ekskrecija albumina, a – p<0,05 – poređenje grupe sa makro- u odnosu na grupu sa normoalbuminurijom, b – p < 0,05 – poređenje makro u odnosu na grupu sa mikroalbuminurijom, JGB - jačina glomerulske filtracije



Graph 1. Distribution of the ET-1 values in the examined groups

Grafikon 1. *Distribucija vrednosti endotelina-1 u ispitivanim grupama*

Legend: 1 - Normo, 2 - Micro, 3 - Macro and 4 - Control Group

Legenda: 1 - Grupa sa normoalbuminurijom, 2 - Mikroalbuminurijom, 3 - Makroalbuminurijom i 4 - Kontrolna grupa

<0.001). Significantly lower plasma concentrations of ET-1 were found in the respondents in the control group compared to the patients with diabetes. There was a significant difference in the values of ET-1 compared to albuminuria. The patients with albuminuria values over 300 mg/24 h (macroalbuminuria) had significantly higher values of ET-1 levels compared to those with microalbuminuria (30-299 mg/d), and those with the normoalbuminuria ($p < 0.05$). The values of ET-1 were also significantly higher in patients with microalbuminuria in comparison to the patients with normoalbuminuria ($p < 0.05$).

The **Graph 1** shows the value of plasma ET-1 in relation to the experimental groups: group with normolabuminuria, microalbuminuria, macroalbuminuria, as well as the control group.

There was a statistically significant correlation between plasma levels of ET-1 and the measured values of albuminuria, proteinuria and GFR in the group of patients with type 2 DM. The patients with type 2 diabetes and higher values of plasma concentration of ET-1 had higher levels of urinary albumin excretion and proteinuria. However, they had lower values of mGFR. Multiple regression analysis was used to determine the correlation level between ET-1 and albuminuria, proteinuria and mGFR. In the model ($R = 0.65$, $R2 = 0.63$), plasma concentrations of ET-1 were independently and significantly associated with albuminuria ($B = 0.01$, $P = 0.009$), proteinuria ($\beta = 0.02$, $P < 0.001$) and GFR ($\beta = -0.01$, $P = 0.0006$).

Graph 2 shows the correlations ET-1 with albuminuria, proteinuria and mGFR

Discussion

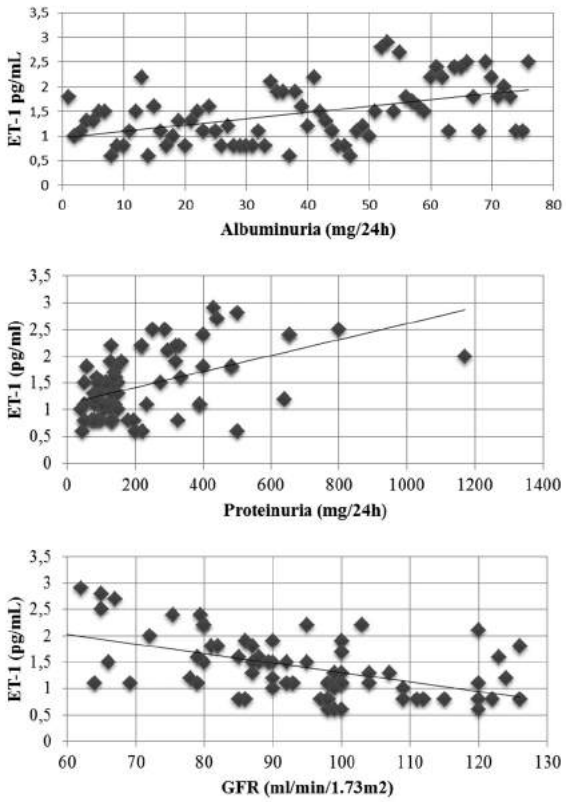
Endothelin-1 is a potent vasoactive factor with proliferative, profibrotic and proinflammatory properties with a high expression in the renal vasculature and parenchyma. In this study, there was an increase in the plasma concentration of ET-1 with increased levels of urinary albumin excretion in the patients with type 2 DM. The value of plasma ET-1 was significantly higher in the group of diabetic patients with macroalbuminuria than in the group of patients with micro and normoalbuminuria, and significantly higher plasma ET-1 in the group with microalbuminuria than in the patients with normoalbuminuria**.** There was also a significant correlation of plasma concentrations of ET-1 with the values of urinary albumin excretion and proteinuria in the patients with type 2 DM. Similar results were obtained in studies of Zanatta et al., who found a significant association of elevated plasmatic concentration of ET-1 with the degree of albuminuria in diabetic patients [15]. The study of Bruno CM revealed elevated levels of plasma ET-1 in the group of normotensive diabetic patients with microalbuminuria compared to the healthy population, as well as its significant correlation with the severity of urinary albumin excretion [15, 16].

One of the possible mechanisms by which ET-1 affects the glomerular damage and contributes to the development of proteinuria is podocyte damage. Podocytes are highly differentiated cells with complex morphology, which play an important role in maintaining the integrity of filtration membranes. It is believed that the influence of ET-1 leads to podocyte effacement and disruption of the podocyte actin cytoskeleton. Furthermore, it leads to a loss of protein such as nephrin**,** which plays an important role in maintaining intercellular conjunctions. In their *in vitro* experimental study Morigi et al. have found that podocytes are subject to phenotype changes, i.e. dedifferentiation influenced by autocrine and paracrine functioning of ET-1, which leads to damage of glomerular filtration membrane [16]. These data are consistent with the evidence of *in vivo* study in a mice model of "overload" proteinuria obtained by Benigni A. et al. which exhibit an enhanced renal production of ET-1 leading to the development of some structural damage to podocytes [17, 18]. Another possible mechanism is the hemodynamic effect of ET-1, which in conjunction with other vasoactive factors lead to an increase in intraglomerular capillary pressure which increases glomerular permeability and thus leads to increased filtration of proteins [18, 19]. Considering the role of ET-1 in the development of proteinuria, the results of a number of experimental studies have pointed to renoprotective action of endothelin receptor blockers [20, 21].

As for the presence of hypertension, 82% of the total number of patients with diabetes had hypertension. It is known that hypertension in newly diagnosed cases of type 2 DM is usually already present, and it had often existed before type 2 DM was diagnosed. The data indicate that the prevalence of hypertension in patients diagnosed with type 2 diabetes is about 50%, and with the development of microalbuminuria this percentage increases to about 80%. On the other hand, the prevalence of hyperten-

sion in patients diagnosed with type 2 DM with development of macroalbuminuria is about 90% [21, 22]. This corresponds to the findings of our study.

The findings of this study showed that diabetic patients with a higher degree of UAE or macroalbuminuria had lower GFR than the diabetic patients with microalbuminuria and normoalbuminuria**.** This was expected considering the fact that proteinuria itself is one of the most important independent factors of progression of renal disease. A significant correlation was also found between the values of plasma ET-1 and the GFR, i.e. the diabetic patients with higher values of plasma ET-1 had lower GFR. In addition to the already well-known fact that the value of plasma ET-1 in patients with DM is elevated compared to the healthy population, numerous studies have turned to examining its role in the development and progression of microvascular complications [21–23]. The experimental studies done on diabetic rats so far suggest a role of elevated levels of ET-1 in glomerular and interstitial renal damage, which were proportional to the plasma concentration of ET-1 [24–28]. However, previous clinical studies dealing with the relationship of ET-1 and GFR in diabetic patients yielded different findings, which could have resulted from the number of patients involved and the status of the functional kidney. Namely, no significant correlation was found between ET-1 and GFR in the group of patients with relatively preserved kidney function, while studies involving respondents with greater reduction of GFR revealed a significant correlation between ET-1 and the status of kidney function [29–34].



Graph 2. Correlation between ET-1 and albuminuria, proteinuria and mGFR
Grafikon 2. *Korelacija između endotelina-1 i albuminurije, proteinurije i jačine glomerulske filtracije*

Conclusion

The findings from this study show that the higher values of plasma endothelin-1 concentrations are independently correlated with a higher degree of albuminuria and proteinuria, which supports the hypothesis of potential role of vasoactive peptides in the development of microalbuminuria in diabetic nephropathy. In addition, an independent correlation of plasma concentrations of endothelin-1 and glomerular filtration rate indicates a potentially harmful effect of elevated levels of endothelin-1 on kidney function, which contributes to the further progression of diabetic nephropathy. The above findings suggest a possible role of endothelin receptor antagonists in preventing the development and further progression of diabetic nephropathy.

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PROGNOSTIC FACTORS FOR POSTOPERATIVE VISUAL OUTCOME IN SURGICALLY TREATED SUPRASELLAR MENINGIOMAS

UTICAJ PROGNOSTIČKIH FAKTORA NA VIDNU OŠTRINU NAKON HIRURŠKOG LEČENJA MENINGEOMA OPTOHIJAZMALNE REGIJE

Desanka GRKOVIĆ[1,2] and Sofija DAVIDOVIĆ[1,2]

Summary

Introduction. The prognosis of postoperative visual acuity in patients with surgically treated suprasellar meningiomas is influenced not only by the size and precise localization of meningiomas in the optochiasmatic region and their compressive effect, but also by certain parameters, such as the age of patient, duration of symptoms, and preoperative visual acuity. The purpose of this study was to analyze the influence of these factors on postoperative visual acuity in the patients with surgically treated optochiasmatic meningioma as well as to determine their prognostic value in the recovery of visual function after surgery. **Material and Methods**. The study sample consisted of 43 patients operated for suprasellar meningioma. All tumors were diagnosed by computed tomography or nuclear magnetic resonance scans. Visual acuity was analyzed both before surgery and six months after surgery. The effects of age, preoperative visual loss, duration of visual symptoms and tumor size on visual outcome were analyzed. **Results.** Postoperative improvement of visual acuity was observed in 50% of eyes (68.4% of patients). Visual outcome was better in the younger patients. The patients with better preoperative visual acuity had better postoperative visual acuity outcome. Chances of achieving better postoperative visual function and favorable tumor resection outcome were inversely proportional to the increased length of history of disease and tumor size. **Conclusion**. Postoperative visual acuity prognosis in suprasellar meningioma surgery was favorably affected by the mean duration of symptoms of less than 24 months, tumor size less than 30 mm, and preoperative visual acuity loss below 0.1.

Key words: Prognosis; Visual Acuity; Meningioma; Optic Chiasm; Neurosurgical Procedures; Treatment Outcome; Recovery of Function

Sažetak

Uvod. Prognoza u pogledu postoperativne vidne oštrine kod pacijenata operisanih od supraselarnih meningeoma ne zavisi samo od veličine i lokalizacije meningeoma u optohijazmalnoj regiji i njegovog kompresivnog efekta, već i od drugih parametara kao što su starost pacijenta, dužina trajanja simptoma i preoperativna vidna oštrina. Cilj rada je analiziranje uticaja pomenutih faktora na postoperativnu vidnu oštrinu kod pacijenata operisanih od meningeoma optohijazmalne regije i utvrđivanje uticaja prognostičkih faktora na stepen postoperativnog oporavka vidne oštrine. **Materijal i metode.** Analizirano je 43 pacijenata sa operisanim supraselarnim meningeomom. Prisustvo tumora dijagnostikovano je kompjuterizovanom tomografijom ili simanjen magnentnom rezonancijom. Vidna oštrina ispitivana je pre operacije i šest meseci posle operacije. Analiziran je efekat starosti pacijenta, redukcije preoperativne vidne oštrine, dužine trajanja simptoma i veličine tumora na postoperativno poboljšanje vidne oštrine. **Rezultati.** Postoperativno poboljšanje vidne oštrine utvrđeno je kod 50% ispitivanih očiju – (68,4 pacijenta). Vidna oštrina bila je bolja kod mlađih pacijenata. Pacijenti sa boljom vidnom oštrinom preoperativno imali su bolju postoperativnu vidnu oštrinu. Šanse za postizanje bolje postoperativne vidne oštrine obrnuto su proporcionalne dužini trajanja simptoma i veličini tumora. **Zaključak.** Prognoza postoperativnog poboljšanja vidne oštrine bolja je ako je, vreme proteklo od prvih simptoma do postavljanja dijagnoze manje od 24 meseca, veličina tumora manja od 30 mm i preoperativno redukovana vidna oštrina veća od 0,1.

Ključne reči: prognoza; vidna oštrina; meningeom; optička hiazma; neurohirurške procedure; ishod lečenja; oporavak funkcije

Introduction

Suprasellar meningiomas account for 5 to 10% of all intracranial meningiomas [1, 2]. Meningiomas affecting the visual pathway originate from the basal meninges of tuberculum sellae, planum sphenoidale, chiasmatic sulcus and from diaphragma sellae. The subchiasmal growth of meningiomas may cause compression, elevation and dislocation of optic nerves and optic chiasma, which lead to visual function deterioration [3–6].

Progressive visual acuity loss and defects of certain parts of visual field are an indication for surgical treatment of meningiomas [3, 4, 7–9]. Surgical treatment of meningiomas enables decompression of optochiasmatic complex, prevents further vision function deterioration, and enables visual acuity improvement at the same time [7–12].

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Abbreviations

CT – computed tomography
MRI – magnetic resonance imaging
VA – visual acuity

Despite constant neuromicrosurgical technique improvements, with total or subtotal tumor excision, data in the literature suggest that there is no significant postoperative visual function recovery. Therefore, many authors have analyzed different predictive factors [7, 8, 13–18], which influence postoperative visual restoration along with successful surgical technique. Some of these factors are the age of patient, time elapsed from the appearance of first symptoms until definite tumor diagnosis and surgical treatment, degree of preoperative visual pathway damage, size of the tumor itself, and its localization and adherence to other cranial structures.

The aim of the study was to analyze visual function preoperatively and after surgical treatment of meningiomas of optochiasmatic region, and to determine which factors, including the age of patient, duration of symptoms, degree of visual function damage, and size of the tumor, affect postoperative visual function recovery.

Material and Methods

We reviewed the medical records of patients who had been operated for meningiomas in the optochiasmatic region at the Institute for Neurosurgery of Clinical Center Serbia, in Belgrade, Serbia, and at the Department of Neurosurgery, Clinical Center of Vojvodina, Novi Sad, Serbia, in 2002. There were 160 patients, and all of them had had brain optochiasmatic tumor detected and confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scans who were divided into additional groups of patients with suprasellar or parasellar meningiomas according to the postoperative pathohistological analysis. Transcranial surgical approach was applied in 77 (48.1%) patients and 83 (51.9%) patients were subjected to transsphenoidal surgical approach. Complete tumor resection was achieved in 105 (65.6%) patients, while surgical treatment was incomplete in 55 (34.4%).

Out of 54 patients with supra- and parasellar localised meningiomas, 43 (79.6%) had positive ophthalmology anamnesis and visual field defects at ophthalmic examination. After detailed anamnesis and complete neuroophthalmic examination, those patients with different type of eye or optic nerve disease were excluded from the study. Complete neuroophthalmic examination included the visual acuity test, color vision test, visual field analysis (Goldman), pupillary reaction test, oculomotor nerve test, Hertel exophthalmometry, and ophthalmoscopy of ocular fundus. The eye examination was performed before and after surgery, on the day of hospital discharge (10 days after surgery), one month and six months after surgery.

The following prognostic and predictive factors were analyzed: the age of patient, duration of symptoms, preoperatove visual function damage, and size of the tumor.

The patients were divided into two groups according to their age: those under and over the patients' average age in the study sample.

Three groups of patients were formed based on the duration of ocular symptoms before definitive meningioma diagnosis was made: group I consisted of the patients who had preoperative symptoms lasting less than six months, in group II the symptoms lasted from six to 24 months, and in group III optochiasmatic meningioma diagnosis was made and surgery was performed more than 24 months after initial vision-related symptoms had developed. Preoperative visual acuity in the patients with surgical therapy for meningiomas in our study was also noted. Snellen charts were used to measure visual acuity (VA). According to VA level and its reduction, the patients were subdivided into four groups. Group I included the patients with normal VA (VA 1.0), the patients in group II, III and IV had mildly reduced VA (VA 0.5-0.9), moderately reduced VA (VA 0.1-0.4), and severely reduced VA (VA below 0.1), respectively.

According to the size of optochiasmatic memingioma, the patients were divided into the group below 30 mm tumor size, group from 31 to 70 mm, and group above 70 mm tumor size.

Our data were classified and statistically analyzed. A possible correlation of factors that were observed in our sample was obtained by stochastic test of correlation. X^2 test was used for a possible influence of these predictive factors on postoperative results.

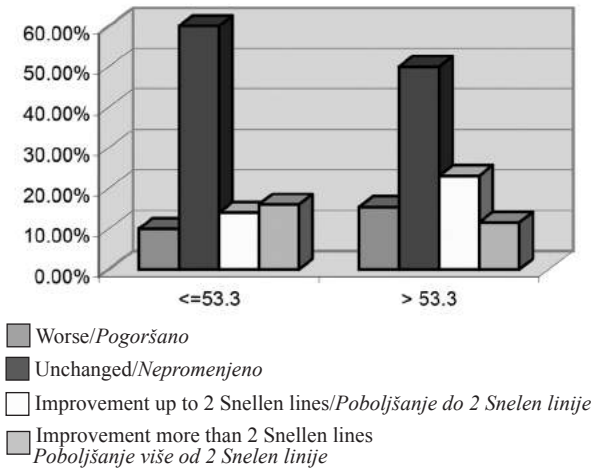
Statistical analysis was performed by Statgraphics v. 3.0. software.

Results

Out of 54 patients with supra-or parasellar tumor location, 43 (79.6%) had changes in their ophthalmology status, 32 (74.4%) were women and 11 (25.5%) were men. The average age of patients in our sample was 53.3 years, their age ranging from 36 to 71 years. The average age of women and men was 51.8 and 57.4 years, respectively.

In clinical manifestation of suprasellar meningiomas, the most important subjective complaint of the patients was visual disturbance with a reduction in VA, starting usually in one eye, and then affecting the other eye as well. Out of 43 patients, 41 (95.3%) reported VA deterioration. Monocular VA reduction was noted in 16 patients (37.2%). Binocular VA reduction was recorded in 25 (581%) 43 patients, being asymmetrical in 18, and symmetrical in 7 patients.

Headache, as a subjective complaint, either affecting the vision or not, was recorded in 9 patients (20.9%). Neurological complaints, such as mild mental or motor dysfunction, vertigo, epileptic attack, hyposmia, were present in a much lower de-

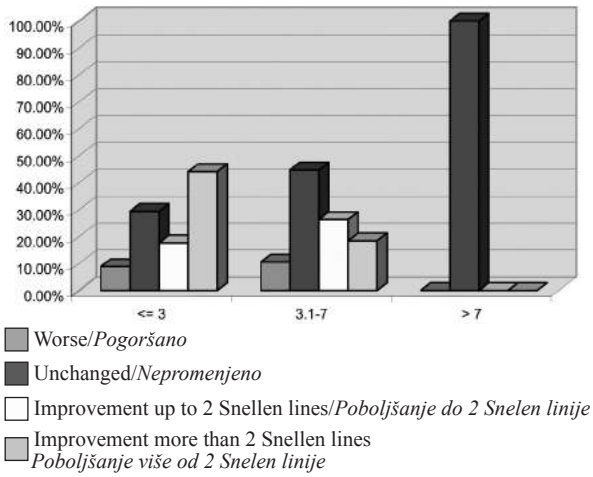


Grap 1. Influence of patients' age on postoperative visual acuity change
Grafikon 1. *Uticaj starosti pacijenata na promenu postoperativne vidne oštrine*

gree (from 2.3 to 9.3% of patients) in addition to oculomotor paresis with subjective complaints of diplopia and proptosis.

Time interval from the development of initial symptoms to making diagnosis and radiological confirmation of optochiasmatic meningioma was from 2 months to 11 years (21.5 months on average). The diagnosis was made within the first 6 months in 18 out of 43 patients (it took 2 months to make it in 4 patients after the occurrence of symptoms), from 7 months to 2 years in 17 patients, and more than two years in 8 patients.

The origin and precise anatomic localization of meningioma insertion were radiographically defined by MRI or CT scans of the head, and confirmed during brain surgery. The most frequent localization of meningioma was tuberculum sellae (27.9%),



Graph 2. Influence of meningioma size on postoperative visual acuity change
Grafikon 2. *Uticaj veličine meningeoma na promenu postoperativne vidne oštrine*

followed by the inner end of small wings of sphenoid bone (23.2%) with two cases of tumor evasion to the cavernous sinus and with two cases of propagation of tumor into the orbit. Planum sphenoidale and processus clinoideus were the origin of tumor in 18.6% of patients, and meningiomas of olfactory region were found in 9.3% of the cases.

The size of tumor, defined by its biggest diameter, was measured during MRI or CT scan recording. We had the precise tumor size noted in 40 of our patients. Tumors of medium size (30 to 70 mm) were the most dominant and they were found in 23 patients (57.5%), 13 patients (32.5%) had small tumors less than 30 mm in size and tumors bigger than 70 mm were present in 4 patients (10%).

As for our hypothesis that six months postoperative VA of our patients was equal to preoperative VA, the following results were obtained according to the data analyzed with t-test. Our statistical t value was 5.78527, for $p=4.35 \times 10^{-7}$.

In this case, with $p<0.01$, we can discard our hypothesis as false with 99% safety interval. And we can confirm that there was a statistically significant difference between preoperative and postoperative VA in surgically treated optochiasmatic meningiomas. Our patients had significantly better VA six months after meningioma surgery in the chiasma region.

The influence of predictive factors of optochiasmatic meningioma surgery on postoperative visual acuity outcomes:

Age of patient

The improvement in VA six months after surgery was observed in 30% of patients under 53.3 years of age, and in 34.6% of those over 53.3 years of age **(Graph 1)**.

X^2 test showed $X^2=0.04$ for $p=0.8364$. Since $p>0.05$, we can discard the hypothesis that the changes of VA after meningioma surgery are in correlation with the age of patient. Therefore, the age of patient did not significantly influence the postoperative VA outcome in our sample.

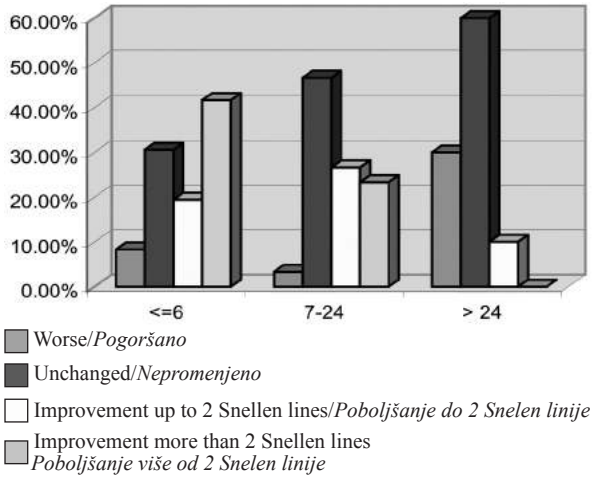
Size of Tumor

An impairment of postoperative VA was found in only 8.8% of patients with tumor size less than 30 mm after six-month follow up. No change in VA was observed in 29.4% of cases, while the highest percentage of patients (61.8%) had postoperative VA improvement.

A significant (over 20%) VA improvement (more than two lines at Snellen chart) was observed in 44.1% of patients having 31-70 mm tumor size; 44.7% patients had no change in postoperative VA, and 44.7% of patients had improved VA.

There was no change in postoperative VA in the patients having a tumor exceeding 70 mm **(Graph 2)**.

As for the patients with tumor size less than 30 mm, 55% of them had improvement of postoperative VA, 22% of them stabilized VA at least in one



Graph 3. Influence of symptom duration on postoperative visual acuity change
Grafikon 3. *Uticaj dužine trajanja simptoma na promenu postoperativne vidne oštrine*

eye, and only 5% had an impairment of postoperative VA; whereas 37.5% of patients with tumors 31-70 mm had an improvement, no change was found in 36.8% of them, and 6.2% of these patients had an impairment of postoperative VA. An impairment of VA was noted in 50% of patients having tumors of 70 mm or larger, mortality being as high as 50%.

According to X^2 testing, X^2 was 11.95 for p=0.043. With p<0.05, it was confirmed that there was a statistically significant direct influence of preoperative tumor size on postoperative VA six months after optochiasmatic meningioma surgery.

Duration of Symptoms

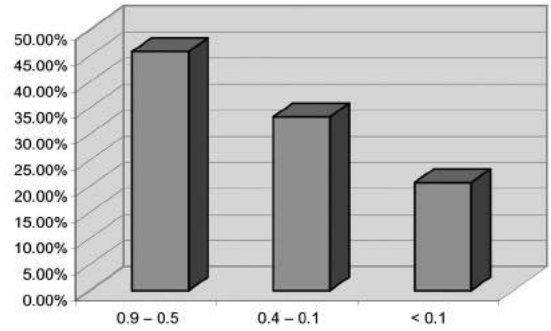
Visual acuity improvement was confirmed in 61.1% of the patients having had the symptoms for less than 6 months before meningioma surgery, with a significant VA improvement of more than 20% (two Snellen chart lines) in 41.7% of cases. The overall VA postoperative improvement was observed in 50% of the patients having had symptoms for 7 months to two years, with two chart lines gain in 23.3%. VA improvement was observed in 10 patients having had the symptoms for more than two years before meningioma surgery, no improvement occurred in 60%, and VA impairment was recorded in 30% of cases **(Graph 3)**.

Visual acuity was improved in 75% of patients with symptoms lasting less than 24 months, with up to 1.0 VA improvement in at least one eye in 28.6%.

With X^2 test, our X^2 was 16.74 for p=0.0103. Therefore, with p<0.05, we suggest that there is a significant direct influence of duration of symptoms before meningioma surgery on postoperative VA in our patients.

Degree of Preoperative Visual Reduction

It was found that 94.4% of eyes with normal preoperative VA remained stable and showed no impairment of VA six months after surgery. Out of 38 eyes with mild or moderate preoperative VA impairment (09 to 0.1), 81.6% showed improved or stable postoperative VA, comparing to 58.6% of patients who had a significant reduction of preoperative VA.



Graph 4. Influence of preoperative reduction of visual acuity on postoperative visual acuity improvement in all eyes
Grafikon 4. *Uticaj preoperativne redukcije vidne oštrine na poboljšanje posoperativne vidne oštrine*

The overall VA postoperative improvement was observed in 38 eyes, being mild, moderate and significant preoperative VA reduction in 45.8%, 33.3% and 20.7% of these eyes, respectively **(Graph 4)**.

By X^2 test, we gain X2=12.32, for p=0.0035. Since in this analysis p<0.05, we concluded that preoperative VA in brain tumor surgery was a significant prognostic factor, and directly contributed to better postoperative VA in the patients with chiasmatic meningeoma.

Discussion

According to data available in literature, the age of patient at the time of meningioma surgery has limited influence on postoperative visual function [7–9, 16]. Though some authors emphasize that patients younger than 40 at the time of surgery show better postoperative visual function recovery compared to patients over 60 and more years of age [2, 15, 17]. In our data sample, we did not find a statistically significant difference in postoperative visual recovery between two different age groups. Postoperative VA was improved by two or more Snellen chart lines in 33.3% of the patients under 40 years of age, whereas VA improvement was observed in 16.7% of the patients over 60 years of age.

These results may be interpreted as follows: the predominant reason for VA reduction in the patients with compressive optic neuropathies is ischemia of nerve fibers, which is more efficiently repaired after cranial surgery with a better microcirculation recovery after chiasma or optic nerve decompression in younger individuals than in older patients with meningiomas [15].

In our results, the degree of preoperative VA reduction has a statistically significant influence on the postoperative VA recovery. The better the preoperative VA, the better postoperative VA is in ot-

pochiasmatic meningioma surgery. 94.4% of eyes with preoperative VA of 1.0 by Snellen chart had the same postoperative VA in the six month follow up. There was an improvement of VA in the postoperative period in 79.2% of 38 eyes with mildly and moderately reduced preoperative VA (0.9-0.1). In the first 6 months after surgery, a postoperative VA improvement was observed in only 20.8% of patients with severe preoperative VA damage due to tumor compression.

Our data are in accordance with data of other authors, where the importance of preoperative VA status and its possible reduction are important contributing factors for the postoperative VA recovery [7, 8, 15–11]. For instance, Zevgaridis et al. [15] found the postoperative VA recovery in 77.7% of patients with the preoperative VA above 0.2 Snellen chart compared to 45.8% of eyes with an improvement in patients with the preoperative VA below 0.2.

There are suggestions that patients with less severe preoperative visual loss present the involvement of optic nerve and chiasma with tumor to a lesser degree intraoperatively [7, 15, 18]. Therefore, the postoperative chances for visual improvement after surgical decompression are bigger.

A slow, gradual progression of visual function defects, headaches, neurological deficits, or mental changes in a great number of patients contributes to the late or delayed diagnosis of tumor with a loss of valuable time. Meningiomas of optochiasmatic regions are precisely detected most frequently at the time when VA in one eye is already significantly damaged, and the tumor has a reached bigger size [6, 14, 15, 18, 19].

Due to its slow growth and gradual progression of invasion in other nearby tissues, especially if meningiomas are situated in mute, non functional neurological zones, meningiomas of optochiasmatic regions are usually without any clinical symptoms and manifestations for a long period. There is usually a transitory, mild, monocular visual function reduction, with gradual peripheral visual field narrowing. These symptoms are often misdiagnosed and overseen both by the patient and ophthalmologist.

A proper diagnosis of intracranial tumor of optochiasmatic region is most often not made until the other eye is affected, and/or VA in the primary eye is significantly reduced [6, 14, 20].

On the other hand, such signs and symptoms, which are in a way nonspecific vision-related, may be underestimated both by the patient and ophthalmologist, or they may be misdiagnosed as retrobulbar neuritis or ischaemic optic neuropathy. Systemic corticosteroid therapy may improve VA and vision related complaints, which masks proper diagnosis of meningioma. Therefore, every case with a mild and transient VA improvement, or with a lack of response to systemic corticosteroid therapy, must be regarded as a warning sign of compressive lesion of optic nerve or chiasmal region, and it should warrant a proper and prompt neuroimaging diagnostics (MRI or CT head scans).

Nowadays, in the era of advanced MRI or CT diagnostics, most authors emphasize a non-justified prolonged time interval between first meningioma symptoms until tumor diagnosis [8, 15, 21–23]. Most of the papers published in last several years suggest that average time interval and duration of tumor symptoms is longer than 24 months [14, 15, 21, 23, 24]. Some authors state that this time interval may be even 30 to 39 months [6, 20], while, according to some of data, the average time of duration of meningioma symptoms is less than 24 months - 15 months and 13 months according to Pucner [18], Zevgaridis [15], respectively.

It has been suggested by our data analysis that an average time interval between first symptoms and meningioma diagnosis is 21.5 months, ranging from 2 months to 11 years. According to our data, longer time until meningioma diagnosis is established is an unfavorable prognostic factor for better postoperative visual function recovery. In our group of patients, who had had symptoms for less than 24 months, a postoperative VA improvement was noted in 75% of the cases, with VA of 1.0 by Snellen chart in one eye at least in 28.6%. Those patients who had had symptoms for more than 24 months presented with significantly worse VA after six months after surgery.

In their earlier works Pucner et al. [18], Ohta et al. [14], as well as Lee at al. [5], have given evidence that the duration of symptoms below 2 years, especially below 6 months before diagnosis of meningieoma and subsequent surgery, enables quicker and more successful postoperative VA recovery after surgical decompression and evacuation of suprasellar meningioma.

All possible pathogenic mechanisms for nerve fibers damage in meningioma cases, such as direct compression of nerve fibers by tumor tissue, stopping of axoplasmatic transport, ischemia of nerve fibers due to pressure on fine feeding microvasculature, have consequences such as demyelination, degradation and degeneration of axons. These processes are prolonged in cases with long standing and non recognized meningioma symptoms. After surgical decompression, chronically ischemic and partially demyelinated nerve fibers have a potential to recover and improve their function, but only in cases where they have retained their significant biological recovery potential [25, 26]. Atrophy of nerve fibers develops with prolonged, severe preoperative ischemia, as well as with advanced degeneration and demyelination of nerve fibers. The recovery potential is irreversibly lost and there is an impairment of neurologic function even after surgical decompression in treatment of meningioma [5]. It is estimated that the critical preoperative period for postoperative recovery of nerve fibers and visual function is 24 months.

Time elapsed from first meningioma symptoms until making the diagnosis of tumor is also connected with the tumor size, and possibility of its proper,

complete (total) or incomplete (subtotal) surgical excision and treatment, with minimal postoperative residual complications and consequences. On the other hand, prolonged compression on fine nerve fibers of optochiasmatic region with ischemia leads to an irreversible loss of their function even with proper tumor decompression surgery.

Tumors from 30 to 70 mm size were detected in 55.5% of cases. Small tumors of less than 30 mm size were found in 33.3% of cases, and big tumors, exceeding 70 mm were found in 11.1% of cases. A statistically significant correlation was found between the tumor size and postoperative visual function recovery. Visual recovery was observed in 55% of cases in group with small tumors, and 22% of those patients regained visual acuity of 1.0 by Snellen chart at least in one eye, whereas postoperative VA impairment was found only in 5% of patients. In comparison, in large tumor size group, VA deterioration six months after surgery was 50%, and there was also a high risk mortality rate of 50%.

As early as in 1962, Jane and McKissok [27] were the first to find that the size of suprasellar tumors affected the operative mortality and postoperative visual function. According to their findings, the mortality rate in patients having tumors bigger than 30mm was 42%. Out of 18 of the patients who survived meningioma surgery, 38% had postoperative improvement of VA, 33% had no change in VA, and 28% had VA impairment similar to preoperative values. In group of patients with tumor less than 30mm in size, there were no lethal cases, 53% of them had postoperative VA improvement, and VA remained stable in 47%.

Galal et al. [8] suggest that the tumor size has a very important role for operative mortality, recovery of visual function, and tumor recurrence. By analyzing medical records of 21 patients with tuberculum sellae meningioma, they found statistically significant postoperative VA improvement in cases with tumor smaller than 30mm, comparing to those having tumors of 30 mm or bigger.

In the last several years, some authors [6, 14, 17, 21, 23] have reported that the tumor size in the optochiasmatic region has the major role in postoperative VA improvement, although other authors have reported contradictory data [10, 15, 28–30].

Our study has confirmed data and conclusions found in many contemporary papers [7, 8, 13, 28, 31], stating that the degree of postoperative visual function recovery, with optimal surgical resection, has several co-dependent factors. In the first place, these are the age of patient, time relapsed from first symptoms of tumor until tumor diagnosis and surgical treatment of tumor, degree of visual impairment preoperatively, and the size of tumor itself.

Conclusion

Visual acuity of patients operated for meningiomas of optochiasmatic region was improved in half of the patients 6 months after surgery. Improvement by up to two lines and more than two lines at Snellen visual acuity chart was observed in 21% (16/76) of eyes and in 29% (22/76) eyes, respectively. In addition to prompt and precise surgical resection of tumors of optochiasmatic region, there are other important factors that affect postoperative visual function improvement. Good postoperative prognosis for visual acuity recovery is related with preoperative visual acuity better than 0.2 Snellen chart, duration of symptoms of less than 2 years, and the size of tumor below 30 mm. The degree of visual function recovery after surgical treatment of optochiasmatic meningioma is inversely proportional to the duration of symptoms and the size of tumor itself.

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THE IMPACT OF COMBINED MENISCUS TEAR ON QUALITY OF LIFE AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

UTICAJ UDRUŽENE POVREDE MENISKUSA NA KVALITET ŽIVOTA POSLE REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA

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Summary

Introduction. An anterior cruciate ligament injury represents a significant epidemiological problem worldwide, especially due to involving young, sporty and active working–age population. This study has been conducted in order to compare the quality of life of patients who had isolated anterior cruciate ligament tear and of those who suffered from an associated meniscal injury. **Material and Methods.** This study included 185 patients who had undergone reconstruction of the anterior cruciate ligament at the Department of Orthopedic Surgery and Traumatology in Novi Sad from January 1st, 2012 to December 31st, 2012. The patients were divided into 2 groups: group A consisted of patients who had anterior cruciate ligament reconstruction only, and group B consisted of patients who had partial meniscectomy in addition to the anterior cruciate ligament reconstruction. The follow-up period was 12 months. **Results.** Distribution of patients by gender was significantly in favor of men. In our study, 146 patients were male and 39 patients were female. The average age of patients was 26.1 years overall (16-55 years), being 26.9 years for men, and 23.3 years for female patients. Out of 185 patients, 110 had an isolated anterior cruciate ligament injury, while 75 suffered both meniscus, internal or external, and anterior cruciate ligament injury. **Conclusion.** The comparison of the quality of life of patients in both groups showed no statistically significant difference. Therefore, we were not able to prove the hypothesis about the superior quality of life of those patients who had suffered from a ruptured anterior cruciate ligament only.

Key words: Quality of Life; Anterior Cruciate Ligament Reconstruction; Menisci, Tibial; Knee Injuries; Questionnaires; Lysholm Knee Score; Joint Instability; Age Factors; Sex Factors; Multiple Trauma

Sažetak

Uvod. Povrede prednjeg ukrštenog ligamenta predstavljaju značajan epidemiološki problem širom sveta, posebno zbog najveće učestalosti među mlađom, sportski i radno aktivnom populacijom. Ova studija je sprovedena sa ciljem ispitivanja kvaliteta života pacijenata koji su imali izolovanu povredu prednjeg ukrštenog ligamenta, u poređenju sa onima koji su imali udruženu povredu meniskusa. **Materijal i metode.** Istraživanjem je obuhvaćeno 185 pacijenata koji su podvrgnuti rekonstrukciji prednjeg ukrštenog ligamenta na Klinici za ortopedsku hirurgiju i traumatologiju u Novom Sadu od 1. januara do 31. decembra 2012. godine. Ispitanici su podeljeni u dve grupe: grupa A se sastojala od pacijenata koji su imali samo rekonstrukciju prednjeg ukrštenog ligamenta, a grupa B od pacijenata koji su osim rekonstrukcije prednjeg ukrštenog ligamenta imali i parcijalnu meniscektomiju. Period praćenja iznosio je 12 meseci. **Rezultati.** Distribucija pacijenata prema polu bila je značajno u „korist" muškaraca. U našoj studiji 146 pacijenata su bili muškarci, a 39 pacijenata bile su žene. Prosečna starost ispitanika bila je 26,1 godina (16−55 godina), za muškarce 26,9 godina, i 23,3 godine za žene. Od ukupno 185 ispitanih pacijenata, 110 je imalo izolovanu povredu prednje ukrštene veze, dok je preostalih 75 imalo i udruženu povredu unutrašnjeg ili spoljašnjeg meniskusa. **Zaključak.** Upoređujući kvalitet života pacijenata u obe grupe, nije bilo statistički značajne razlike. Stoga nismo bili u mogućnosti da dokažemo hipotezu o boljem kvalitetu života onih pacijenata koji su imali izolovanu povredu prednjeg ukrštenog ligamenta.

Ključne reči: kvalitet života; rekonstrukcija prednjeg ukrštenog ligament; meniskusi; povrede kolena; upitnici; Lysholm skala; nestabilnost zgloba; uzrast; pol; udružene povrede

Introduction

An anterior cruciate ligament (ACL) injury is an epidemiological problem in the world because it affects young, sporty and working population [1,2]. In the last five years the annual number of reported cases and the number of completed reconstruction of the ACL has doubled [3]. The primary goal of

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Abbreviations

ACL – Anterior Cruciate Ligament
QOL – Quality of Life
WHO – World Health Organization
OA – Osteoarthritis
HRQOL – Health Related Quality of Life
ACLR – Anterior cruciate ligament rehabilitation
KCV – Clinical Center of Vojvodina

ACL reconstruction is to regain stability as well as to maintain the range of motion, increase the quality of life (QOL), and thus prevent early degenerative changes in the cartilage and possible new ones.

According to the World Health Organization (WHO), the QOL is a personal perception of their own life plan in the context of culture and value systems in which the person lives according to their goals, expectations, standards and interests [4]. It consists of the physical health, psychological status, material independence, social relationships and relationship to the major characteristics of the environment [5]. The concept of QOL has recently been given a great significance and important role in the analysis of various clinical situations in modern medical practice [6]. There are two aspects of the QOL: the subjective or personal evaluation and the objective evaluation made by an observer. A scale was designed to assess the extent of personal QOL satisfaction [6].

Ten years after the ACL reconstruction [7], 13% of people with an isolated rupture of the ACL and 48% of people with the accompanying meniscus develop knee osteoarthritis (OA). Since the data on QOL after ACL rupture and its surgical treatment are scarce, the aim of this study has been to determine whether there is a difference in QOL between the patients with isolated ACL rupture and those who had an associated injury especially meniscal tear.

Material and Methods

With the permission of the Ethics Committee, the study was conducted at the Department of Orthopedic Surgery and Traumatology, Clinical Center of Vojvodina, and it included 185 patients from the register of patients who had undergone surgery during the period from January 1st to December 31st 2012.

Group A consisted of 110 patients with an isolated ACL injury while group B included 75 patients who had both ACL and meniscal tear **(Graph 1)**.

The study was designed as a retrospective-prospective study. When collecting data from patients, the "KOOS" questionnaire was used [8], fully translated from English and adapted to the study. The original questionnaire was not changed, and only added to the issues important for our research. The questionnaire "KOOS" is an extension of osteoarthritis index Western Ontario and McMaster University (WOMAC) and the most commonly used instrument for the assessment of relevant effects of therapy in patients with OA. The questionnaire designed to assess the short-and long-term results after a knee injury is divided into five sections: the first covers the QOL following surgery for ACL, the second part includes information related to pain in different activities, the third unit of the questionnaire is related to daily activities that a patient can perform during the day, the fourth part is related to the level of physical activity, Lysholm score, and the final fifth part focuses on the very consciousness of the patients' QOL and how they perceive their injury. Prior to surgery, all patients completed a questionnaire about the details of the injury and subjective scores. The questionnaire also represents the register of injuries of the ACL at the Department of Orthopedic Surgery and Traumatology in Novi Sad, where it is publicly available.

The questionnaire on the QOL, which was sent by electronic mail (e-mail) to all patients a year after surgery, explained its own purpose and asked the participants to give the consent so that their replies could be used for scientific purpose. The patients who were not willing to take part in the research or those who failed to respond to email or phone call were excluded from this study.

The standard scoring system as per "KOOS" questionnaire was used in the QOL evaluation [8]. According to the "KOOS" scoring scale, a higher score means better QOL and a better condition of the participants.

Within the descriptive statistic the parametric characteristics were determined by size: middle, standard deviation, minimum and maximum. For nonparametric characteristics, the frequency of the presence of certain categories was examined. Student's t-test was used to calculate the differences in the middle values of attributes between the groups. For non-parametric characteristics, Pearson's χ^2-test was used to compare the differences in the intensity of the observed groups. All data were presented either in tables or graphs for each group.

Results

The rupture of the ACL was combined with the meniscal injury in 75 patients, whereas the ACL rupture was isolated in the remaining group of 110 patients.

According to the analysis of data by gender, age, type of sports activity, sports activity level, and the parameters based on the right or left knee injury, the difference between group A patients who had only damaged ACL and group B patients who had both the ACL damage and torn knee meniscus was not statistically significant **(Tabela 1).** A significant difference was observed only regarding the time elapsed from the time of injury to the time of surgery; namely, the patients from group A underwent earlier reconstruction of the ACL than those in group B.

Preoperative and postoperative Lysholm score was compared between these two groups. Preoperative Lysholm score was 79.5 and 71.9 for group A and group B, respectively; whereas postoperative score was 90.38 and 88.7 for group A and group B, respectively. There was no statistically significant difference

between two groups before and after surgery. However, according to the comparison of each of the two groups before and after surgery, there was a significantly better postoperative Lysholm score **(Table 2)**.

When assessing the QOL, scoring was done according to the „KOOS" questionnaire [14]. The comparison of all sections of "KOOS" scale showed better QOL in the group of patients who had an isolated ACL injury than those with combined meniscal tear but the difference was not significant **(Table 3)**.

Discussion

The instability of the knee caused by the ACL rupture has been attracting attention for more than a hundred years [9]. The main reason for the ACL reconstruction is to enable people to return to sports without any limitations, as well as to their daily activities, and to prevent early development of secondary degenerative changes [1].

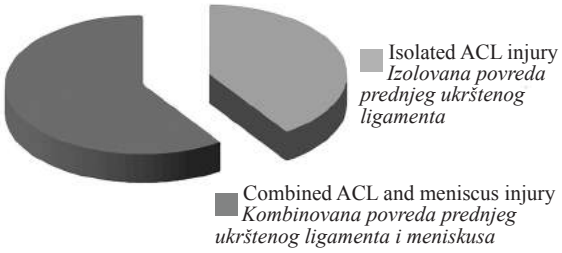
The ACL rapture is more likely to occur in male population [9]. Our study sample consisted of 146 male and 39 female patients. In the study of La Prade [10] there were 16 men out of 20 participants. A significantly higher prevalence of male population is attributed to the greater involvement of men in sports [3].

In our study the average age of patients was 26.1 years (ranging from 16 to 55 years), whereas the average age of men was 26.9 years and 23.3 years for women. The average age of the participants in the study conducted by Rios and Leger [11] was 24

Table 1. A comparison of different parameters in group A and group B
Tabela 1. *Poređenje različitih parametara između grupe A i grupe B*

		Group A (ACL) *Grupa A (ACL)*	Group B (ACL + meniscus tear) *Grupa B (ACL + lezija meniskusa*
Sex/*Pol*	Men/*Muški*	87	59
	Women/*Ženski*	23	16
Age/*Uzrast*	Arithmetic mean (AM) *Aritmetička sredina (AS)*	25.7	26.7
	Standard deviation (SD) *Standardna devijacija (SD)*	7.5	8
	min./*min.*	16	15
	max./*max.*	55	45
Place of injury *Mesto povređivanja*	Sport/*Sport*	106	72
	Walking/*Hodanje*	4	1
	Training/*Trening*	0	1
	Traffic accident *Saobraćajna nezgoda*	0	1
Sports activity *Vrsta sportske aktivnosti*	Recreational activities *Rekreativne aktivnosti*	51	44
	Professional sports *Profesionalni sport*	53	31
	Other activities/*Ostalo*	6	0
Sports activity level *Nivo sportske aktivnosti*	Recreation/*Rekreativan*	42	40
	Regional/*Regionalan*	16	12
	Republic/*Republički*	28	15
	International/*Međunarodni*	18	8
	Other activities *Van sportske aktivnosti*	6	0
Damaged knee *Strana povrede*	Right/*Desno*	70	42
	Left/*Levo*	40	33
Time elapsed from injury to operation (in months) *Vreme proteklo od povrede do operacije (u mesecima)*	Arithmetic mean (AM) *Aritmetička sredina (AS)*	6.5	11.8
	Standard deviation (SD) *Aritmetička sredina (AS)*	1.3	21.9
	min./*min.*	1	1
	max./*max.*	24	99

ACL - prednja ukrštena veza



Graph 1. The structure of the sample by the type of injury
Grafikon 1. *Struktura uzorka prema tipu povrede*

years (ranging from 16 to 54 years), 34 and 29 years for men and women, respectively. The reason for these results could be the fact that younger people, both males and females, take up more extreme physical activities than older people.

The reason for finding ACL injuries in people of varying age during the research may lie in the fact that more and more people of different age are involved in strenuous activities, both professionally and recreationally and because of higher incidence of the traffic accidents in recent years [3].

Concomitant intraarticular injuries are more frequently found in patients with a ruptured ACL. Approximately half of all patients who have torn the ACL suffer from meniscus and cartilage damage as well [12]. Among these patients, 35% of diagnosed meniscus injuries were treated operatively during the same procedure [13]. Mechanical symptoms such as knee locking, decreased range of motion, crackle and periodical effusion are indicative of the meniscus tear. Clefts of the outer meniscus occur slightly more often than the inner meniscus splits with acute ACL injuries (56 % and 44 %, respectively), and internal rifts meniscus is more commonly found in patients with chronic ACL injury [13]. A delay in the ACL reconstruction for more than six months after the injury increases the risk of damaging the interior of the meniscus and it is therefore important to treat them in a timely manner [14]. Associated injuries of the meniscus and ACL lead to a greater prevalence of development of degenerative changes in the knee compared with isolated ACL injury [15]. OA occurs in 8% to 35 % patients after surgeries on the meniscus [16]. Losing the meniscus leads to the increased anterior laxity of the knee joint which becomes particularly relevant in situations associated with the insufficient ACL. Other important functions of the meniscus include shock absorption, and the fact that they help in the lubrication and nutrition of articular cartilage. Meniscus includes mechanoreceptors and nociceptors, which are located in the outer zone, and thus perform an important function in the proprioception [17]. The reported literature rates of recovery after meniscus repair range from 65% to 96% [18-20] which is very important in comparison with the rate of early degenerative changes after partial and especially total meniscectomy.

The incidence of overall combined injury of the meniscus and ACL in the study done by Michalitsis et al. [21] was 63% (29% of the medial meniscus, 19% of the lateral and of both in 15% of cases), which is consistent with the data from other studies [22,23]. The overall incidence of violation of one or both menisci was greater in the knees that had undergone a reconstruction of ACL more than 12 months after the injury. The rate of meniscus and ACL injury varies from 3.5% to 80% in the literature [21-23]. Papastergiou et al. [23] found a frequency of 55.7% (25% for the inner meniscus, 17% for the outer, and of both in 14%). There were 6 groups in our study sample formed according to the time of reconstruction, i.e. 1.5, 3, 6, 12 and 24 months after the injury. It was observed that significantly higher incidence of meniscus injury occurred in the patients who had undergone the ACL reconstruction more than 3 months after the injury, that being different from Michalitsis et al. study [21]. Tandogan et al. [24] and Church and Keating [25] reported an increased incidence of meniscus injuries in the patients who had undergone the ACL reconstruction 12 months after the injury. In case of 12 months being the time point, the incidence of injuries of the meniscus was 55% and 74% in "0-12 months" group and in "more than 12 months" group, respectively.

These findings are consistent with the published results. The study of Michalitsis et al. [21] documented a higher incidence of medial meniscus, which coincides with the results of Tandogan et al. [24] but not with those of Cipolla et al. [26], where the external meniscus injury was significantly more frequent.

Based on an analysis of data according to the time between the time of injury and the time of surgery, we found in the present study that considerably

Table 2. Comparison of group A and group B regarding the Lysholm score and type of injury
Tabela 2. *Poređenje grupe A i grupe B po pitanju Lišolmove bodovne skale i tipa povrede*

Lysholm and type of injury/*Lysholm i tip povrede*					
Preoperational/*Preoperativno*			Postoperational/*Postoperativno*		
t=3.04			t=1.32		
p=0.002 (<0.05)			p=0.18 (>0.05)		
	$\bar{X}$	SD		$\bar{X}$	SD
Group A/*Grupa A*	79.5	14.4	Group A/*Grupa A*	90.4	8.2
Group B/*Grupa B*	71.9	17.9	Group B/*Grupa B*	88.7	8.9

Table 3. Descriptive data on the significance of differences in „KOOS" scale questionnaires by the type of injury and gender
Tabela 3. *Deskriptivni podaci značajnosti razlike vrednosti KOOS bodovne skale u odnosu na tip povrede i pol*

	Arithmetic mean/*Aritmetička sredina*				SD/*SD*			
	Injury/*Povreda*		Sex/*Pol*		Injury/*Povreda*		Sex/*Pol*	
	ACL *ACL*	ACL+meniscus damage *ACL + povreda meniskusa*	M *M*	F *Ž*	ACL *ACL*	ACL+meniscus damage *ACL + povreda meniskusa*	M *M*	F *Ž*
Life Quality Index *Indeks kvaliteta života*	17	16.3	16.6	17	2.8	2.8	2.7	3.1
Pain Intensity/*Jačina bola*	10.5	10.2	10.5	10.2	1.5	1.8	1.7	1.6
Usual activities *Uobičajene aktivnosti*	19.8	19.4	19.7	19.7	2.9	2.7	2.8	3.2
Sports activities *Sportske aktivnosti*	47.4	45.8	46.5	47.8	11.4	12.4	11.8	12.1
Life quality awareness *Svesnost o kvalitetu života*	15.9	14.8	15.3	15.9	3.2	3.7	3.4	3.6

ACL- prednja ukrštena veza

less time had elapsed in group A (6.5 months on average) than in group B (11.8 months on average). This could be due to a lower number of initial injuries of the meniscus and ACL and later acceptance of indicated surgery in group B patients, but this is something that we cannot prove objectively. Michalitsis et al. [21] divided their study sample into three groups: group A consisted of patients who had undergone surgery in the first 3 months after injury, group B – the patients who had undergone surgery from 4 to 12 months, and group C – more than 12 months passed between the injury and surgery. The most important finding of their study was that the incidence of intraarticular cartilage injuries in particular increased with the time elapsed from the time of injury to the time of surgery, and according to them 12 months is a critical landmark for the reconstruction of the ACL.

In our study 110 out of 185 patients had an isolated tear of the ACL, and 75 of them had an associated injury either of internal or external meniscus. The study performed by Michalitsis et al. [21] included 109 patients. The combined injury of ACL and meniscus was present in 69 of them. Ihara et al. [27] reported that 40 out of 65 patients had the associated injury of the ACL and meniscus. The study of Røtterud et al. [28] analyzed 3,674 patients and 1,661 of them (20%) had just an ACL rupture, 1,219 patients (14%) had the associated lesion of medial or lateral meniscus, 657 patients (8%) had injury of both menisci, and 137 patients (2%) had an undiagnosed injury.

The postoperative results were evaluated by means of the Lysholm scoring system and they were higher than the preoperative score in both groups (the increase was from 79.5 to 90.4 and from 71.9 to 88.7 in group A and group B, respectively) with a statistically significant difference. In the analysis of the functional results, Jagodzinski et al. [29] found the Lysholm score to be 92.3 after surgery, whereas it had been 71.6 before treatment. Zhao et al. [30] reported the increase in the value of preoperative Lysholm score from 48.2 to 94.1 twenty-four months after surgery. Hamer et al. [31] found the Lysholm score after reconstruction of the ACL to be at level of 82.1, where 59% were rated as excellent or good. Paxton et al. [20] published an overview of literature in relation to sewing of the meniscus and a partial tear of the ACL. In the long term, sewing of the meniscus showed a higher Lysholm score in comparison with a group of patients who had partial meniscectomy.

The ACL reconstruction is a successful operation with rare complications which allows faster return of patients to everyday living, working and sports activities. It also reduces the total cost of treatment of these injuries [32]. Surgical reconstruction of the ACL is "quality of life" surgery, which allows young people to return to professional life and sports activities, and protects the knee against early irreversible degenerative problems. The overall objective is to restore the biomechanics of the knee, allow the continuation of activities that existed before the injury and perform optimization of HRQOL [33]. Psychological factors, such as fear of re-injury, can contribute to the limitation of participation in sports and poorer QOL 2-4 years after the injury of the ACL [34]. Other factors such as the persistent pain and post-traumatic OA [7] can be associated with each other and can influence the QOL. Any changes that occur after damage to the ACL lead to a difficulty in walking, running and jumping, especially when changing the direction of movement and significantly reduce the QOL of patients, particularly of those who have not given up sports activities after the injury [1]. In addition, the ability of the athlete to cope with stress shows the result in the recovery and progress of the rehabilitation program. The inadequate psychological response can be harmful and adversely affect the ability of the athlete to return to the previous level of sports participation and competition. This can eventually affect the sports perform-

ance as well and therefore increase the risk of reinjury [35].

Statistical analysis of our data showed a significant difference only in one chapter of „KOOS" questionnaire in terms of reduced QOL. Group A (ACL reconstruction only, 110 patients) showed a greater awareness of the QOL in comparison with group B (ACL reconstruction with partial meniscectomy, 75 patients). These results include all five sub-scales of the "KOOS" questionnaire. Ahlden et al. [33] in their study reported that the patients who had associated injuries, such as damage of the meniscus, had nearly the same QOL as those with an isolated rupture of ACL, and after 5 years the same study showed no significant difference between these two groups within the sub-scales related to sports and recreation. Barenius et al. [34] in their eight-year study observed that the patients who had had only ACL injury had higher scores in all five sub-scales of the "KOOS" questionnaire in comparison with the patients who had had associated injuries. Røtterud et al. [28] concluded in their two-year study that associated injuries with tearing the anterior cruciate ligament were not as common. They also stated that the results in all "KOOS" questionnaire sub-scales were approximately the same, and that there was no difference in quality of life observed among these groups.

According to the assessment done one year after the ACL reconstruction there was no difference in QOL, which did not mean that it may not change later in life. Several studies [15, 16] showed the development of degenerative changes after meniscectomy and with prolonged follow-up a lower QOL was observed when damaged meniscus had been removed. However, one of the values of our study is that it shows the direction of future research to be done on this issue and its implications on QOL.

The limitation of this study is a relatively small number of patients and short follow-up period; therefore, the long-term follow-up should provide a true picture of the QOL of these patients. Since the Department of Orthopedic Surgery and Traumatology in Novi Sad regularly keeps update to a register of these patients, it will be possible to continue this research in the coming years with an increased number of participants and a longer follow-up period.

Conclusion

A register of operated patients and questionnaires about quality of life a year after surgery, in which patients express their opinion and assessment of response to treatment and quality of life, provide basic and initial information about the effectiveness of treatment.

The patients with isolated rupture of the anterior cruciate ligament compared with the group of the patients with combined meniscus tear had a shorter period from injury to operation. There are statistically significant differences in the Lysholm score in both groups of patients before and after surgery, while no statistically significant differences were found when comparing these groups. When analyzing the data obtained in our study we found no statistically significant difference in quality of life between the patients who had only ruptured anterior cruciate ligament and those who in addition to injury of the anterior cruciate ligament had a damaged meniscus after 1-year follow-up. The difference was observed in terms of raising the quality of life where group A had significantly better awareness of quality of life compared to group B. This result could be due to a short follow-up and this was the main weakness of this study.

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THE RELATIONSHIP BETWEEN THE RANGE OF MOTON OF THE HIP JOINT WITH RUPTURED ANTERIOR CRUCIATE LIGAMENT

POVEZANOST OBIMA POKRETA ZGLOBA KUKA SA KIDANJEM PREDNJEG UKRŠTENOG LIGAMENTA KOLENA

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Summary

Introduction. A knee injury, especially anterior cruciate ligament, has recently become more common significantly affecting the life standard. There are many factors that cause an injury of the anterior cruciate ligament, and one of them is limited range of motion in the hip joint. This study has been aimed at finding a relationship between the range of motion in the hip joint and the anterior cruciate ligament injury. **Material and Methods.** Of 88 male athletes included in the study sample in 2014, 60 (68%) had ruptured knee anterior cruciate ligament and 28 (32%) were without an injury. There was no significant difference in sex, height, weight, age and time of injury between the two groups. **Results.** Significant differences were found in the range of motion between the left and right leg in both groups. The athletes with a ruptured anterior cruciate ligament had an abduction limit of the hip joint (p=0.007) and a wider range of motion of the knee joint (p=0.002) than the athletes without the injury. **Conclusion.** Data obtained in this study suggest a possible relationship between a limited hip abduction of range of motion in athletes and an increased risk of anterior cruciate ligament injury.

Key words: Anterior Cruciate Ligament; Knee Injuries; Hip Joint; Range of Motion, Articular; Athletes; Athletic Injuries; Risk Factors; Age Factors; Sex Factors

Sažetak

Uvod. Povrede kolena, a naročito prednjeg ukrštenog ligamenta, dešavaju se sve češće poslednjih godina i značajno utiču na kvalitet života. Postoji veliki broj faktora koji utiču na povredu prednjeg ukrštenog ligamenta, a jedan od mogućih jeste ograničenje pokreta u zglobu kuka. Cilj našeg rada bio je pronaći povezanost obima pokreta u zgobu kuka sa kidanjem prednjeg ukrštenog ligamenta kolena. **Materijal i metode**. U ispitivanju, sprovedenom 2014. godine, učestvovalo je 88 ispitanika muškog pola, od toga 60 (68%) su bili sportisti sa pokidanim prednjim ukrštenim ligamentom kolena i 28 (32%) sportisti bez povrede. Između posmatranih grupa nije bilo značajne razlike prema polu, visini, težini, starosti i vremenu proteklom od povrede. **Rezultati.** Kod ispitanika obe grupe se uočavaju značajne razlike u obimu pokreta između leve i desne noge. Kod sportista sa pokidanim prednjim ukrštenim ligamentom postoji ograničenje odvođenja u zglobu kuka (p = 0,007) i veći obim pokreta u zglobu kolena (p = 0,002) u odnosu na sportiste bez povrede. **Zaključak.** Dobijeni podaci ukazuju na moguću povezanost ograničenja odvođenja u zglobu kuka sa kidanjem prednjeg ukrštenog ligamenta.

Ključne reči: prednji ukršteni ligament; povrede kolena; zglob kuka; opseg pokreta zgloba; sportisti; sportske povrede; faktori rizika; uzrast; pol

Introduction

More than 400 million years of evolution of quadrupeds resulted in the human knee, which is the most complex of the joints of the human body. Its anatomy, which is almost perfect, enables the static as well as huge functional features that distinguish it from other joints [1]. Normal functioning of all its parts allows the harmony of movement, stability, orthograde posture and constant protection against injuries. A knee injury, especially of the anterior cruciate ligament (ACL), has become more frequent in recent years as a result of increased sport activity, work engagement and involvement in traffic accidents [1]. Because of the additional damage to the soft tissue and bony structures of the knee and early development of secondary degenerative changes, an injury of ACL is the "beginning of the end of the knee" [2]. These injuries are a significant epidemiological problem, especially because they usually occur to young people who are sport and work active [2]. The nature of ACL injuries is multifactorial and the risk factors are divided into external and internal, as well as into changing and unchanging factors. External factors include the environmental circumstances such as the type of surface, type of footwear, weather conditions and the type of sport [3]. The group of internal factors consists of anatomical fac-

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Abbreviations
ACL – anterior cruciate ligament
ROM – range of motion

tors; then anthropometric differences between the sexes, height, weight, body mass index (BMI); hormonal influences, primarily the effect of estrogen on the incidence of the injury and the strength of the ligaments; static parameters, the size of the "Q" angle, i.e. the pelvis width being the most important; neuromuscular factors with a focus on the relationship of agonists and antagonists; biomechanical factors and, finally, a previous injury and the age of the patient as a potential risk factor [4].

Identification of risk factors in ACL injury is an important step in the development of the injury prevention. The analysis of etiological factors is primarily aimed at defining their share in the incidence of the injury, but at the same time at defining the factors that can influence it in terms of prevention. Today there is no complete agreement on the most important factor that is the most accountable for ACL rupture [2]. Therefore, it is very important to assess the risk factors to reduce the incidence of the injury because this injury does not only restrict sports activity, but also affects the quality of life [5]. One of the possible causes of the frequent ACL injury is the difference in range of motion (ROM) of the hip and knee according to the studies of Tainaka et al. [6] and Gomes et al. [7]. The aim of our study is to determine the relationship between ACL injury and our patients' hip and knee ROM.

Material and Methods

Having been given the permission by the Ethics Committee of Clinical Center a prospective study was conducted at the Department of Orthopaedic Surgery and Traumatology. It included 60 male athletes with a torn ACL prior to the surgery in the time period from March 28 to July 10 2014 and 28 male athletes without an injury to ACL who agreed to participate in the study. The measurement was conducted within the first six months after the patients had suffered the injury. The patients who had refused to participate in the study as well as those who had reported previous injuries and diseases of the hip and knee were excluded from the study. The study included only men in order to exclude hormonal influences and hormonal differences between the sexes.

In the group of athletes with the torn ACL there were 60 men, whose average age was 24.86 years (15-46 years), average body weight was 82 kg (53-110 kg) and average height was 181 cm (155-203 cm). According to sport activities, the majority of them were football players (34), then handball players (10), volleyball players (5), basketball players (4) and other athletes (7). Of the total number of athletes, 31 had the left knee injury, while 29 athletes had the right knee injury. The meniscus was damaged in 40% of athletes and the cartilage lesions were found in 10% of the athletes.

The control group of athletes with no torn ACL included 28 men, whose average age was 23.16 years (15-35), average weight and height was 81 kilograms (50-108 kg) and 181.16 cm (155-194 cm), respectively. There were 20 football players, 6 handball players and 2 athletes. The right leg was dominant in over 90% of the participants from both groups.

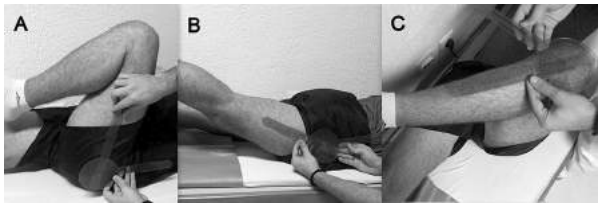

Figure 1. Measuring ROM in the hip with goniometer. A. Flexion, B. Extension, C. External rotation
Slika 1. *Merenje obima pokreta u kuku uglomerom. A. Savijanje, B. Ispružanje, C. Spoljašnja rotacija*

Figure 2. Measuring ROM in the hip with goniometer. A. Internal rotation, B. Adduction, C. Abduction
Slika 2. *Merenje obima pokreta u kuku uglomerom. A. Unutrašnja rotacija, B. Privođenje, C. Odvođenje*

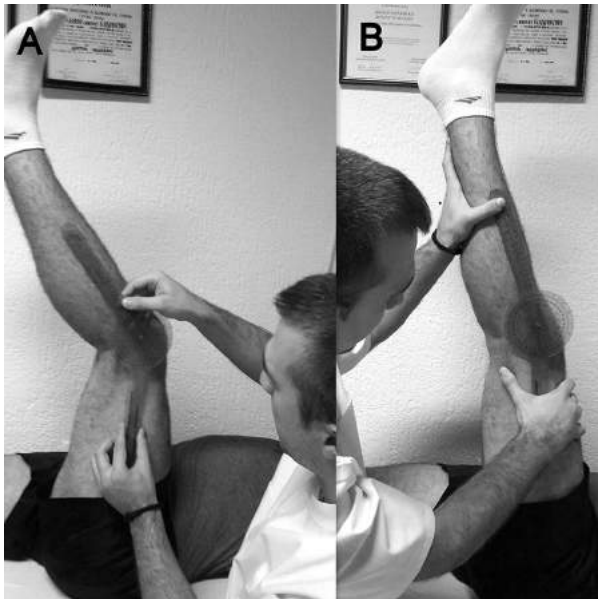

Figure 3. Measuring ROM in the knee with goniometer. A. The active knee extension test, B. The passive knee extension test
Slika 3. *Merenje obima pokreta u kolenu uglomerom. A. Aktivno ispružanje kolena, B. Pasivno ispružanje kolena*

Table 1. Movements of the hip joint between the left and right leg of patients with torn ACL
Tabela 1. *Pokreti u zglobu kuka između leve i desne noge kod pacijenata sa pokidanim prednjim ukrštenim ligamentom*

Movements of the hip joint *Pokreti u zglobu kuka*	Side/*Strana*	Average value *Srednja vrednost*	Standard deviation *Standardna devijacija*	p
Internal rotation/*Unutrašnja rotacija*	Left/*Levo*	31.29	11.151	
	Right/*Desno*	30.88	9.303	0.761
External rotation/*Spoljašnja rotacija*	Left/*Levo*	39.06	11.664	
	Right/*Desno*	40.62	10.569	0.140
Flexion/*Savijanje*	Left/*Levo*	122.16	9.306	
	Right/*Desno*	121.80	8.446	0.627
Extension/*Ispružanje*	Left/*Levo*	10.09	7.294	
	Right/*Desno*	9.32	6.529	0.266
Abduction/*Odvođenje*	Left/*Levo*	56.48	11.749	
	Right/*Desno*	54.52	12.186	0.0378 *
Adduction/*Privođenje*	Left/*Levo*	25.78	6.343	
	Right/*Desno*	30.35	6.519	0.000 **

* Abduction of the left hip vs. abduction of the right hip/*Odvođenje u levom kuku vs. odvođenje u desnom kuku*, p = 0.0378;
** Adduction of the left hip vs. adduction of the right hip/*Privođenje u levom kuku vs. privođenje u desnom kuku*, p = 0.000

According to the obtained data from the group of patients with ACL rupture and the control group, there were no significant differences in the average age, height, weight and dominant hand, so the two groups were comparable. The measurement was done on a flat surface using a standard goniometer, the values were expressed in degrees. The maximal movement of the hip joint (flexion, extension, external rotation, internal rotation, adduction, abduction) and knee (the active and passive knee extension test) was measured.

The hip joint flexion **(Figure 1A)** was measured while the participant was lying on his back with the maximally flexed leg at the hip joint to the body without the help of hands. The center of goniometer was placed in the region of the hip, the fixed part of goniometer was placed horizontally and the mobile part followed the movement of the thigh. The hip joint extension **(Figure 1B)** was measured while the participant was lying down on stomach, stretching out his legs.

The hip external rotation **(Figure 1C)** was measured when the center of goniometer was placed on the knee in the level of the shaft of the femur bone, the fixed part was in the level of the line connecting the hip joint while the dynamic part of goniometer followed the movement of the lower leg. The hip joint internal rotation **(Figure 2A)** was measured in the same way except that the lower leg rotated laterally.

The hip joint adduction **(Figure 2B)** was measured when the center of goniometer was set on the region of spina iliaca anterior superior, the fixed part was in the bispinal line while the dynamic part followed the upper leg. The hip joint abduction **(Figure 2C)** was measured

Table 2. Movements of the hip joint between the left and right leg of athletes without torn ACL
Tabela 2. *Pokreti u zglobu kuka između leve i desne noge kod sportista bez pokidanog prednjeg ukrštenog ligamenta*

Movements of the hip joint *Pokreti u zglobu kuka*	Side/*Strana*	Average value *Prosečna vrednost*	Standard deviation *Standardna devijacija*	p
Internal rotation/*Unutrašnja rotacija*	Left/*Levo*	30.2188	5.94455	
	Right/*Desno*	31.8438	5.83156	0.064
External rotation/*Spoljašnja rotacija*	Left/*Levo*	39.5625	8.03997	
	Right/*Desno*	38.8438	8.10061	0.518
Flexion/*Savijanje*	Left/*Levo*	122.0625	7.86555	
	Right/*Desno*	122.9688	6.61125	0.357
Extension/*Ispružanje*	Left/*Levo*	12.6875	5.15212	
	Right/*Desno*	11.8750	6.48945	0.777
Abduction/*Odvođenje*	Left/*Levo*	61.8438	10.34286	
	Right/*Desno*	60.1250	11.18683	0.131
Adduction/*Privođenje*	Left/*Levo*	28.2813	6.01736	
	Right/*Desno*	26.4688	5.76969	0.005 *

* Adduction of the left hip vs. adduction of the right hip/*Privođenje u levom kuku vs. privođenje u desnom kuku*, p = 0.005

Table 3. Movements of the hip joint in the patients with a torn ACL and athletes without injury
Tabela 3. *Pokreti u zglobu kuka između pacijenata sa pokidanim prednjim ukrštenim ligamentom i sportista bez povrede*

Movement of the joint/*Pokreti u zglobu*	Injured/*Povređeni* (N= 60)	Uninjured/*Nepovređeni* (N= 28)	p
Internal rotation of the left hip *Unutrašnja rotacija levog kuka*	29.25	9.339	0.609
External rotation of the left hip *Spoljašnja rotacija levog kuka*	39.09	12.240	0.848
Flexion of the left hip *Savijanje u levom kuku*	121.50	122.0625	0.775
Extension of the left hip *Ispružanje u levom kuku*	10.88	11.6875	0.075
Abduction of the left hip *Odvođenje u levom kuku*	55.69	61.8438	0.007*
Adduction of the left hip *Privođenje u levom kuku*	27.66	28.2813	0.688
Active extension test of the left knee *Aktivno ispružanje levog kolena*	136.63	129.2188	0.002**
Passive extension test of the left knee *Pasivno ispružanje levog kolena*	145.66	139.8438	0.003‡
Internal rotation of the right hip *Unutrašnja rotacija desnog kuka*	30.13	31.8438	0.465
External rotation of the right hip *Spoljašnja rotacija desnog kuka*	41.91	38.8438	0.131
Flexion of the right hip *Savijanje u desnom kuku*	120.34	122.9688	0.105
Extension of the right hip *Ispružanje u desnom kuku*	10.53	11.8750	0.130
Abduction of the right hip *Odvođenje u desnom kuku*	52.75	60.1250	0.007¶
Adduction of the right hip *Privođenje u desnom kuku*	26.66	27.2813	0.688
Active extension test of the right knee *Aktivno ispružanje desnog kolena*	138.16	130.0938	0.002†
Passive extension test of the right knee *Pasivno ispružanje desnog kolena*	146.03	140.1250	0.003§

* Abduction of the left hip/*Odvođenje u levom kuku*, injured vs. uninjured/*povređeni vs. nepovređeni*, p = 0.007; ** Active extension test of the left knee/*Aktivno ispružanje levog kolena*, injured vs. uninjured/*povređeni vs. nepovređeni*, p = 0.002; ‡ Passive extension test of the left knee/*Pasivno ispružanje levog kolena*,injured vs. uninjured/*povređeni vs. nepovređeni*, p = 0.003; ¶ Adduction of the right hip/*Privođenje u desnom kuku*, injured vs. uninjured/*povređeni vs. nepovređeni*, p = 0.007; † Active extension test of the right knee/*Aktivno ispružanje desnog kolena*, injured vs. uninjured/*povređeni vs. nepovređeni*, p = 0.002; § Passive extension test of the right knee/*Pasivno ispružanje desnog kolena*, injured vs. uninjured/*povređeni vs. nepovređeni*, p = 0.003;

in the same way; however, in this movement the participant moved the leg laterally, away from the body.

The active knee extension test **(Figure 3A)** was done when the participant was lying on his back with the leg flexed at the hip at the angle of 90 degrees and stretching his lower leg in the knee joint to the maximum of his free will. The center of goniometer was placed in the region of the knee joint, the fixed part followed the axis of the thigh and the dynamic part of goniometer followed the lower leg. The passive knee extension test **(Figure 3B)** was done in a similar way, except that the examiner stretched out the lower leg of the participant while he rested and relaxed the muscles of the legs.

The Statistical Package for the Social Sciences (SPSS) version 19.0 for Windows was used in the analysis. The results are presented in tables expressed as mean values and standard deviations. In all comparisons, $p<0.05$ was considered a statistically significant difference.

Results

The comparison of the ROM between the left and right leg of the patients with a torn ACL revealed statistically significant differences in abduction and adduction of the hip **(Table 1)**. The range of abduction was higher for the left leg (for 3±1 degree;

p=0.0378), while the range of adduction was higher for the right leg (5 degrees; p=0.000).

Statistically significant differences in the hip adduction between the left and right leg were observed in the control group of athletes without a torn ACL **(Table 2)**. The range of adduction was higher for the left leg (for 3±1 degree; p=0.005).

The comparison of the ROM of the hip and knee between the patients with ruptured ACL and the participants without injuries **(Table 3)** revealed statistically significant differences in the hip joint abduction as well as the active and passive knee extension. Abduction of the left and right hip in the injured athletes was smaller than abduction in the athletes without the injury (an average of 8 degrees; p=0.007). The injured athletes showed higher ROM during the active (average of 8 degrees; p=0.002) and passive knee extension (average of 6 degrees; p=0.003) than the athletes without an ACL injury.

Discussion

Anterior cruciate ligament injuries are injuries that are commonly found in athlete population. According to the available epidemiological data in the United States, it is estimated that the annual incidence of ACL injuries varies from 100,000 to 250,000 injuries, and more than 70% of these injuries happen to the population who engage in sports [9, 10]. In Vojvodina, which has about two million people, about 400 reconstructions of the ACL (2 reconstructions per 10,000 residents) are performed per year. As for the European countries, the most accurate data are those from Denmark, where three injuries happen to 10,000 residents per a year, the frequency of occurrence being higher among athletes [11]. These data are very similar to the data from the United States, where it is estimated that injuries occur in one out of every 3,000 people in the general population [9]. The reason for this epidemiological situation certainly lies in the fact that the number of participants in the sport is constantly growing on the global level. Sports activities are becoming an important part of modern life; however, more and more people spend their free time in recreation and entertainment. The number of men and women who become members of fitness and various sports clubs is increasing [12]. All this matches with the fact that a significant increase in injuries of ACL was recorded in last 10-15 years [13].

Another reason for a higher incidence of knee and ACL injuries is the growing popularity of extreme sports such as snowboarding, skateboarding and extreme cycling [14]. However, in our country these sports still do not have a high number of fans. Since the most popular sports in our country are ball sports, the injuries of ACL are most common in football, basketball, handball and volleyball [3].

An ACL injury is affected by a number of external and internal factors such as gender, condition of the knee joint, ground conditions, condition of surface, part of the training, the ranking of the competition [15, 16]. Many researchers have made an effort to find potential risk factors that can predispose towards injury of ACL [17, 18]. Detection of risk factors is essential for finding specific training programs in order to reduce the incidence of injury [10]. Hewett et al. [15] included contact with an opponent, the effect of wearing corsets on the knee and contact sports shoes with the ground in their study on the group of external factors. It is often thought that artificial surface is a reason for development of a large number of injuries [19], but data from many studies do not support this statement because serious injuries occur on natural surfaces as well as on the parquet floor [19].

Anterior cruciate ligament injuries are more common among women but since the proportion of men engaged in sport is higher, the number of injuries of ACL is much higher in males [17, 18, 20]. Measurements in our study were performed only in males due to a small number of women who were operated during this period and to avoid the influence of hormonal changes during the pre-ovulatory period as a potential confounding risk factor for an ACL injury. Gomes et al. [7] also performed measurements only in males in their research. Of 44 participants included in the study performed by Tainaka et al. [6], 23 were men and 42 were women. Reurink et al. [21] included 50 participants in their research on injury of the biceps thighs, 46 men and 4 women.

In our study, the average age was 24.86 (ranging between 15 and 46 years), that being in accordance with the data from previous studies which suggest that knee injuries happen most frequently to men and women between the ages of 20 and 29 years [10]. There were 28 males, whose average age was 25.8±4.4 years, in the study done by Gomes et al. [7]. The average age of the participants in the study conducted by Reurink et al. [21] was 28 years. The structure of sports that our patients were involved in has only confirmed earlier epidemiological studies (Swärd et al. [22]), which recognize that intensive sports such as football and volleyball involving movements of rotation, valgus knee and anterior translation are risky and related to the occurrence of injuries of ACL.

Anatomical variations of the proximal tibia and intercondilar groove are considered to be risk factors in an ACL injury [23]. A statistically significant difference in the value of the posterior tibial slope was observed between the groups with and without torn ACL [24]. Tibial articular surfaces in the knee joint form, with the axis of the tibia, the angle of the posterior slope of the tibia of 7-10 degrees. A larger posterior tibial slope creates a larger anterior displacement of the tibia [25]. Since ACL is the main stabilizer of this motion, this results in its increased workload. This leads to increased internal rotation of tibia and greater acting force on the ACL [26]. Shelbourne et al. [27] observed the relationship between intercondilar groove and noncontact ACL injury and concluded that when the groove was 15 mm wide or less, there was a higher incidence of contralateral ACL tear than when it was 16 or more mm wide.

Anatomical variations are one of the risk factors for injuries of the ACL [28]. In the group of athletes with a torn ACL, significant differences can be observed in the range of abduction (p=0.037) and adduction (p=0.000) of the hip joint between the left and right leg. Adduction of the right leg is higher (3±2 degrees) than adduction of the left leg, while abduction is higher for the left leg (5±2 degrees).

In the control group consisting of athletes without an injury, there was a statistically significant difference only in adduction of the hip joint between the left and right leg. ROM of the left hip was usually by 3 ± 2 degrees (p = 0.005) wider than of the right hip, the probable reason being that the left leg was the jumping leg in most of our patients going in for jumping sports. Baltaci et al. [29] in their study compared the range of flexion of the left and right hip joint at different positions of the body and the results showed that there was a difference between the left and right leg depending on the flexibility of the muscles.

The comparison of the ROM in the controls and the patients with a torn ACL revealed statistically significant differences. The following statistically significant difference was observed in the range of hip abduction (p=0.007): ROM was smaller in the athletes with a ruptured ACL, i.e. the muscles of internal part of the thigh were less stretched, which could be a possible risk factor for ACL injury.

Hartig et al. [28] have reported that flexibility of posterior thigh muscles is very important in sports and that argument has been confirmed by the results of their research which shows that the number of injuries of the lower extremities decreases with proper and good flexibility of posterior thigh muscles. A statistically significant difference was observed in the active knee extension test (p=0.002) and in the passive knee extension test (p=0.003), where the patients with torn ACL had wider ROM showing a good muscle flexibility of posteior part of thigh. Tainaka et al. [6] found a limit in the external and internal rotation of the hip joint in the athletes with noncontact ACL rupture. In their study they compared the ROM of the hip joint between the group of 44 athletes with torn ACL and the control group of 123 athletes without injury of ACL. They have observed that the risk of rupture is rapidly increasing with a decrease in ROM, in external and internal rotation of the hip. Gomes et al. [7] measured the ROM of the hip joint and the connection with the re-tearing the ACL where limited external and internal rotation of the hip joint was determined.

In our study no statistically significant difference was found in the external and internal rotation of the hip joint between the athletes without injuries and those with a torn ACL. A possible cause for different results is that our participants had higher average body weight (82kg), height (181cm) and possibly different motives to participate in the study.

Limitations of this study is that it did not include all patients with torn ACL who were in hospital during the study and we did not have an magnetic resonance imagfing or X-ray of the hip and knee joint of each patient we measured. The biggest limitation of this study is that this kind of measuring the patients is a completely subjective method so its results can be significantly affected by the will and motivation of examinees and examiners.

Conclusion

According to the results of this study, there is a statistically significant difference in the range of motion of the hip and knee joint between the athletes with a torn anterior cruciate ligament and those without an injury. The athletes with a torn anterior cruciate ligament were found to have a wider range of motion for active and passive knee extension (greater muscle flexibility of posterior part of thigh) and abduction limit of the hip joint. These results suggest a possible connection between an anterior cruciate ligament injury and the size of abduction of the hip joint. It is therefore necessary to increase the muscle flexibility of internal part of thigh during training time in order to increase the range of motion of abduction of leg so as to reduce the risk of anterior cruciate ligament injury.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
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AN INCIDENTAL FINDING OF THYMIC CARCINOMA DURING ELECTIVE CORONARY ARTERY BYPASS GRAFTING

SLUČAJAN NALAZ KARCINOMA TIMUSA TOKOM ELEKTIVNE HIRURŠKE REVASKULARIZACIJE MIOKARDA

Živojin S. JONJEV[1], Milorad PAVLOVIĆ[2], Bojan ILIĆ[2] and Golub SAMARDŽIJA[1,3]

Summary

Introduction. Thymoma is a rare malignant tumor of the anterior mediastinum. Thymic squamous cell carcinoma has been recognized as an aggressive form of thymoma with different behavior. It is associated with paraneoplastic syndromes, variety of clinical presentations, different way of treatment and complex prognosis. Improved imaging techniques show that an early diagnosis of thymoma is possible, which makes thymoma a potentially dangerous but preventable disease. **Case Report.** In this report, we describe the clinical and histological findings of a patient with incidental finding of squamous cell thymic carcinoma presented during elective coronary artery bypass grafting surgery.

Key words: Thymoma; Mediastinal Neoplasms; Elective Surgical Procedures; Myocardial Revascularization; Coronary Artery Bypass; Thymectomy; Immunohistochemistry; Carcinoma, Squamous Cell; Early Diagnosis; Morphological and Microscopic Findings

Sažetak

Uvod. Timomi su retki maligni tumori prednjeg medijastinuma. Skvamocelularni karcinom timusa tretira se kao agresivna forma timoma sa značajnom patološkom nepredvidljivošću. U čestoj je korelaciji sa paraneoplastičkim sindromom, varijabilne je kliničke prezentacije, zahteva kompleksno lečenje koje prati nepredvidiva prognoza. Savremene dijagnostičke tehnike ukazuju na to da je rana dijagnoza timoma moguća. Na taj način povećava se verovatnoća za uspešnijim lečenjem timoma, kao potencijalno smrtonosnog oboljenja. **Prikaz slučaja.** U ovom prikazu opisana je klinička slika, patohistološki i imunohistohemijski nalaz skvamocelularnog karcinoma timusa koji je slučajno identifikovan kod pacijenta tokom elektivne hirurške revaskularizacije miokarda.

Ključne reči: karcinom timusa; karcinomi medijastinuma; elektivne hirurške procedure; miokardijalna revaskularizacija; bajpas koronarnih arterija; timektomija; imunohistohemija; skvamozni karcinom; rana dijagnoza; morfološki i mikroskopski nalazi

Introduction

All thymomas are malignant tumors [1]. They are rare with an incidence of 0.15 cases per 100,000 adults. However, thymoma is one of the most frequent mediastinal tumor accounting for 21% of all mediastinal tumors [2]. Thymomas occur as encapsulated formations, locally invasive tumors or thymic epithelial carcinomas [3, 4]. While most of thymic epithelial tumors are easily classified into one of these groups, the new immunohistochemical and genetic knowledge redefined the "4th edition of the World Health Organization Classification of Tumors of the Lung, Pleura, Thymus and Heart" as a valuable tool for pathologist, cytologist and clinical oncologists [5]. In this report, we present a case of a Caucasian man with an incidental finding of thymic carcinoma during elective coronary artery bypass grafting (CABG) surgery.

Case Report

A 54-year-old man was transferred from an outside hospital for elective CABG surgery. Preoperative posteroanterior (PA) chest radiography did not show any mediastinal mass, and electrocardiogram confirmed regular sinus rhythm (heart rate=68/min). Transthoracic echocardiogram revealed a slightly decreased left ventricular systolic function (ejection frac-

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Abbreviations

RCA – right coronary artery
LAD – left anterior descending coronary artery
Cx – circumflex coronary artery
CABG – coronary artery bypass grafting
CK – cytokeratin

Figure 1. Gross view of resected mediastinal mass (7 x 3 x 3 cm)
Slika 1. *Makroskopski prikaz resecirane medijastimalne tumefakcije (7 x 3 x 3 cm)*

tion≈50%). Coronary angiography showed a chronic occlusion of the right coronary artery (RCA), and significant stenosis (≥ 75%) of the left anterior descending artery (LAD) and circumflex artery (Cx). A day after the patient had been admitted, he was scheduled for elective CABG surgery.

Routine medial sternotomy was performed. An irregular mass (7x3x3 cm) was found in the anterior mediastinum arising from the thymus. The mass was infiltrating the underlying pericardium at the level of aortic arch and distal ascending aorta and reflection of the pericardium to the aortic arch in diameter of 4 cm. The rest of the mediastinum, pericardium, heart and great vessels were without invasion and/or contact with the tumor tissue. Radical excision of the tumor was performed with resection of adjacent mediastinal fat

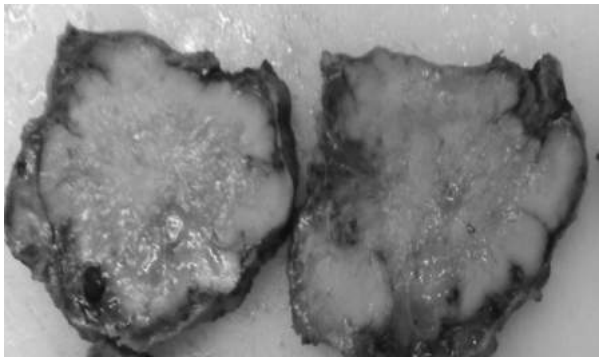

Figure 2. Cross-section of tumor tissue: whitish, homogeneous material with smaller yellowish areas of necrosis.
Slika 2. *Presek tumorskog tkiva: beličaste boje, homogene građe sa manjim žućkastim područjima nekroze*

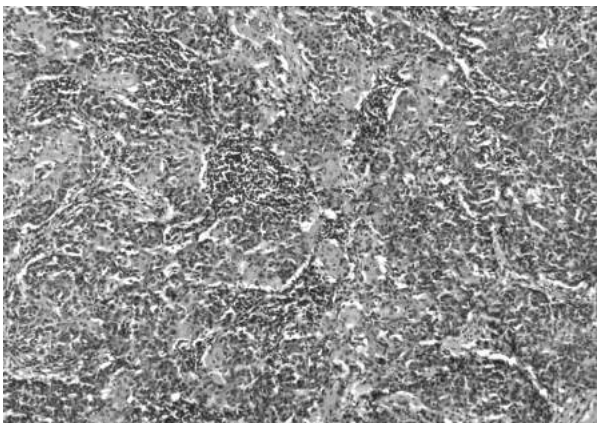

Figure 3. Histological section of the resected thymic carcinoma. Tumor presents with multiple tumor cells with keratinization and stroma infiltrating lymphocytes (H&E x10)
Slika 3. *Histološki prikaz reseciranog karcinoma timusa. Tumor prezentuju multiple atipične skvamocelularne ćelije sa disperzovanim hromatinom, celularna hiperplazija i atipična mitotska aktivnost (H & E x10)*

and pericardium **(Figure 1).** On cross-section the tumor node was whitish, homogeneous material with smaller areas of yellowish necrosis. Some of the material was cystic, and the cysts were filled with a gelatinous substance **(Figure 2)**. The macroscopically described cystic areas corresponded to the parenchyma of the thymus which was defined as an infiltrative tumor tissue. The heart was arrested and standard on-pump procedure was carried out. The LAD was grafted with the left internal mammary artery; and saphenous veins were used for grafting the RCA and Cx artery.

According to the microscopic examination the tumor node consisted of atypical squamous epithelial cells, with hyperchromatic irregular nuclei, and disturbed nucleo-cytoplasmic relationship with obvious pathological mitoses, arranged in irregular strips and nests. Some small areas of keratinization and necrosis of tumor tissue were also present. Desmoplastic stroma was partly hyalinized and focally filled with lymphocytes and giant cells with washed needle crystals of cholesterol **(Figure 3)**.

Immunohistochemical examination of the specimen was positive for cytokeratin (CK)18, CK19, CK5/6 and CD5 and CD117, and negative for CK7, TTF1, CD56 and CD20 markers **(Figure 4)**. Thus, the diagnosis of thymic squamous cell carcinoma stage III (Masaoka-Koga staging system) was confirmed [3].

Discussion

Thymic carcinoma is a rare primary tumor which is able to invade the local tissue aggressively and produce distant metastasis [1]. It originates from carcinoid neuroendocrine cells (Kulchitsky cells) usually present in the thymus gland [6]. The diagnosis of carcinoma of the thymus is sometimes very difficult. A differential diagnosis includes: metastatic cancer, thymoma, large cell lymphomas, metaplastic thymoma and ger-

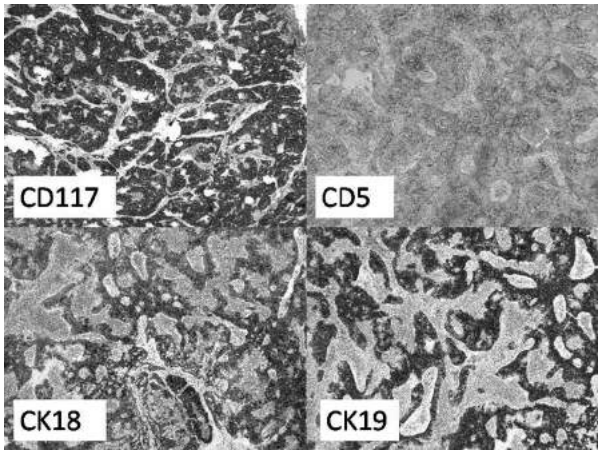

Figure 4. Immunohistochemistry of the tumor cells positive for CD117, CD5, CK18 and CK19 markers (H & E x 10)
Slika 4. *Imunohistohemijsko bojenje na CD117, CD5, CK8 i CK19 markere (H & E x10)*

mline cell thymoma. Therefore, the accurate diagnosis requires the basic clinical, radiological, morphological and immunohistochemical analysis of tumors [3, 7]. Although thymoma can be of any histological type, the tumor component is usually a well or poorly differentiated squamous cell carcinoma. This histological type is usually accompanied by expression of epithelial membrane antigen (EMA), CK 7, 8, 18 and 19 as well as the p53 protein [9]. Thymic carcinoma often expresses positivity on CD5 and CD117 markers that are normally negative in thymoma. CD5 is positive in 62 to 80% of all thymic carcinoma but is always negative in thymomas. CD117 is positive in 80% to 86% of all thymic carcinoma and only 0% to 4% in thymomas [9, 10]. In our case, the tumor was positive for CK18, 19 and CD5 and CD117 markers.

At present time, modern computed tomography makes it relatively easy to detect such tumors and to determine the staging of disease. However, incidental finding of thymic carcinoma during heart surgery is possible due to a great variety in clinical presentations [2, 6, 11].

In cases of incidental finding of thymic carcinoma during open heart surgical procedures both procedures (tumor excision and heart surgery) should be performed during the same surgery [2, 6]. A delay in cardiac procedure could result in an unpredictable clinical course with potentially fatal outcome. If a tumor is not resectable without sacrificing vital structures, total thymectomy with major tumor resection should be performed. This should be followed with cardiac procedure, and the rest of the tumor tissue should be marked for adjuvant radiotherapy [3, 11].

Conclusion

This is a very rare case of incidental finding of thymic carcinoma during an open heart surgical procedure. The postoperative course of the patient was unremarkable and the patient was discharged on the postoperative day 8. Later on, adjuvant radiotherapy was administered with a target dose of 60 Gy and he stayed well and without symptoms 8 months after surgery.

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SEMINAR FOR PHYSICIANS
SEMINAR ZA LEKARE U PRAKSI

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CRITICAL REVIEW OF AVAILABLE TREATMENT OPTIONS FOR TREATMENT REFRACTORY DEPRESSION AND ANXIETY – CLINICAL AND ETHICAL DILEMMAS

KRITIČKI PREGLED RASPOLOŽIVIH TERAPIJSKIH METODA ZA TERAPIJSKI REZISTENTNU DEPRESIJU I ANKSIOZNE POREMEĆAJE – KLINIČKE I ETIČKE DILEME

Dušan KOLAR[1,2] and Michael V. KOLAR[1]

Summary
Treatment-resistant mood and anxiety disorders require an intensive therapeutic approach, and it should balance benefits and adverse effects or other potential detrimental effects of medications. The goal of treatment is to provide consistent and lasting improvement in symptoms of depression and anxiety. Benzodiazepines are effective for anxiety symptoms, but with no sustained treatment effects. Other medication treatment options for anxiety disorders are outlined. Ketamine is usually very effective in treating major depressive disorder but without sustained benefits. Long-term use may pose a significant risk of developing tolerance and dependence. Stimulant medication augmentation for treatment-resistant depression is effective for residual symptoms of depression, but effects are usually short-lasting and it sounds more as an artificial way of improving energy, alertness and cognitive functioning. Synthetic cannabinoids and medical marijuana are increasingly prescribed for various medical conditions, but more recently also for patients with mood and anxiety disorders. All of these treatments may raise ethical dilemmas about appropriateness of prescribing these medications and a number of questions regarding the optimal treatment for patients with treatment-resistant depression and treatment refractory anxiety disorders.
Key words: Depressive Disorder, Treatment-Resistant; Anxiety Disorders; Depression; Treatment Outcome; Risk Factors; Benzodiazepines; Ketamine; Pregabalin; Central Nervous System Stimulants; Cannabinoids; Prescription Drug Overuse; Drug-Related Side Effects and Adverse Reactions

Sažetak
Terapijski rezistentni poremećaji raspoloženja i anksiozni poremećaji zahtevaju intenzivan terapijski pristup, koji treba da balansira terapijske efekte i sporedne efekte ili potencijalne štetne efekte lekova. Cilj tretmana je obezbediti konzistentno i trajnije poboljšanje simptoma depresije i anksioznosti. Benzodijazepini su efikasni za anksiozne poremećaje, ali bez trajnih terapijskih efekata. Druge terapijske opcije za anksiozne poremećaje su kratko opisane. Ketamin je obično veoma efektivan u terapiji depresivnog poremećaja, ali terapijski efekti ketamina ne traju dugo. Dugotrajna upotreba ketamina je rizična u pogledu stvaranja tolerancije i zavisnosti. Augmentacija psihostimulansima u lečenju terapijski rezistentne depresije je korisna u tretmanu rezidualnih simptoma depresije, ali su rezultati kratkotrajni i obično je to više veštačko poboljšanje pacijentove energije, nivoa budnosti i kognitivnog funkcionisanja. Sintetski kanabinoidi i medicinska marihuana se učestalo propisuju za različite medicinske probleme, ali u skorije vreme takođe za afektivne poremećaje i anksiozne poremećaje. Svi ovi tretmani mogu da stvore etičke dileme o prikladnosti propisivanja ovih lekova i niz pitanja oko toga šta je optimalan tretman za pacijente sa terapijski rezistenim depresijama i anksioznim poremećajima.
Ključne reči: terapijski rezistentna depresija; poremećaji anksioznosti; depresija; ishod lečenja; benzodijazepini; ketamin; pregabalin; stimulansi centralnog nervnog sistema; kanabinoidi; preterano propisivanje lekova; nus pojave i neželjene reakcije lekova

Introduction

Major depressive disorder and anxiety disorders are most common psychiatric conditions in clinical practice. Depression affects upward of 16% of American adults in their lifetimes with a 12-month prevalence of 6.7% [1]. Specific phobia and social anxiety disorder are the most common anxiety disorders with lifetime prevalence rates of 18.4% and 13.0%, respectively. Panic disorder, generalized anxiety disorder, agoraphobia, and separation anxiety disorder have lifetime prevalence rates of 2%–7% [2].

There is an increased number of patients with treatment refractory mood and anxiety disorders which result in higher rates of medical and psychiatric comorbidity, persistent social and vocational disability, increased risk of suicide, higher healthcare utilization and psychiatric hospitalizations.

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Abbreviations

BZDs – benzodiazepines
$SRI_S/SNRI_S$ – selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake
PTSD – posttraumatic stess disorder
TRD – treatment-resistant depression

Treatment-resistant conditions require more intensive multimodal treatment approach, but on the other hand it is important to make sure that there is a good balance of benefits and potential negative effects of treatment. The first and most important rule in any medical treatment is best described by a Latin expression "*primum non nocere*", which means "first, do no harm". There are new treatments that are effective in the short run, but at the same time they are associated with negative effects such as developing tolerance, dependence or metabolic side effects. If the goal of treatment is to produce short-lasting improvements without taking into account potential detrimental effects, this treatment is not justifiable and should not be prescribed. Prescribing medications that could provide an instant symptomatic relief of patient's suffering is popular nowadays in the era when quick solutions and immediate cession of even minimal discomfort are expected from medical professionals.

Benzodiazepines in the Past and Now

Benzodiazepines (BZDs) were commonly prescribed medications in the treatment of anxiety disorders in the last few decades of 20th century. BZDs are effective medications, and for a long time they were first-line treatment for patients with anxiety disorders. No one was thinking seriously about the potential of developing prescription medication addiction at that time. BZDs were overprescribed as a long-term treatment and we have now millions of people who are addicted to BZDs.

According to Substance Abuse and Mental Health Services Administration (SAMHSA) Report in 2012 it was noted that the number of substance abuse treatment admissions for people addicted to both benzodiazepines and narcotic pain relievers increased 5.7 times between 2000 and 2010. SAMHSA Report from 2012 also conferred that benzodiazepine abuse is particularly dangerous at younger ages due to drug interactions which may impair or alter brain development [3].

A strong opposition to the use of BZDs in psychiatry and strict monitoring of benzodiazepine prescriptions started in the last decade**.** Currently, BZDs are not a recommended treatment option and prescribing these medications should be avoided at all costs. Discontinuing BZDs after a long-term use is extremely difficult and patients may require a high dose of quetiapine or olanzapine to have a similar anti-anxiety effect as lorazepam or clonazepam in a low to moderate dose range.

With regards to BZDs we have now a strict monitoring and auditing of BZDs prescription and strong recommendations that prescribing BZDs should be reduced and these medications should be prescribed only if necessary.

Selective serotonin reuptake inhibitors and Venlafaxine or Duloxetine are the first-line option for anxiety disorders, but there is a certain number of patients who respond very partially to these medications and with much better response to BZDs. In a number of cases selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake (SSRI/SNRIs) are not more effective or sometimes even not equally effective when compared to BZDs when it comes to treatment of anxiety disorders.

As a result of SSRI/SNRI inefficacy there is a new trend of recommending BZDs as augmentation strategy for SSRI/SNRIs. Mark Pollack recommends clonazepam augmentation with an average dose of 2 mg daily for patients with refractory anxiety disorders who are responding partially to sertraline and venlafaxine [4]. Patients may respond very well to this treatment strategy, but the main question is if it is augmentation or patient is simply responding to benzodiazepine and not responding to SSRIs. Many patients may develop anxiety again upon discontinuing clonazepam. Another unresolved question is the recommended duration of benzodiazepine augmentation and how to prevent a long-term use of BZDs as it used to be in the past.

It seems that this reintroduction of BZDs into clinical practice under a different form or name (as augmentation) is causing again a risk of long-term treatment. In general, many patients with anxiety disorders prefer BZDs due to their efficacy. Most recently another serious reason for not prescribing BZDs arose and as a result a new viewpoint of demotivatingor scaring patients to not use this class of medication. Long-term use of BZDs may be associated with an increased risk of dementia [5]. Out of the ten studies retrieved, nine reported an increased risk of dementia in benzodiazepine users and have therefore indicated that there appears to be a direct link between benzodiazepine use and dementia [6]. Long-term use of BZDs should be avoided among the elderly, who may be at a higher risk for developing dementia [7].

Alternatives for BZDs in Treatment of Refractory Anxiety Disorders

Gabapentin, pregabalin, buspirone or even atypical antipsychotics are usually recommended for patients with anxiety disorders with a poor response to SSRIs/SNRIs. Clinicians may have ethical dilemmas about using atypical antipsychotics with their metabolic side effects instead of relatively harmless BZDs.

The Canadian guideline for the management of patients with mood disorders and comorbid anxiety disorders recommends gabapentin and quetiapine as a first-line option for the pharmacologic treat-

ment of comorbid anxiety symptoms/disorder in patients with bipolar disorder [8]. Pregabalin is a medication with anti-anxiety potential which may help with reducing an excessive use of BZDs. The results from a Norwegian study demonstrated that patients who started pregabalin reduced more significantly the use of BZDs compared to those on gabapentin [9]. However, there is evidence that both gabapentin and pregabalin are medications with a potential of misuse. Careful evaluation of a previous history of drug abuse is essential while prescribing gabapentin [10]. In our experience, patients with a long-term use of BZDs usually require a higher dose range of gabapentin or pregabalin which in turn increases a potential risk of addiction to these medications.

Buspirone is non-benzodiazepine anxiolytic that was first marketed in 1986. Buspirone is approved for treatment of generalized anxiety disorder, but it is also effective as augmentation in treating depression. Unfortunately, buspirone is usually not very effective for patients with previous long-term use of BZDs.

In summary, most of the available medications for patients with anxiety disorders with no response to antidepressant medications have either undesirable adverse effects/detrimental effects or addictive potential with a long-term treatment.

There is another radical and, we would say, negative movement in the treatment of trauma-related disorders, particularly posttraumatic stress disorder (PTSD) that may also reflect on anxiety disorders per se. This is using synthetic cannabinoids and more recently medical marijuana in the treatment of variety of medical conditions, and a potential of uncritical usage of these substances in the treatment of PTSD, anxiety disorders, and mood disorders.

Synthetic Cannabinoids for PTSD and Other Anxiety Disorders and Mood Disorders

Both endocannabinoids and the compounds in marijuana bind to proteins called cannabinoid receptors in the brain and throughout the body. There are two cannabinoid receptors called CB(1) and CB(2) receptors that can be activated by endogenously released 'endocannabinoids' or exogenously administered compounds in order to reduce the physical and psychological symptoms [11]. Nabilone is a synthetic cannabinoid that was approved for use by Health Canada in 1982 for the treatment of cancer therapy-induced nausea. Nabilone has also been tried in inflammatory bowel disease, dystonia, spasticity in neurological disorders, Parkinsonism, chronic pain, and fibromyalgia.

There is a new practice of using synthetic cannabinoid, nabilone for treating nightmares associated with severe PTSD. Canadian military psychiatrist Fraser published an open label study of using nabilone in patients with PTSD in 2009 and suggested that nabilone is beneficial in the treatment of nightmares associated with PTSD, it increases sleep time and is not being associated with development of tolerance [12]. The results of another study by the same group of authors has demonstrated that nabilone in dose of 3 mg reduces the frequency and intensity of nightmares in the military population of patients with a history of non-response to traditional therapy [13]. Nabilone is currently a commonly prescribed medication for nightmares associated with various clinical conditions. Long-term use of nabilone is unfortunately not uncommon. Some patients may report improvement in mood and anxiety symptoms with cannabinoids and there is a tendency among clinicians of prescribing nabilone or even medical marijuana for patients with anxiety and depression with unknown long-term consequences.

The disadvantages of prescribing nabilone are plentiful, some of which include the fact that there are no data about long-term use and treatment outcomes as well as the occurrence of some patients switching to marijuana over time because it is better tolerated and less expensive [14]. Another major deleterious effect is that nabilone is perceived to produce more undesirable side effects when compared to marijuana. Some of the more common side effects of nabilone include the following: somnolence, dizziness, euphoria, depression, fatigue, apathy, dry mouth, ataxia, visual disturbances, headaches, and concentration difficulties [15]. It is clear that nabilone is not well tolerated and side effect profile is not favorable for psychiatric conditions, particularly mood disorders.

However, there is again paradoxically a tendency to consider cannabinoids in the treatment of mood disorders, probably as a result of the lack of new medications for mood and anxiety disorders. The endocannabinoid (eCB) system may play a role in the control of mood. In one of the recently published papers targeting the endocannabinoid (eCB) system is viewed as an attractive and novel approach to the treatment of depression and other mood disorders [16]. These new treatment trends without any well designed evidence based studies to prove its efficacy and safety may sound more as a big experiment in psychiatry rather than any scientifically justified treatment method.

Augmentation Strategies in Treatment-Resistant Depression

There are a number of augmentation strategies for depressed patients with a partial response to antidepressant medications. Atypical antipsychotic augmentation has become almost the standard of care for treatment-resistant depression (TRD). Stimulant augmentation is less established and less supported augmentation strategy for TRD compared with other more commonly used augmenting strategies and this is because there are no clear recommendations about the dosage of stimulant medication for augmentation, duration of treatment and the clear goal of treatment. In spite of these limitations,

stimulant augmentation is more popular lately, particularly in North America, and many patients prefer stimulants over atypical antipsychotics. Some clinicians unreasonably prescribe stimulant medications with a belief that they are serving the patients' best interests, although there is no strong evidence for the efficacy of stimulant augmentation.

Stimulant medication may produce a prompt and significant reduction in some type of residual symptoms of depression such as daytime sleepiness, poor alertness, lack and concentration and lack of energy. Some individuals may feel better within hours of taking stimulant medication, but there will be no sustained benefits even with prolonged use. Improvements with stimulants disappear almost immediately after discontinuing stimulant medication. There is no consensus if a long-term use of stimulant medication, such as in attention deficit hyperactivity disorder (ADHD), is acceptable in patients with TRD [17].

Australian open study conducted by Gordon Parker and colleagues from the Black Dog Institute in Sydney demonstrated that psychostimulants may be an efficacious antidepressant option for managing unipolar or bipolar melancholic depression. In the group of 50 patients stimulants were 'very effective' in managing symptoms of melancholia for 20% of the bipolar and unipolar patients, 'somewhat effective' for 50% in each group and 'ineffective' for some 30% of each group [18]. Authors used methylphenidate (5-60 mg daily) and dextroamphetamine (5-20 mg) and most patients (84%) received stimulant as an augmentation strategy.

In the literature review from 1988 to 2013 conducted by Corp et al. Modafinil and Armodafinil are effective treatment options for refractory unipolar and bipolar depression. Randomized clinical trials data on dopaminergic stimulants are too limited to justify their use as the first-line augmentation for depression with the exception of some promising results with lisdexamfetamine [19], but still limited data mostly pertaining improvement in executive dysfunctions and depressive symptoms with lisdexamfetamine in patients with mild major depressive disorder (MDD) [20].

The main issue which arises is that sometimes, even with partial improvements in energy level and cognitive symptoms of depression with stimulant medications, clinicians may continue prescribing stimulants for a few years or longer.

Long-term use of stimulants in a higher dose range for augmentation is not recommended and should not be acceptable. At the same time, a new trend of promoting stimulants as antidepressant might justify a long-term use of stimulants. However, if we accept Gordon Parker's suggestion of using stimulant medications potentially as antidepressant instead of augmentation, it will be a big shift in psychiatry, giving up of etiological treatments in psychiatry and simply providing the medications for symptoms or a group of symptoms. Such treatment conceptualization would be a change of paradigms in psychiatry. Hopefully it will be only a temporary crisis in psychiatry.

Ketamine in Treatment-Resistant Depression

Ketamine is a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist which was used as an anesthetic induction agent for diagnostic and surgical procedures, primarily in pediatric surgery and veterinary medicine. In terms of drug class, ketamine can be categorized as a dissociative anesthetic, hallucinogen, and psychotomimetic medicine. Recreationally it is used for its psychedelic and dissociative effects [21]. Ketamine abusers generally tend to take the drug either parenterally, intranasally, or orally in doses of 60+ mg, 100+ mg and 200+ mg range per each instance, and it is sometimes taken up to 2-3 g per day by frequent abusers.

Ketamine is usually effective for depression and produces fast improvement in depressive symptoms. There are trials of ketamine in patients with TRD and ketamine has rapid antidepressant effects in patients with TRD [22]. Ketamine is typically administered by a series of up to six IV infusions (0.5 mg/kg). Ketamine causes depersonalization and some patients develop depersonalization after each infusion. Effects of ketamine are short-lasting and there is no sustained benefit. About 76% of patients relapse two to three weeks after stopping ketamine infusions [23].

There is a tendency of using oral formulations of ketamine and intranasal ketamine, but if the goal of prescribing oral ketamine is providing more sustained antidepressant effects, and if treatment should be provided for an extended period of time, then the risk of addiction may be increased. There are not set guidelines when it comes to deciding on how long ketamine should be administered [21]. A possible outcome of this practice, when the patients are given ketamine orally, could result in a very similar situation as with benzodiazepine in the past, perhaps even worse. Scientific community is aware that there are risks when it comes to ketamine use which may eventually lead to dependence, but at the same time there remain a number of questions which will have to be answered such as defining a safe dose, recommended frequency, and the extent of the dependence and tolerance to this drug. The duration of maintenance therapy has not yet been defined and this will be a crucial step in order to try to retain some benefits obtained from the treatment.

Long-term exposure to ketamine, particularly in a higher dose range, may result in developing tolerance, drug craving, flashbacks, and possible physiological withdrawal symptoms. Ketamine potential for abuse and neurotoxicity should not be neglected [24]. Finally, it is also important to mention that while there are a number of articles on ketamine dependence in literature, there are no large-scale studies, and hence the prevalence of ketamine dependence is to this day unknown.

Controversies about Medical Marijuana

Medical marijuana has emerged recently as a possible treatment option for various medical conditions including cancer, hepatitis C, Parkinsonism, spasticity associated with multiple sclerosis (MS), chronic pain, neuropathic pain, and Glaucoma. High-tetrahydrocannabinol (THC) medical marijuana (15-22% THC) prescribed to patients for medical conditions is very potent and it is not known if this new marijuana is more addictive than marijuana as a recreational drug. Therefore, it would be essential to have a clear policy about prescribing medical marijuana [21].

Whiting et al. completed a systematic review of benefits and adverse events of cannabis and cannabinoids and established that there was low-quality evidence to support the use of cannabinoids in nausea and vomiting due to chemotherapy, weight gain in human immunodeficiency virus (HIV) infection, sleep disorders, and Tourette syndrome. The paper also stated that cannabis and cannabinoids did not show efficacy for suppressing anxiety, although it did mention that there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity [25]. Common adverse events as a result of using cannabis and cannabinoids include dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

Psychiatric patients are unlikely candidates for medical marijuana. In case of patients with history of substance use disorder physicians should be very cautious with prescribing medical marijuana for medical conditions [21].

There is a misconception that medical marijuana compared with recreational marijuana may have anti-anxiety effects. In general, marijuana may transitory help anxiety, but it increases baseline anxiety. It should be pointed out that marijuana could trigger panic attacks, particularly in younger people. Chronic cannabis use is associated with higher prevalence of anxiety disorders, although cannabis use is not the only risk factor sufficient for the development of a long-term anxiety [26].

Several studies show an association between marijuana use and onset of mood disorders and psychosis. Regular marijuana use is also associated with increasing symptoms of depression. Marijuana use also worsens the course of bipolar disorder. Regular cannabis use leads to an increased risk for suicidal ideation in males and possibly increased suicide attempts. Lastly, we should take into consideration the detrimental effects of marijuana on the brain development, especially in adolescents.

Nowadays there is a tendency of recommending medical marijuana for psychiatric conditions, including schizophrenia, depression and anxiety disorders. Papini et al. reported of marijuana being used successfully in treating PTSD symptoms in veterans [27]. It is a bit surprising because substance abuse, including cannabis abuse is a common psychiatric comorbidity/complication in patients with PTSD, but now we have a situation of using cannabis for PTDS treatment. We can ask ourselves again the same question about the nature of this change in psychiatry and it may be interpreted either as a change of paradigm in psychiatry or a temporary confusion around appropriateness of using cannabis in treating psychiatric conditions.

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ALTERNATIVES OF MENOPAUSAL HORMONE THERAPY

ALTERNATIVE HORMONSKE TERAPIJE U MENOPAUZI

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Summary

Introduction. It has been generally accepted that the benefits of menopausal hormone therapy outweigh the risks, but there are still some concerns about the administration of menopausal hormone therapy, which has introduced alternative treatments. **Pharmacological Alternatives.** Central alpha-2 agonist clonidine is only marginally more effective than placebo, and significantly less effective than estrogen. Antiepileptic drug gabapentin reduces hot flashes; however, it is less effective than estrogen. Selective serotonin reuptake inhibitors (paroxetine and fluoxetine) and selective noradrenaline reuptake inhibitors (venlafaxine) reduce vasomotor symptoms and improve depression, anxiety and sleep. Results of studies about dehydroepiandrosterone effects on menopausal symptoms are inconsistent and additional investigations are needed. **Non-Pharmacological Alternatives.** Stellatum ganglion blockade is a successful treatment for reducing vasomotor symptoms in patients with contraindications for menopausal hormone therapy. Efficacy of acupuncture, homeopathy and reflexology should be proved by adequate studies. Phytoestrogens could reduce vasomotor symptoms but to a lesser extent than conventional menopausal hormone therapy. However, they have not been proved yet to provide cardiovascular protection and prevention of osteoporosis, nor they could be recommended instead of traditional menopausal hormone therapy. There is a concern about their undesirable effects. Adequate diet, unchanging body weight within ideal values and adequate physical activities have beneficial long-term effects, first of all on preservation of bone density. **Alternatives for Atrophic Changes of Vaginal Epithelium.** Menopausal symptoms resulting from vaginal atrophy could be resolved by use of hydrophilic preparations, lubricants and topical lidocaine cream or 4% lidocaine water solution for dyspareunia. **Conclusion.** If there are contraindications to menopausal hormone therapy or patients are unwilling to take hormone therapy, alternative treatments, which can also solve menopausal symptoms, should be considered.

Key words: Estrogen Replacement Therapy; Perimenopause; Complementary Therapies; Treatment Outcome; Pharmaceutical Preparations; Phytoestrogens

Sažetak

Uvod. Generalno je prihvaćeno da korist od hormonske terapije u menopauzi prevazilazi rizik kod adekvatno izabranih pacijentkinja, a ipak postoji zabrinutost koja prati upotrebu hormonske terapije u menopauzi, što je i dovelo do pojave alternativnih tretmana. **Farmakološke alternative.** Centralni alfa-2-agonist klonidin je samo marginalno efikasniji od placeba, a znatno manje od estrogena. Antiepileptik gabapentin redukuje talase vrućine, ali manje uspešno od estrogena. Selektivni inhibitori preuzimanja serotonina (fluoksetin i paroksetin) i inhibitori preuzimanja serotonina-epinefrina (venlafaksin) redukuju vazomotorne simptome, popravljaju depresiju, anksioznost i kvalitet sna. Rezultati ispitivanja efekata dehidroepiandrosterona na simptome menopauze su nekonzistentni i potrebne su dodatne studije. **Nefarmakološke alternative.** Blokada gangliona stelatum uspešno rešava vazomotorne simptome pacijentkinja sa kontraindikacijama za primenu hormonske terapije u menopauzi. Efikasnost akupunkture, homeopatije i akupresure tek treba da se dokaže. Fitoestrogeni mogu da redukuju vazomotorne simptome, ali u manjoj meri od konvencionalne hormonske terapije u menopauzi. Za sada nema adekvatnih dokaza za povoljan efekat na kardiovaskularni sistem i sprečavanje osteoporoze, niti da se preporučuju umesto tradicionalne hormonske terapije u menopauzi. Postoji bojazan od neželjenih dejstava. Pravilna ishrana, stabilna telesna težina u idealnim granicama i adekvatna fizička aktivnost imaju povoljne dugoročne efekte, najpre na očuvanje gustine kosti. **Alternativni tretmani atrofičnih promena epitela vagine.** Simptome menopauze koji su posledica atrofičnih promena je moguće kupirati vaginalnom upotrebom hidrofilnih preparata, lubrikanata i lidokaina u obliku krema ili 4% rastvora za dispareuniju. **Zaključak.** Ako postoje kontraindikacije za hormonsku terapiju u menopauzi ili pacijentkinja ne želi da uzima hormone, treba razmatrati alternativne mogućnosti koje takođe mogu da pomognu u kupiranju simptoma menopauze.

Ključne reči: estrogenska supstituciona terapija; perimenopauza; alternativne terapije; ishod lečenja; farmakološka terapija; fitoestrogeni

Introduction

Benefits of menopausal hormone therapy (MHT) are clear: it is efficient in resolving menopausal symptoms – vasomotor problems (hot flushes), atrophic changes (superficial dyspareunia and sense of vaginal dryness) and urinary problems (frequent urination and urgency).

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Abbreviations

MHT – menopausal hormone therapy
DHEA – dehydrepiandrosterone
SERM – selective modulators of estrogen receptors
SNRI – serotonin-norepinephrine reuptake inhibitors
SSRI – selective serotonin reuptake inhibitors

On the other hand, there are numerous reports showing that MHT is associated with the risk for developing unwanted complications. In spite of the statement that the benefits from MHT are more likely to overweight the risks in symptomatic women under 60 years of age or if it is started within 10 years after menopause [1–3], the concern which is associated with the use of MHT is understandable. [4]. The aim of this article is to present current alternatives to MHT in the treatment of menopausal symptoms **(Table 1).**

Pharmacological Alternatives

Alpha-2 Agonists – Clonidine

In spite of its popularity in the western countries as an alternative therapy for the menopausal vasomotor problems, centrally active alpha-2 agonist clonidine is only marginally more effective than placebo, but considerably less efficient than estrogen [5]. Undesirable effects of clonidine are dry mouth, sense of dryness and insomnia [3].

Gabapentin – Antiepileptic

Antiepileptic gabapentin reduces hot flushes, but to the lesser extent than estrogen does [6]. It is a possible alternative for patients with natural or artificial menopause, who cannot receive estradiol, or for the patients who do not want to receive hormone replacement therapy. It is administered at dose of 600 to 2400 mg/day in divided doses, with gradually increased doses. Side effects are somnolence, sense of dryness and weakness, peripheral edemas, being most prominent during the first two weeks of the therapy [7]. A recent trial of gastroretentive gabapentin in the form of tablet with gastric retention up to 10 hours, which gradually releases gabapentin allowing optimal resorption, showed that gabapentin in this form is a modestly effective non hormone therapy for the treatment of moderate to severe menopausal vasomotor problems. This route of administration allows less frequent daily administration (600 mg am/1200 mg pm), better medicament titration, with fewer side effects [8].

Selective Serotonin Reuptake Inhibitors and Serotonin-norepinephrine Reuptake Inhibitors

Since serotonin is known as the "hormone of happiness", it is logical to think that selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors/selective noradrenaline reuptake inhibitors (SNRI) could be useful in the management of menopausal symptoms. SSRI used for such purposes are fluoxetine (20 mg/day), paroxetine (12.5 – 25 mg/day), medicaments that have already been used in psychiatry. SSRI are modestly effective in the management of menopausal symptoms, escitalopram being the most effective [9]. They reduce the frequency and severity of hot flushes, improve depression, anxiety and sleeping disturbances.

Side effects of such therapy are nausea, dizziness, dry mouth, constipation, somnolence, sweating, decreased libido, sexual dysfunction and rush, but with the time and dose titration, all these side effects disappear [9, 10].

SNRI used for such purposes is venlafaxine taken at a dose of 37.5 mg twice daily, with similar side effects [4]. Its analogue (desvenlafaxine succinate) is also efficient, with fewer side effects [11].

It seems that SSRI and SNRI could be a reasonable alternative treatment for menopausal vasomotor symptoms in women who cannot take the menopausal hormone therapy or are concerned about the long-term effects of estrogen, but those medications are not an optimal choice for the patients with no contraindication for conventional MHT.

Dehydroepiandrosterone

The levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulaphate (DHEASO4) fall in the postmenopausal period. DHEA is a precursor for sex steroids. DHEA does not improve menopausal symptoms, but raises the levels of testosterone. Other studies have shown positive effects on bone density, cognitive functions, libido and improvement of vaginal atrophic changes [12]. Beneficial effects of DHEA on fertility have been reported recently, but further studies are needed for definitive conclusions [4].

Adverse cardiovascular effects are possible due to unfavorable effects of DHEA on lipid profile (decreasing the levels of high density lipoproteins) [10].

Current guidelines are against the routine administration of DHEA and testosterone in patients with low androgen levels due to hypopituitarism, surgical menopause, glucocorticoid administration and other conditions associated with low androgen levels because there are no adequate long-term studies about the effectiveness and safety of such therapy [13].

Non-Pharmacological Alternative Treatments

Stellate Ganglion Blockade

Stellate ganglion blockade means an injection of local anesthetic into the stellate ganglion. This intervention is successful in resolving vasomotor menopausal problems in patients with contraindications for menopausal hormone therapy. Complications are few [14].

The other possibilities of non-pharmacological treatments for vasomotor menopausal problems are acupuncture, homeopathy, reflexology (application of pressure to specific points of the feet, hands and ears), but the efficiency of such treatments has not been proved by adequate studies [4].

Phytoestrogens

It is generally believed that complementary therapies are safer and more natural alternatives

Table 1. Alternative treatments for menopausal problems
Tabela 1. *Alternativni tretmani problema u vezi sa menopauzom*

Alternative pharmacological therapies/*Alternativne farmakološke terapije*
- Alpha 2 agonist - clonidine/*Alfa 2 agonist - klonidin*
- Gabapentin/*Gabapentin*
- Selective serotonin reuptake inhibitors (SSRI) and serotonin - norepinephrin (noradrenaline) reuptake inhibitors (SNRI)
Selektivni inhibitori preuzimanja serotonina i inhibitori preuzimanja serotonina - nerepinefrina (noradrenalina)
- Paroxetine/*Paroksetin* - Venlafaxine/*Venlafaksin*
- Fluoxetine/*Fluoksetin* - Desvenlafaxine succinate/*Dezvenlafaksin sukcinat*
- Dehydroepiandrosterone/*Dehidroepiandrosteron*
Non-pharmacological treatments/*Nefarmakološki tretmani*
- Ganglion stellate blockade for vasomotor symptoms/*Blokada gangliona stelatum za vazomotorne simptome*
- Phytoestrogens/*Fitoestrogeni*
- Physical activity/*Fizička aktivnost*
- Vitamin D3, calcium, omega 3 supplementation/*Suplementacija vitamina D, kalcijuma i omega 3 kiselinama*
Alternative treatments for atrophic changes (dyspareunia)/*Alternativni tretmani atrofičnih promena (dispareunije):*
- Vaginal moisturizers/*Vaginalni hidrofilni preparati*
- Vaginal lubricants/*Vaginalni lubrikanti*
- Topical lidocaine for dyspareunia /*Površno lidokain za dispareuniju*

than the traditional menopausal hormone therapy, but the efficacy and real safety of majority of these preparations have not been proved yet [4].

Phytoestrogens are nonsteroidal plant substances with estrogen activity. The major classes are isoflavones (the most potent), lignans and coumestans. The term phytoestrogens also includes stilbenes, flavanones, flavonols and flavones [15]. Isoflavones can be found in soya, red clover and probably in other legumes such as peas and beans. Oils extracted from seeds are rich in lignans (e.g. from flaxseed, bran and whole grains, vegetables, legumes, fruits). Phytoestrogens, structurally not identical to human hormones, have mixed estrogenic and anti-estrogenic effects, which depend on the tissue. These effects are mediated via estrogen receptors (ER) (α- and β-), and possibly G protein coupled estrogen receptor (GPER). It is postulated that phytoestrogens act as selective modulators of estrogen receptors (SERM): during premenopausal period, when the endogenous estrogen levels are high, they demonstrate anti-estrogenic effects; in postmenopausal period, when the endogenous estrogen levels are low, phytoestrogens act as weak agonists stimulating ER. Phytoestrogens show higher affinity for β-ER than for α-ER: estrogenic activity is more expressed in the central nervous system, vasculature, bones and skin; it is less on the uterine level and breast. Experimental studies have reported beneficial effects of phytoestrogens on the endothelium, vascular smooth muscle and extracellular matrix, as well as on the lipid profile, inflammation, angiogenesis and tissue damage by reactive oxygen species, which could delay atherosclerosis. Considering all the above mentioned, it seems that phytoestrogens could be ideal alternatives to traditional menopausal therapy.

The conclusions of clinical studies are slightly different. Benefits of those substances are small: they can reduce hot flashes, but not significantly, and to the lesser extent than conventional MHT. Meta-analysis of 43 randomized controlled trials including 4,364 participants has failed to confirm the efficacy of phytoestrogens to reduce vasomotor menopausal problems although isoflavons derived from soya, with the most potent estrogenic action, deserve further investigation. Significant placebo effect in reduction of vasomotor symptoms was noticed in the majority of included trials (from 1% to 50%). This meta-analysis has also confirmed that there are no proofs for estrogenic stimulation of endometrium, vagina, nor unwanted effects during two years of use [16].

Phytoestrogens reduce the levels of low density lipoproteins, they do not affect high density lipoproteins, that being true only for intact soya proteins. Phytoestrogens may ameliorate insulin resistance and could be considered a beneficial dietary factor for prevention and management of type 2 diabetes [17]. On the other side, some studies have shown that phytoestrogens may have beneficial effects on bone density (improving the density of vertebra, with no effects on the hip) and on cardiovascular system, but there is no strong evidence to support this [1].

Phytoestrogens have no impact on the endometrium or symptoms of genital atrophy. A protective effect on breast is possible [10]. Many plants are used traditionally for menopausal symptoms, but adequate studies to prove their efficacy are still lacking. The placebo effect must be taken into consideration [4].

Meta-analyses of reported trials have showed that so far there is no adequate evidence to recommend phytoestrogens instead of conventional MHT, or to support their role in prevention and treatment of cardiocvascular diseases [15]. On the other hand, many herbal medications do have pharmacological performances, thus they might have undesirable effects. That is why phytoestrogens should be avoid-

ed in circumstances when estrogen is contraindicated: in the presence of estrogen dependent tumors, thromboembolism and cardiovascular diseases. The attention should be paid to possible hepatotoxicity caused by some of those plants [18], as well as possible interactions with pharmacological medications.

Physical Activity, Diet and Supplements as Alternatives to MHT

Changes in the lifestyle cannot help too much in resolving actual menopausal symptoms. On the other hand, adequate diets, unchanging body weight within optimal limits and adequate physical activity have favorable long-term effects.

Introduction of optimal diet and adequate physical activity should be a part of routine management of all women in perimenopausal period and later [1, 19].

It is important to maintain body weight within optimal limits in order to preserve bone density and decrease the incidence of fractures in the postmenopausal period. Weight gain, as well as its unplanned loss, is associated with increased incidence of fractures of different localization. Planned body mass reduction is associated with a slightly increased incidence rate of lower limb fracture, but the incidence of hip fracture is lower [20].

Physical activity can alleviate menopausal symptoms, and very important factors are the type of personality and active life style [21]. A recent study [22], examining the association of demographic, lifestyle parameters and perceived severity of menopausal symptoms, has shown that regular exercises (three times a week) can also alleviate menopausal symptoms, measured by Greene climacteric score, with lowered total and somatic subscores, especially psychological and sexual subscores. More frequent exercises (both aerobic and non aerobic) reduced the severity of menopausal symptoms although sexual and vasomotor subscores remained unchanged. It was interesting that mothers of three and more children had lower Greene score, which was also reported in other studies [23].

A recent meta-analysis examining the effectiveness of physical activity on menopausal symptoms reduction reported that evidence was not strong enough to show that exercises were an effective treatment for vasomotor symptoms, or that they were more effective than yoga or conventional MHT [24]. Low moderate intensity physical activity during postmenopausal period decreases the inflammatory cytokine plasma levels, which correlates with more favorable reproductive hormone profile comparing with the sedentary way of life [25]. It has also been reported that physical activity increases bone density, improves bone strength and prevents bone loss in the elderly [26].

A recent study has reported a favorable effect of physical activity on the mammographic density, better lobular involution among postmenopausal women and a possible protective effect on the breast [27].

Decreased estradiol levels after surgical or natural menopause cause decreased expression of genes for effective energy consumption, as well as genes for catabolism of lipids. This is, at least partially, the cause of obesity and its consequences after menopause. Animal experiments have shown that physical activity in combination with restrictive diet prevents the development of metabolic syndrome induced by high caloric diet in association with estrogen deficiency or artificial menopause [28, 29]. Human studies have confirmed this conclusion [30].

Physical activity and omega-3 supplementation in the postmenopausal period have synergistic effect in attenuating inflammation and augmenting bone density in postmenopausal osteoporosis [31].

Common sense solutions could be effective in the treatment of vasomotor problems: cooling and cold drinks, avoidance of hot and alcoholic drinks as well as hot and spicy food, smoking cessation, excessive weight loss and layering of clothing [3, 4].

Alternative Treatments for Vulvovaginal Atrophy

Menopausal symptoms caused by atrophic changes of vaginal epithelium could be managed by vaginal use of hydrophilic preparations, moisturizers, rehydrating vaginal tissue, which are a good alternative to vaginal estrogen, acting more physiologically than vaginal gels [1, 4].

Recent studies have demonstrated that topical lidocaine cream application is very effective before speculum examination in postmenopausal women [32] or 4% aqueous lidocaine solution for dyspareunia [33]. Lubricants and regular sexual activity could also be helpful [34, 35]. Thereby, special attention should be paid to the preservation of normal vaginal flora. Future studies of vaginal microbiome could become the base for the new treatment options.

Conclusion

If there are contraindications for menopausal hormone therapy or the patient does not want to take hormones, alternative treatments for menopausal symptoms should be considered. Alternatives to menopausal hormone therapy include pharmacological treatments (clonidine, gabapentin, selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors, dehydroepiandrosterone) and non-pharmacological alternatives (ganglion stellatum blockade for vasomotor problems, phytoestrogens, physical activity and adequate diet, as well as omega-3, vitamin D and calcium supplementation).

Further studies are needed to confirm the efficacy and safety of some complementary treatments. All mentioned alternatives are less successful in treatment of menopausal symptoms than conventional menopausal therapy.

Adequate diets, unchanging body weight within optimal limits and adequate physical activity have

favorable long term effects on bone density in the first place.

Menopausal symptoms resulting from atrophic changes of vaginal epithelium could be treated by vaginal use of hydrophilic preparations, moisturizers, lubricants and topical lidocaine cream or 4% lidocaine aqueous solution for dyspareunia.

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HEALTH EFFECTS OF SLEEP DEPRIVATION ON NURSES WORKING SHIFTS

EFEKTI NEDOSTATKA SNA NA ZDRAVLJE MEDICINSKIH SESTARA U SMENSKOM OBRASCU RADA

Čedomirka STANOJEVIĆ[1], Svetlana SIMIĆ[2,3] and Dragana MILUTINOVIĆ[4]

Summary

Introduction. Atypical work schedules cause reduced sleep, leading to drowsiness, fatigue, decline of cognitive performance and health problems among the members of the nursing staff. The study was aimed at reviewing current knowledge and attitudes concerning the impact of sleep disorders on health and cognitive functions among the members of the nursing staff. **Sleep and Interpersonal Relations in Modern Society.** The modern 24-hour society involves more and more employees (health services, police departments, public transport) in non-standard forms of work. In European Union countries, over 50% of the nursing staff work night shifts, while in the United States of America 55% of nursing staff work more than 40 hours a week, and 30-70% of nurses sleep less than six hours before their shift. **Cognitive Effects of Sleep Deprivation.** Sleep deprivation impairs the performance of tasks that require intensive and prolonged attention which increases the number of errors in patients care, and nurses are subject to increased risk of traffic accidents. **Sleep Deprivation and Health Disorders.** Sleep deprived members of the nursing staff are at risk of obesity, diabetes, gastrointestinal disorders and cardiovascular disease. The risk factors for breast cancer are increased by 1.79 times, and there is a significantly higher risk for colorectal carcinoma. **Conclusion.** Too long or repeated shifts reduce the opportunity for sleep, shorten recovery time in nurses, thus endangering their safety and health as well as the quality of care and patients' safety. Bearing in mind the significance of the problem it is necessary to conduct the surveys of sleep quality and health of nurses in the Republic of Serbia as well in order to tackle this issue which is insufficiently recognized.

Key words: Nursing Staff, Hospital; Nurses; Sleep Deprivation; Sleep Disorders, Circadian Rhythm; Burnout, Professional; Workload; Cognition; Attention; Arousal; Risk Factors; Obesity; Diabetes Mellitus; Neoplasms; Quality of Health Care

Sažetak

Uvod. Atipični radni rasporedi uzrokuju restrikciju sna dovodeći do pospanosti, umora, pada kognitivnih performansi i zdravstvenih problema medicinskih sestara. Cilj ovog rada je prikaz trenutnih saznanja i stavova o uticaju poremećaja sna na zdravlje i kognitivne funkcije medicinskih sestara. **San i odnosi u savremenom društvu.** Savremeno *24-časovno društvo* uključuje sve više zaposlenih (zdravstvo, policija, transport) u nestandardne obrasce rada. Preko 50% medicinskih sestara u zemljama Evropske unije radi u noćnim smenama, dok u Sjedinjenin Američkim Državama 55% sestara radi više od 40 sati nedeljno a 30−70% spava manje od 6 sati između smena. **Kognitivni efekti lišavanja sna.** Lišavanje sna narušava izvršavanje zadataka koji zahtevaju intenzivnu i prolongiranu pažnju što povećava broj grešaka u nezi pacijenata a sestre izlaže povećanom riziku od saobraćajnih udesa. **Nedostatak sna i poremećaji zdravlja.** Sestre koje nedovoljno spavaju izložene su povećanom riziku od nastanka gojaznosti, dijabetesa, gastrointestinalnih poremećaja i kardiovaskularnih bolesti. Rizik od karcinoma dojke veći je 1,79 puta, a značajno je povećan rizik i od karcinoma kolorektuma. **Zaključak.** Duge ili uzastopne smene smanjuju priliku za san, skraćuju vreme oporavka medicinskih sestara ugrožavajući njihovu bezbednost i zdravlje kao i kvalitet nege i bezbednost pacijenata. S obzirom na značaj problema, potrebno je i u Republici Srbiji sprovesti istraživanja kvaliteta sna i zdravlja medicinskih sestara sa ciljem sagledavanja ovog problema koji je nedovoljno prepoznat.

Ključne reči: bolničko osoblje; medicinske sestre; nedostatak sna; poremećaj sna, cirkadijalni ritam; profesionalno izgaranje; preopterećenost poslom; kognicija; pažnja; budnost; faktori rizika; gojaznost; dijabetes melitus; karcinomi; kvalitet zdravstvene nege

Introduction

Sleep is a biological necessity essential for life and our optimal health. We are capable of altering most of our habits significantly, but we cannot give up sleep for longer than short periods of time. Nowadays, there are professions and vocations across the world whose specific duties oblige their members to follow reverse work-sleep schedule, sleeping during daylight hours and being awake during the night. However, poor sleep quality, insufficient amounts of sleep, and wrongly adjusted sleep cycle may negatively affect mental and physical functioning in the waking state [1].

Nurses in healthcare systems play a central role in patients' care and health care teams by performing

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Abbreviations
BMI – body mass index
CVD – cardiovascular disease

countless tasks critically associated with risks for a patient's safety [2], as well as managing a number of dynamic work processes under conditions of extreme workload, and multiple time pressure [3]. Although nurses are known for their commitment to health promotion, the irony is that they are, more than any other profession, at risk from exposure to many serious health disorders and disturbed mental and social well-being, resulting in a reduction of job performances which can affect both the quality of care and patients' safety because of the nature of their work and work schedules. Night shift work is preconditioned by the need to provide 24- hour care and may result in reduced sleep due to desynchronization in the regulation of endogenous circadian rhythms, leading to accumulated "sleep debt", sleepiness and fatigue, which, in turn, results in increased physical and psychological health problems in nurses [4].

The data reported in the literature have shown that sleep disorders, and related health problems, are at least as prevalent in nurses as in other professional groups that are traditionally considered risky. Despite the fact that nurses in Serbia comprise one of the largest segments of professionals working in the healthcare system, the literature review for our country reveals that there is no indication of addressing adequately the adverse effects of sleep deprivation on health and cognitive functioning in nurses. Thus, this study was aimed at determining the current knowledge and attitudes about sleep deprivation and its effects on nurses' health and cognitive functioning.

Sleep and Modern Society Relationships

Throughout the development of civilization, humans mainly worked and lived modulating their everyday activities to day/night cycle. The emergence of modern industrial society with its sociocultural and technological evolution contributed to the disruption of this natural rhythm, whereas the introduction of artificial light, continuous technological processes and shift work have established preconditions for developing sleep disorders [3]. The society, therefore, as a result of social changes, economic and technological progress and globalization of markets, is moving ever closer towards a "24-hour society ". Due to these changes more and more of the working population is involved in some of the non-standard working patterns (shift work, night shift work, readiness shifts etc.). This is primarily related to those working in service sector (health, police and transport), for whom there is an expectation, as well as an actual need of constant availability in the course of 24 hours [5]. Although public services that are at disposal 24 hours a day may benefit society, shift work might have adverse effects on the workers themselves (poor health, family/social issues), as well as on the society as a whole (accidents and performance errors) [6]. In European Union (EU) countries, shift work is most common in the health care sector, with about one-third engaged in shift work [5].

Sleep and Atypical Patterns of Work as a Phenomenon of Professional Nursing Practice

Atypical work schedules of nurses in hospital sector were arranged as a result of two conflicting problems: the growing demands for higher quality patients' care and the global phenomenon of health-systems financial constraints that require "maximum effective work with a minimum staffing". Thus, extended work shifts of twelve hours, or longer, which began towards the end of the 80's, have now become omnipresent within nursing [7], creating over-demanding work environment for nurses. They have to provide care for a large number of patients, often with no breaks, or a rest during working hours, as well as without sufficient hours of rest between shifts [8]. Consequently, nursing staff are often fatigued and uncertain about whether they are able to make sound judgments to provide adequate care for patients, prompting them to leave nursing profession. All remaining nurses are forced into working overtime, and workload increases due to a staff shortage, thus completing what has been described as the vicious cycle [9].

Secondary analysis of data collected from eight countries, as a part of longitudinal NEXT study, has revealed that over 50% of nurses work night shifts, whereby in France most nurses (15.6%) work a permanent night shift, whereas the highest number of nurses working rotating night shifts has been found in Slovakia (70.8%) and Poland (68.4%) [10]. According to data survey conducted by the American Nurses Association (ANA), 53% of nurses work unplanned overtime, 55% work more than 40 hours per week [11], while 9% work more than 60 hours per week [9]. Despite recommendations and even legal provisions in certain countries (the United States of America) limiting the shift length to 12 hours and prohibiting overtime except in emergency situations, they are used very flexibly, depending on the approval of the hospital or the decisions made by the nurses themselves, regarding their overtime work [12]. Nurse mandatory overtime regulations do not limit nurses' voluntary overtime work hours [9]. Their 12- hour shift is actually more than 13 hours in length- either to complete documentation, admit a new patient, report shift handover, assist a colleague, to increase their income, or to accumulate more days off in a row [7].

Regardless of whether nurses are motivated by altruism, a sense of responsibility, fear of job loss, or monetary gain, they risk their health and safety when they are sleep-deprived and chronically tired. Data analysis from a study done by Geiger-Brown et al. showed that daily sleep time for day- and night-shift nurses was 5.7/5.2 hours following a first 12-hour shift, and 7.7/5.5 hours following a second

consecutive 12-hour shift [7]. More than 29% of the 11,387 shifts studied were staffed by nurses who had slept fewer than six hours before starting work [9]. Similarly, results of a multicenter study conducted in Brazil in 2,518 nurses, report a short sleep duration in 70.1% of participants, while insomnia was reported by 48.6% [13]. Another Brazilian study of 264 hospital nurses shows that 56.1% of nurses reported sleep disorder. The same study indicated a negative correlation between the quality of sleep and the quality of life [14]. A study carried out in nurses from four general hospitals in Taiwan has revealed that 82.3% of those working shifts have poor sleep quality [15].

Sleep problems in hospital nurses related to work arise from discrepancies between altered sleep/wake patterns, internal timing mechanisms, and external environment and demands it imposes. Various atypical working time arrangements of hospital nurses such as overtime, permanent night shift, rotating shift work patterns with a large number of night shifts and short rest periods between work shifts, can result in circadian non-compliance, sleep disorders and fatigue [16, 17]. The study carried out in the nurses in the Emergency Centre of Vojvodina has also revealed that the intensity of work-related fatigue affects sleepiness in nurses [3]. In fact, nurses working shifts are forced into working and sleeping at times that conflict with normal social and biological patterns [17].

Mechanisms of Sleep Regulation

The cycle of sleep-wakefulness is a natural part of human life, which includes sleep through the night and wakefulness during the day [18]. Our sleep pattern is governed by two basic physiological processes: a) homeostatic sleep pressure is referred to the pressure of sleep after consecutive hours of wakefulness and makes us more wakeful as the day progresses; b) the circadian body clock promotes wakefulness at usual times for everyday activities, as well as sleepiness at the usual bedtime. [19]. Thus, the homeostatic system tends to make us sleepier as time goes on, whereas circadian wake-promoting signal prevents us from falling asleep.

Circadian modulation of sleep pressure, or circadian variations in susceptibility to sleep, primarily depend on the signal from the circadian pacemaker located in the hypothalamic suprachiasmatic nuclei, which is in the close interaction with various environmental and social markers [20]. Suprachiasmatic nuclei receive light intensity–dependent signals [21], interpret them, then pass on signals to the pineal gland, which in response secretes more or less of the hormone melatonin. [22]. Inhibition of suprachiasmatic nuclei released in the dark phase leads to increased secretion of melatonin, which, in turn, promotes transition to sleep and sleep onset [23]. Light stimulates the suprachiasmatic nuclei via the suppression of melatonin production, and in response to hypothalamic-pituitary-adrenal axis activation stimulates increased cortisol levels, helping to wake up in the morning [24]. The circadian wake-promoting signals decrease during the evening hours with an increase of homeostatic sleep pressure, resulting in the onset of sleep [20].

Therefore, altered levels of melatonin due to prolonged exposure to light result in desynchronization between the internal hormonal environment and external environment, explaining poor sleep quality of nurses working night shifts [23]. Consequently, nurses experience misalignment of their circadian rhythms in relation to their rotating schedules, particularly at night, attempting to work and sleep at the "wrong circadian phase". Their homeostatic and circadian sleep systems no longer act synergistically to maintain the adequate sleep-wake relationship and they have to fight to stay awake during the night, faced with the increase in homeostatic sleep pressure and absence of wake-promoting signal from suprachiasmatic nuclei [22]. Only a small number of nurses are able to adjust their circadian rhythm with a sleep/wake ratio as required by their profession, while the majority of them in different ways deal with the problems that result from shift work by experiencing various inconveniences and disturbances. Getting enough rest after a night shift can help to alleviate sleep disorders in nurses working rotating shifts [23]. However, short breaks between shifts can accumulate sleep deprivation over several consecutive nights resulting in sleep debt mounting. Thus, further increasing fatigue and sleepiness involve decline in performance and increased risk of accidents and errors [20].

Effects of Acute and Chronic Sleep Deprivation on Cognitive Performance

Failure to satisfy the needs for both adequate and appropriately timed sleep can result in a noticeably reduced ability to learn, remember, use sound judgment, focus effectively and perform tasks safely [11], particularly those that require intensive, or prolonged attention [25].

Sleep loss changes the activity of the prefrontal cortex involved in higher-order cognitive processing, such as decision-making. Consequently, sleepy nurses can be prone to use inadequate algorithms for decision making [26] and routinely solving a problem, and they can fail to identify available alternatives clearly, which increase the likelihood of risky decisions and adverse outcomes for patients [19, 25, 26]. Communication skills decrease as sleep deprivation increases. The nurse may have trouble finding the right word, or properly interpret what others have said, or written. This can lead to nurses' misjudgment of situation, and result in avoiding communication, or communicating inadequately [25].

Overworked nurses tend to make mistakes in judgment thus causing medication errors, negligent patients' care and accidents [26]. Studies have shown that nurses who work 12-hour shifts when compared to those who work 8-hour shifts nearly triple the chance of making an error [25]. Bjørnevatn et al., [18] by referring to Scott et al. study of inten-

sive care unit nurses, conducted in the United States, suggest that during the 28-day study period errors were reported in 27% of nurses, "almost error" in 38% and 20% of nurses fell asleep at least once during that period. Alertness, concentration and caution, crucially important to provide safe and high-quality care, have been lowered in sleep-deprived and overworked nurses. A study conducted in Norway shows that unintended sleep episodes at work occur eight times more frequently in nurses working in intensive care than in women from a Norwegian general population sample [18].

Additionally, sleep deprivation and fatigue in nurses is an important public health issue. Due to their demanding work schedules, sleep-deprived nurse fatigue becomes a potential hazard to nurses themselves, and other road users [25]. Eanes [11], citing a study by Scott et al. conducted in the United States, said that during the four-week study period, 67% of nurses in night shifts reported at least one episode of drowsy driving home, and 2.4% reported having experienced drowsy driving after every shift. According to the results of a Swedish study, 25% of the night shift nurses were sleepy while they were getting themselves ready to drive home [7].

Sleep Loss and Health Related Disorders in Nurses

Sleep Loss and Obesity

In addition to poor dietary habits, increased caloric intake and lack of exercise, sleep loss is considered to be a potential risk factor for obesity. Those who consistently sleep less than 6 hours in a 24-hour period are significantly more likely to have a higher body mass index (BMI) [11]. The data of cross-sectional study of 2,103 nurses, conducted in the United States, suggested that irregular shifts, working extended hours, poor eating habits and sleep insufficiency were related to obesity in nurses [27]. Low levels of hormone leptin (appetite-suppressing hormone) and high levels of ghrelin (appetite stimulant) in the serum of individuals have been associated with sleeping less than seven hours a day, which may explain an increased hunger and intake of calorie-dense foods and obesity in those with insufficient sleep [11].

Sleep Loss and Diabetes

Researchers believe that chronic, partially reduced sleep may increase the risk of diabetes independent of changes in BMI [11]. Twenty years of research which included the 177,000 nurses within the Nurses' Health Study showed that the major risk factor for type 2 diabetes increased with the number of years of shift work. Nurses with 1-2 years of shift work had a 5% higher risk than those who did not work in shifts, while the risk was 60% higher in nurses with more than 20 years of shift work [28]. Chronic sleep loss may lead to persistent insulin resistance and hyperinsulinemia, resulting in excess plasma glucose, which ultimately increases the risk of diabetes [29]. In addition, short sleep duration alter the secretion of growth hormone, elevate the cortisol level and increase the sympathetic tone, all of which affect the activity and release of insulin [11].

Sleep Loss and Disorders of the Gastrointestinal Tract

Chronic disruption of biological rhythms due to shift work has been associated with the development of serious gastrointestinal disease. The results of a study conducted in Michigan showed significantly higher prevalence of inflammatory bowel disease in nurses working rotating night shifts than in day shift nurses [30]. In addition, nurses who work the night shift have a higher incidence of peptic ulcers and disorders, such as constipation and diarrhea [29].

Sleep Loss and Cardiovascular Problems

The onset of arterial hypertension due to disturbed circadian rhythm of blood pressure and diabetogenic profile potentiates atherosclerosis and can cause a cardiovascular disease (CVD) [31]. Studies have shown that prolonged sleep deprivation increases the risk of developing CVD and induces insulin resistance by augmenting proinflammatory cytokine production (interleukin-6) [32, 33]. In addition, higher rates of obesity and cigarette smoking may contribute to increasing the risk of CVD in the shift worker population [29]. In a Brazilian study which included 620 nurses, the prevalence of CVD was 18% and 21% of nurses who worked only day shift and those who worked only night shift, respectively. The presence of nocturnal sleep disorders increased the probability of occurrence of CVD 2.79-fold, while the presence of the nocturnal and diurnal sleep disturbances increased this probability 3.07-fold [34].

Sleep Loss and Risk of Malignant Diseases

According to the data from the Nurses' Health Study showed that the nurses who had been working at least three rotating night shifts a month for 15 years, or more, had a significantly greater risk of developing colorectal cancer as compared with nurses who did not report working rotating night shifts [30]. The nurses who reported more than 20 years of rotating night shift work were 1.79 times more likely to have an increased risk of breast cancer than nurses who never worked shifts [29]. It has been accepted that the risk of cancer increases as a result of the reduced levels of melatonin production at night [11, 29, 33–35]. The decline in melatonin secretion levels leads to immunosuppression including the reduced natural killer cells activity (NK), which can also be one of the variables affecting the increased cancer risks in the studied population [33].

Conclusion

Long or more frequent shifts reduce the chances for nurses to get enough sleep and decrease the length of recovery time between shifts. Despite speci-

fic recommendations that nurses working shifts in any day do not exceed 12 hours, these recommendations, as well as legal provisions, are being slowly adopted and flexibly interpreted. These data are worrisome since the degree of sleep loss is associated with significant adverse effects on the overall safety, health and well-being of nurses, as well as neurocognitive dysfunction which may have negative implications for patients' safety and can have adverse consequences on the quality of care delivered as well.

Numerous studies have shown a high prevalence of sleep disorders among shift working nurses, but on the other hand, in our country, it has been an underrecognized and underestimated problem both from a research and a clinical point of view. Thus, further research is required to assess the association between the sleep quality and health related quality of life in nurses in order to clarify the observed problem.

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BIBLID.0025-8105:(2016):LXIX:5-6:183-188.

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Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

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Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

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∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

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Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

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CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG*, *GIF*, *TIFF*, *EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

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A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

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