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SADRŽAJ

ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

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ASTHMA PREVALENCE AND THE IMPACT OF NUTRITIONAL STATUS ON PRESCRIBED ASTHMA MEDICATIONS IN CHILDREN

UČESTALOST ASTME I UTICAJ NIVOA UHRANJENOSTI NA PREPISANE LEKOVE ZA ASTMU KOD DECE

Vesna PETROVIĆ[1], Vesna VUJIĆ ALEKSIĆ[2, 3], Tanja ROŽEK MITROVIĆ[1] and Aleksandra HRISTOV[1]

Summary

Introduction. Asthma and obesity are the most common chronic health disorders in children. Although heredity plays a significant role in their development, environmental factors and early exposure have contributed to the increasing incidence of both disorders in recent decades. The aim of the study was to estimate asthma prevalence in schoolchildren in Inđija, Srem District, Serbia, and to investigate differences in nutritional status of children with asthma as well as differences between their nutritional status and prescribed asthma medications. **Material and Methods**. A cross-sectional retrospective cohort study was conducted at the Primary Health Center in Inđija. Of all the medical records of children aged 6 - 14 years, a cohort of children with asthma was formed. The retrospective study evaluated their nutritional status and the prescribed asthma medications. **Results.** The prevalence of asthma in children aged 6 - 14 was 6.9%. Children with asthma were significantly more overweight and obese (40.5%) than children without asthma. Boys accounted for 63.7% of children with asthma, with a statistically significant gender difference. Abnormal nutritional status was found in 44.3% of children with asthma and boys with asthma were significantly more obese (23%) compared to girls (7.8%). Overweight and obese children with asthma were not prescribed significantly more medications to relieve asthma symptoms than normal-weight children. **Conclusion.** The prevalence of asthma among schoolchildren in Inđija was 6.9%. Children with asthma were more likely to be overweight and obese than children without asthma, whereas boys with asthma were significantly more obese than girls. No significant differences were found between their nutritional status and prescribed asthma medications.

Key words: Asthma; Nutritional Status; Therapeutics; Obesity; Overweight; Child; Primary Health Care; Prevalence

Sažetak

Uvod. Astma i gojaznost su najčešći hronični zdravstveni poremećaji kod dece. Iako nasleđe ima značajnu ulogu u njihovom razvoju, spoljni faktori i rana izloženost doprinose povećanju učestalosti oba poremećaja poslednjih decenija. Cilj rada bio je da se proceni prevalencija astme kod dece školskog uzrasta u Inđiji, Srem, Srbija i da se istraži različitost nutritivnog statusa kod dece sa astmom kao i razlike između njihovog nutritivnog statusa i lekova propisanih za astmu. **Materijal i metode.** U Domu zdravlja Inđija sprovedena je retrospektivna kohortna studija preseka. Od svih zdravstvenih kartona dece uzrasta 6–14 godina formirana je kohorta dece sa astmom u kojoj je retrospektivno praćen nutritivni status i propisani lekovi za astmu. **Rezultati.** Prevalencija astme kod dece uzrasta 6−14 godina bila je 6,9%. Deca sa astmom su bila više prekomerno uhranjena i gojazna (40,5%) od dece bez dijagnoze astme. Dečaci su činili 63,7% dece sa astmom, sa statistički značajnom razlikom po polu. Abnormalan nutritivni status bio je prisutan kod 44,3% dece sa astmom, a dečaci sa astmom su bili znatno gojazniji (23%) u poređenju sa devojčicama (7,8%). Prekomerno uhranjenoj i gojaznoj deci nije propisano znatno više lekova za olakšanje simptoma astme ili lekova za kontrolu astme u odnosu na normalno uhranjenu decu. **Zaključak.** Prevalencija astme kod dece školskog uzrasta u Inđiji iznosila je 6,9%. Deca sa astmom češće su imala prekomernu telesnu masu i gojaznost u odnosu na populaciju dece koja nisu obolela od astme, a dečaci sa astmom su bili značajno gojazniji nego devojčice. Nisu pronađene značajne razlike između njihovog nutritivnog statusa i propisanih lekova za astmu.

Ključne reči: astma; nutritivni status; terapija; gojaznost; prekomerna težina; dete; primarna zdravstvena zaštita; prevalenca

Introduction

Asthma and obesity are two of the most prevalent chronic disorders in children with a great impact on public health. The prevalence of overweight and obesity among children has been rapidly increasing over the past 20 years and it is the same period in which the increase in asthma prevalence has occurred [1].

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Abbreviations
ICD – International Classification of Diseases
BMI – body mass index

Asthma is a common, chronic respiratory disease affecting 1 – 18% of the population in different countries [2]. The majority of pediatric asthma presents before the age of 5 and has a strong familial aggregation [3]. Childhood asthma is more common in boys, while adult asthma is more common in women [4].

Changes in lifestyle such as diet, physical activity, and early life exposure are likely to be important factors contributing to the increase in the prevalence of both asthma and obesity [5, 6]. A physical or mechanical effect of obesity on the respiratory system seems likely to play a role in the obesity-asthma association [7]. Both conditions are characterized by chronic tissue inflammation, which includes numerous, although different inflammatory markers which may increase the bronchial responsiveness in patients with asthma [8]. Obesity is both a major risk factor and a disease modifier of asthma in children [5]. Although overweight/obesity and childhood asthma are associated, the causal pathway and temporal aspects of this relationship remain unanswered and deserve further epidemiological investigation [9]. Understanding the relationship between obesity and asthma may lead to new therapeutic strategies [10].

The aim of this study was to estimate asthma prevalence in children aged 6 – 14 in Inđija, Srem District, Serbia, in 2019, and to investigate differences in nutritional status of children with asthma as well as differences between their nutritional status and prescribed asthma medications.

Material and Methods

A cross-sectional retrospective cohort study was conducted at the Primary Health Center "Dr. Milorad Mika Pavlović", Inđija. Inđija is a town and a municipality located in the Srem District of the Autonomous Province of Vojvodina, Serbia. In 2011, the town had a total population of 26,025, while the municipality had 47,433 inhabitants [11]. The Pediatric Department of the Primary Health Center had approximately 6,850 medical records of children aged 0 – 18 years in the study period, out of which 3,263 children were born during 2005 – 2013.

All medical records, whether paper-based or electronic, of children born from 2005 to 2013, were reviewed during one month (February 1 to February 29, 2020) to identify children with the diagnosis of asthma using the International Classification of Diseases (ICD)-10 (J45) that were documented by evidence of pediatric pulmonologist's report. Out of these, the study included only children who visited the Pediatric Department at least once during the previous year (January 1 to December 31, 2019). Exclusion criteria were children whose height and/or weight were not recorded during the previous year. Out of the 3,263 children born from 2005 to 2013, 1,625 (49.8%) were boys and 1,638 (50.2%) were girls. During the 2019, the children's height and weight were recorded in 2,802 medical records.

Medical records of children that met the inclusion criteria formed a cohort and were reviewed. Patient descriptive characteristics including the year of birth, sex, height, weight, age at which asthma was diagnosed, as well as prescribed asthma medications and data regarding referral to a hospital due to asthma exacerbations (J45-J46) during the previous year (January 1 to December 31, 2019) were extracted.

There were 226 children diagnosed with asthma, out of which 221 met the inclusion criteria. The children whose height and/or weight were not recorded during the previous year were excluded (n=9), leaving 212 children with asthma to be included in the study.

In 2019, the Pediatric Department had 15,760 curative care visits of children born from 2005 to 2013, out of which 867 (5.5%) were due to asthma diagnosis (J45-J45.9 and J46 according to ICD-10). Consequently, the average number of visits to a primary care pediatrician per child aged 6 – 14 with asthma diagnosis was 3.9.

The classification of nutritional status was based on body mass index (BMI). The BMI was calculated by dividing the child's weight in kilograms by the square of height in meters. The cut-offs used to define underweight, normal, overweight, and obesity in children and adolescents are different from those used in adults and vary by age and sex because of the natural growth in childhood and adolescence. Underweight is defined as a BMI below the 5th percentile, normal weight is defined as BMI at or above the 5th percentile and below the 85th percentile, overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile, and obesity is defined as a BMI at or above the 95th percentile for children and teens of the same age and sex [12].

Prescribed asthma medications were identified and categorized as reliever medications (salbutamol, fenoterol/ipratropium bromide), controller medications (fluticasone propionate, budesonide, fluticasone/salmeterol, budesonide/formoterol, montelukast), or both. If no asthma medication was prescribed, it was categorized as "no therapy".

Asthma prevalence in 2019 was calculated as the proportion of children diagnosed with asthma in the population of children born from 2005 to 2013 based on sex and age. Differences between groups were calculated by the chi-square test. The p-value of < 0.05 was considered significant. The data were analyzed using Statistical package for the social sciences for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA).

The study was approved by the Ethics Committee of the Primary Health Center "Dr. Milorad Mika Pavlović", Inđija.

Results

The demographic and clinical characteristics of the total number of children with and without asthma are summarized in **Table 1**. The children with asthma were significantly more overweight/obese (40.5%)

Table 1. Descriptive characteristics of the total population of children, with and without asthma
Tabela 1. *Deskriptivne karakteristike ukupne populacije dece, dece koja nisu i dece koja su obolela od astme*

Variable/*Varijabla*	Total/*Ukupno*		Asthma No/*Astmu nema*		Asthma Yes/*Astmu ima*		p*
No/*Broj*	2802		2590		212		
Mean years/*Prosečna starost*	9.9		9.8		10.0		
Sex/*Pol*	No/*Br.*	%	No/*Br.*	%	No/*Br.*	%	
Boys/*Dečaci*	1326	47.3	1191	46.0	135	63.7	0.000
Girls/*Devojčice*	1476		1399	54.0	77	36.3	
Nutritional status/*Status uhranjenosti*		52.7					
Underweight/*Pothranjenost*	75	2.7	67	2.6	8	3.8	0.002
Normal weight/*Normalna uhranjenost*	1850	66.0	1732	66.9	118	55.7	
Overweight/*Prekomerna uhranjenost*	453	16.2	404	15.6	49	23.1	
Obesity/*Gojaznost*	424	15.1	387	14.9	37	17.4	
Other/*Ostalo*							
Asthma Dg. < 5 age/*Dg. astme pre 5. g.*	122	4.35	0	0	122 57.5		
Referral to hospital (J45/J46) *Upućivanje u bolnicu J45/J46*	19	0.68	0	0	19 8.9		

*Statistically significant difference at $p < 0.05$/**Statistički značajna razlika kada je p < 0,05*

than children without asthma (30.5%), ($\chi^2 = 9.16$, $p < 0.05$). Boys developed asthma more frequently than girls ($\chi^2 = 24.6$, $p < 0.001$) (**Table 1**). The nutritional status of children with asthma is shown in **Table 2.**

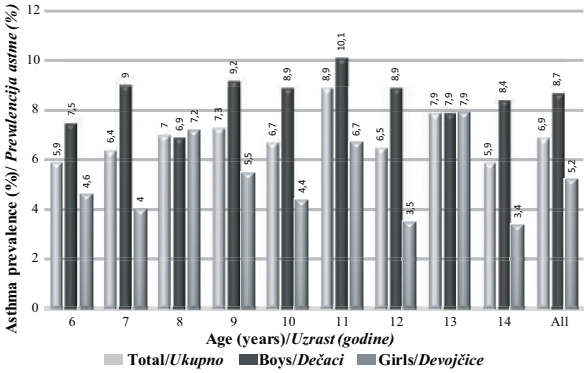
Table 2. Nutritional status and sex distribution of children with asthma referred to hospital
Tabela 2. *Nutritivni status i upućivanje na bolničko lečenje dece obolele od astme po polu*

Variable/*Varijabla*	Total/*Ukupno*		Boys/*Dečaci*		Girls/*Devojčice*		p*
	No/*Br.*	*%*	No/*Br.*	*%*	No/*Br.*	*%*	
	212	100	135	63.7	77	36.3	0.000
Nutritional status/*Status uhranjenosti*							
Underweight/*Pothranjenost*	8	3.8	6	4.4	2	2.6	
Normal weight/*Normalna uhranjenost*	118	55.7	69	51.1	49	63.6	
Overweight/*Prekomerna uhranjenost*	49	23.1	29	21.5	20	26.0	
Obesity/*Gojaznost*	37	17.4	31	23.0	6	7.8	0.005
Referral to hospital J45/J46/*Upućivanje u bolnicu J45/J46*							
Total/*Ukupno*	19	8.9	12	8.9	7	9.0	
Underweight/*Pothranjeni*	0	0	0	0	0	0	
Normal weight/*Normalno uhranjeni*	10	52.6	5	41.7	5	71.4	
Overweight/*Prekomerno uhranjeni*	4	21.1	3	25.0	1	14.3	
Obesity/*Gojazni*	5	26.3	4	33.3	1	14.3	

*Statistically significant difference at $p < 0.05$/**Statistički značajna razlika kada je p < 0,05*

Table 3. Prescribed asthma medications in regard to the nutritional status of children with asthma in 2019
Tabela 3*. Propisani lekovi za astmu prema statusu uhranjenosti dece sa astmom u 2019. godini*

The nutritional status *Status uhranjenosti*	Total *Ukupno*		Underweight *Pothranjenost*		Normal weight *Normalna uhranjenost*		Overweight *Prekomerna uhranjenost*		Obesity *Gojaznost*	
	No/*Br.*	*%*	No/*Br.*	*%*	No/*Br.*	*%*	No/*Br.*	*%*	No/*Br.*	*%*
	212	100	8	3.8	118	55.7	49	23.1	37	17.4
Asthma medications/*Lekovi za astmu*										
Reliever/*Lekovi za olakšanje simptoma*	54	25.5	2	25.0	29	24.6	14	28.6	9	24.3
Controller/*Lekovi za kontrolu astme*	41	19.3	3	37.5	22	18.7	7	14.3	9	24.3
Both/*Oba*	76	35.9	2	25.0	39	33.0	23	46.9	12	32.5
No therapy/*Bez terapije*	41	19.3	1	12.5	28	23.7	5	10.2	7	18.9



Graph 1. Prevalence of asthma by age and sex in 2019
Grafikon 1. *Prevalencija astme prema uzrastu i polu u 2019. godini*

Abnormal nutritional status was found in 94 (44.3%) children with asthma. Boys with asthma were more obese (31/135; 23%) than girls (6/77; 7.8%) and that was statistically significant ($\chi^2 = 7.83$, $p < 0.05$). No sex difference was found regarding referral to hospital due to asthma exacerbations (boys 12/135; 8.9% and girls 7/77; 9%). According to the nutritional status, 9 (47.4%) children with asthma who were referred to hospital were overweight and obese and 10 (52.6%) were normal-weight children. Overweight and obese boys (7/60; 13.2%) were more often referred to hospital than girls (2/26; 7.7%) (**Table 2**). The majority of children (122/212; 57.5%) were diagnosed with asthma before the age of 5 (**Table 1**). Asthma prevalence in 2019 was 6.9%, 8.7% in boys and 5.2% in girls, and the sex distribution is shown in **Graph 1.**

Some kind of asthma medication was prescribed to 81 (86.2%) children with abnormal nutritional status, and to 90 (76.3%) normal-weight children (**Table 3**). Asthma controller medication, alone or in combination with reliever, was prescribed to 51 (59.3%) overweight and obese children, as well as to 61 (51.7%) normal-weight children, and even to 5 (62.5%) underweight children. No significant differences were found between the nutritional status and prescribed asthma medications. However, only 14% of overweight and obese children with asthma were without any prescribed asthma therapy compared to 23.7% of normal-weight children.

Discussion

Asthma is the most common chronic disease in childhood. In the United States, 8.3% of children in 2016 and 1 in 12 children in 2017 had asthma [13, 14]. The study of Živković et al. showed that prevalence of childhood asthma ranged from 2.5% to 9.8% in Serbia and Montenegro [15]. The prevalence of asthma in children in the European Union was 9.4% in 2015 [16]. The prevalence of asthma in children born from 2008 to 2013 in our study was 6.9%, that is, 1 in 15 children had asthma in 2019.

Pre-pubertal boys have a higher asthma incidence, prevalence, and hospitalization rate than girls of the same age, but this trend reverses during adolescence [4]. The reversal of this sex difference in asthma prevalence occurs around puberty, suggesting that sex hormones may play a role in the etiology of asthma [17]. Our study also showed that asthma is significantly more common in boys, given that 1 in 12 boys had asthma, compared to 1 in 21 girls in the study population.

Being underweight, overweight, or obese during childhood and adolescence is associated with adverse health consequences throughout the life-course [18]. Early interventions for children with asthma and/or wheezing may be warranted to prevent a vicious cycle of worsening obesity and asthma that could contribute to the development of other metabolic diseases, including prediabetes and type 2 diabetes later in life [19]. In girls, becoming overweight or obese between the ages of 6 and 11 has been found to increase the risk of developing asthma and to increase bronchial responsiveness during adolescence [20]. Some studies have shown that obese subjects are at an increased risk of asthma, and obese asthmatics have more symptoms, more frequent and severe exacerbations, reduced response to several asthma medications, and decreased quality of life [10]. In patients with obesity and asthma, asthma may occur first and then lead to a higher risk of obesity due to reduced exercise or to frequent corticosteroid therapy [3]. Diet-induced weight loss in children has also been shown to improve asthma control, but without significant changes in airway inflammation [21]. Our study showed that 17.4% of children with asthma were obese, and boys with asthma were significantly more obese.

The study which compared the nutritional status of healthy children and children with asthma showed that there were considerably less normally nourished children, and considerably more underweight and overweight children in the asthmatic group, showing that the two groups differ in the level of growth and development to a certain extent [22]. In our sample, abnormal nutritional status was found in 44.3% of children with asthma.

According to the current asthma guidelines, asthma with obesity is identified as an asthma phenotype where some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation. In the future, some phenotype-guided treatments are expected to be available but this requires further research, especially in children [2]. Some childhood asthma programs showed that overweight and obese children with asthma had a reduced response to inhaled corticosteroids leading to increased prednisone courses and moderate-to-severe exacerbations [23]. On the other hand, some studies showed no association between nutritional status and severity of asthma [24]. In our study, approximately 40% of children with asthma were overweight and obese, but did not get significantly more prescribed asthma medications nor were they referred to hospital more often when compared to normal-weight children. However, our results suggest that overweight and obese children

with asthma are less likely to be without any prescribed asthma medications. This may imply that these children are more symptomatic or have more severe asthma compared to normal-weight children. Asthma reliever medication, alone or in combination with a controller, was prescribed to 67.4% of overweight and obese children in comparison with 57.6% of normal-weight children in our study that may support the previous implication. On the other hand, no prescribed asthma medication could also be due either to good asthma control, or these children had a history of asthma. Regarding the choice of reliever medications, we found fenoterol-ipratropium bromide prescribed to a high number of children, despite the fact that fenoterol is not recommended in current guidelines and ipratropium bromide is not recommended for long-term use [2]. This, however, demands further investigation that is out of the scope of this study.

Age-standardized admission rates for asthma (all ages) in Serbia, 2011 – 2015 were approximately 130 per 100,000, and the mortality rate (ages 5 – 34) for the same period was under 2% [25]. In the United States, asthma is the third-ranking cause of hospitalization among children younger than 15 years [26]. In our research, 9% of children with asthma were referred to secondary or tertiary health care for asthma exacerbation in 2019, 1 in 9 overweight and obese children, and 1 in 12 normal-weight children.

There are several limitations that should be considered in interpreting these results. Medical records included limited data, which enabled further stratification (for example, no data on measures of pulmonary function). The relatively small study sample limited our ability to find proper associations between asthma and overweight and obesity. Conducting cross-sectional study enabled assessing changes in asthma severity and BMI which could be interconnected. Adherence to therapy and additional therapy, were not considered.

Despite the limitations, our study has several strengths. To the best of authors' knowledge, this is the first study examining the possible association between nutritional status and prescribed asthma medications in children in Serbia. Additional strengths of this study include the availability of asthma diagnosis made by a pediatric pulmonologist, rather than reliance on self-reports as well as the availability of asthma-specific prescriptions. This study can serve as a basis for future studies with larger study samples in Serbia.

Conclusion

The prevalence of asthma among children aged 6 – 14 in Inđija, Srem District, Serbia, was 6.9% in 2019. Children with asthma were more overweight and obese than children without asthma. It was more common in boys, and boys with asthma were significantly more obese than girls. In our study, no significant differences were found between nutritional status of children with asthma and prescribed asthma medications.

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PATIENTS' ATTITUDES TOWARD SEASONAL INFLUENZA IMMUNIZATION

STAVOVI PACIJENATA O IMUNIZACIJI PROTIV SEZONSKOG GRIPA

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Summary

Introduction. Immunization is an important measure in the prevention of diseases that can seriously endanger health of the population. The aim of the study was to determine the attitudes of the adult population toward seasonal influenza immunization. **Material and Methods.** This cross-sectional prospective study including 160 adult subjects of both sexes was conducted from November 15, 2019 to December 15, 2019 at the General Medicine Department of the "Liman" Health Center, Novi Sad, Serbia. The respondents filled out a questionnaire, specifically designed for this purpose. The collected data were used to analyze the influence of gender, age and employment status on personal attitudes toward seasonal influenza immunization. **Results.** The study included 160 examinees, 74 (46.2%) men and 86 (53.8%) women, average age of 63 years. There were 88 (55%) employed and 72 (45%) unemployed participants. Of 160 participants, 113 (72.4%) had a positive attitude toward vaccination, 20 (12.8%) had a negative attitude, while 23 (14.7%) respondents were undecided. No statistically significant difference was established between the sexes in attitudes toward immunization. Vaccination coverage was higher in unemployed compared to employed subjects (75% vs. 59.1%; $p < .05$). Unemployed respondents were more regularly vaccinated than the employed examinees (66.1% vs. 46.7%; $p < .05$). **Conclusion.** Higher vaccination coverage rates for planned immunizations against seasonal influenza can be achieved through better promotion strategies and health education of the population.

Key words: Influenza Vaccines; Immunization; Influenza, Human; Patient Acceptance of Health Care; Health Knowledge, Attitudes, Practice; Surveys and Questionnaires

Sažetak

Uvod. Vakcinacija predstavlja važnu meru u prevenciji bolesti koje mogu ozbiljno ugroziti zdravlje populacije. Cilj istraživanja bio je utvrđivanje stavova odrasle populacije prema imunizaciji protiv sezonskog gripa. **Materijal i metode.** Prospektivna studija preseka obuhvatila je 160 ispitanika, oba pola, a istraživanje je sprovedeno u periodu od 15. 11. 2019. do 15. 12. 2019. godine u Službi opšte medicine na odeljenju „Liman" Doma zdravlja „Novi Sad", Srbija. Ispitanici su popunjavali upitnik, posebno konstruisan za potrebe ovog istraživanja. Analiziran je uticaj pola, starosti i radnog angažovanja na stav o imunizaciji protiv sezonskog gripa. **Rezultati.** U istraživanju je učestvovalo 160 ispitanika, prosečne starosti 63 godine. Uzorak su činili 74 (46,2%) muškaraca i 86 (53,8%) žena. Radno aktivnih bilo je 88 (55%), a radno neaktivnih 72 (45%) ispitanika. Pozitivan stav o vakcinaciji imalo je 113 (72,4%), negativan stav 20 (12,8%), dok je neodlučnih bilo 23 (14,7%) ispitanika. Nije potvrđena statistički značajna razlika u stavu prema vakcinaciji među polovima. Obuhvat vakcinacijom je veći kod radno neaktivnih ispitanika u odnosu na radno aktivne (75% vs 59,1%; $p < 0,05$). Radno neaktivni ispitanici se redovnije vakcinišu u odnosu na radno aktivne (66,1% vs 46,7%; $p < 0,05$). **Zaključak.** Povećanje odziva na planirane imunizacije protiv sezonskog gripa može se postići boljom informisanošću i znanjem stanovništva.

Ključne reči: vakcine protiv sezonskog gripa; imunizacija; grip; prihvatanje zdravstvene zaštite od strane pacijenta; znanje o zdravlju, stavovi, praksa; istraživanja i upitnici

Introduction

Influenza is an important public health problem, since it causes significant morbidity and mortality, especially in high-risk groups and among the elderly [1, 2]. In the United States, influenza is estimated to result in 115,000 – 630,000 hospitalizations and 5,000 – 27,000 deaths annually [3, 4]. According to the data published by the World Health Organization (WHO), influenza epidemics result in about 3 – 5 million cases of severe illness and about 290,000 – 650,000 deaths worldwide each year [5, 6]. The European Centre for Disease Prevention and Control (ECDC) similarly estimates that, each year, between 4 and 50 million people in Europe experience symptomatic flu, with 15,000 – 70,000 related deaths [7, 8]. Although influenza affects all age groups [9], the elderly are more vulnerable, since influenza may cause exacerbation of the underlying chronic conditions. Influenza can also induce res-

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piratory, cardiovascular and neurological complications, especially in older patients [10]. Thus, immunization is an essential tool in the prevention of these adverse outcomes. It also contributes to the reduction in sick leave rates and more optimal utilization of healthcare resources, while decreasing antibiotic use and lessening the risk of complications, hospitalizations and influenza-related deaths [11]. Although seasonal flu vaccine is accessible to Serbian population [12], immunization rates vary considerably across age groups [13, 14]. While this disparity can be attributed to many factors, insufficient knowledge about seasonal flu and its potential adverse consequences, as well as the immunization procedure, especially among the elderly, is of particular concern [4, 15, 16].

Thus, the aim of the present study was to gain insight into the attitudes toward seasonal influenza immunization of adult patients attending the General Medicine Department of the "Liman" Health Center, Novi Sad, Serbia.

Material and Methods

This cross-sectional prospective study was conducted from November 15, 2019 to December 15, 2019 at the General Medicine Department of the "Liman" Health Center, Novi Sad, Serbia, and included 160 adult volunteers of both sexes aged 18 – 91 years. Prior to commencing the investigation, approval was obtained from the Institutional Ethics Committee. All participants signed informed consent and were assured that their involvement in the study would be anonymous. They completed a questionnaire designed specifically for this purpose that, in addition to demographic information, investigated their attitudes toward seasonal influenza immunization.

Statistical processing of the results included calculation of descriptive statistics and hypothesis testing. First, the age distribution numerical variable was examined via the Kolmogorov-Smirnov test. Conditions for normal distribution were not met, so non-parametric techniques were used for this variable. Depending on their nature, for other parameters of importance, frequencies, percentages, and sample mean values (median) were used. Statistical tests employed were also governed by the nature of the collected data, with the significance level set at $p < .05$. To test the differences between parameters, Kruskal-Wallis test was conducted in cases where the differences between three or more modalities of the categorical variable were examined with respect to the value of the numerical variable. On the other hand, to examine the differences between two modalities the Mann-Whitney U test was adopted. Relationships between two qualitative variables were examined via the χ^2 test. Statistical processing and analysis was performed using the Statistical Package for the Social Sciences ver. 24 for Windows.

Results

The average age of the sample, including 74 (46.2%) men and 86 (53.8%) women, was 63 years and 88 (55%) of those individuals were employed, as summarized in **Table 1**.

The analysis of participants' responses revealed that 66.3% were immunized at least once in their lifetime, while 55.5% reported regular vaccination against influenza. Specifically, 11.3%, 16%, 17.9% and 54.7% of those that have been previously immunized received one, two, three, and at least five vaccines, respectively. Attitudes toward immunization were largely positive (113; 72.4%), but 23 (14.7%) respondents were undecided, and 20 (12.8%) held negative views on vaccination. When asked about the main factors in their decision to get vaccinated against the flu, 47.8% of respondents indicated the information provided by health professionals, 31% reported fear of illness, while 7.1% did so because they got flu in the previous season. Media were the primary source of information for 11.5% of the sample, while 2.7% sought advice from friends. To establish whether men and women have different attitudes toward immunization, χ^2 test was conducted, revealing statistically significant differences in their reasons for immunization. Men primarily indicated the information provided by healthcare professionals (24.5%), and fear of illness (24.5%), followed by media campaigns (18.9%) and previous flu experiences (3.8%). Women provided the same responses, in different percentages, whereby 43.3% got immunized on the advice of their physician, 36.7% due to fear of illness, 10% because of previous flu experiences, and

Table 1. Sociodemographic characteristics of the study sample
Tabela 1. *Socio-demografske karakteristike uzorka*

	Total sample (%) N = 160/*Ukupan uzorak* (%) (N = 160)
Sex/*Pol*	
Male/*Muški*	74 (46.2%)
Female/*Ženski*	86 (53.8%)
Median age (range) (years)/*Prosečna starost (raspon) (godine)*	63.00 (19−91)
Employed/*Radno aktivni*	
Yes/*Da*	88 (55%)
No/*Ne*	72 (45%)

Legend/*Legenda*: N - number of total sample/*N – ukupan broj ispitanika*

Table 2. Distribution of responses by gender
Tabela 2. *Distribucija dobijenih odgovora po polu*

	Males/*Muški pol* (N = 74)	Females/*Ženski pol* (N = 86)	p	Total sample/*Ukupan uzorak* (N = 160)
Prior immunization, ever, N (%)/*Vakcinacija protiv gripa, ikada, N (%)*				
Yes/*Da*	54 (73%)	52 (60.5%)	>.05[a]	106 (66.3%)
No/*Ne*	20 (27%)	34 (39.5%)		54 (33.8%)
Regular influenza immunization, N (%)/*Redovna vakcinacija protiv gripa, N (%)*				
Yes/*Da*	38 (63.3%)	38 (49.4%)	>.05[a]	76 (55.5%)
No/*Ne*	22 (36.7%)	39 (50.6%)		61 (44.5%)
Number of previously received flu vaccines, N (%)/*Koliko ste puta do sada primili vakcinu protiv gripa, N (%)*				
One/*Jednom*	7 (13%)	5 (9.6%)	>.05[a]	12 (11.3%)
Two/*Dva puta*	10 (18.5%)	7 (13.5%)		17 (16%)
Three/*Tri puta*	10 (18.5%)	9 (17.3%)		19 (17.9%)
Five or more/*Pet i više puta*	27 (50%)	31 (59.6%)		58 (54.7%)
Attitude toward immunization, N (%)/*Stav o vakcinaciji, N (%)*				
Positive/*Za*	53 (74.6%)	60 (70.6%)	>.05[a]	113 (72.4%)
Negative/*Protiv*	11 (15.5%)	9 (10.6%)		20 (12.8%)
Undecided/*Neodlučan/na sam*	7 (9.9%)	16 (18.8%)		2 (14.7%)
Your motives for immunization, N (%)/*Šta je doprinelo odluci za vakcinaciju, N (%)*				
Fear of illness/*Strah od bolesti*	13 (24.5%)	22 (36.7%)	<.05[a]	35 (31%)
Information provided by healthcare professionals/*Informacija od strane lekara*	28 (52.8%)	26 (43.3%)		54 (47.8%)
Information received through media *Informacija od strane medija*	10 (18.9%)	3 (5%)		13 (11.5%)
Information provided by friends *Informacija od strane prijatelja*	0 (0%)	3 (5%)		3 (2.7%)
Previous flu experiences *Preležan grip prethodnih godina*	2 (3.8%)	6 (10%)		8 (7.1%)

Legend: N - sample size; p - statistical significance; [a]χ^2 - chi-square test
Legenda: N – broj ispitanika; p – statistička značajnost; [a]χ^2 – hi-kvadrat test

5% accepted the advice offered by the media or friends, as shown in **Table 2**.

Since participants' age ranged from 18 to 91 years, showing a considerable divergence (Kolmogorov-Smirnov test 0.090; p = .003), age-related differences were tested via nonparametric Mann-Whitney U test and Kruskal-Wallis test. Statistically significant differences were found between vaccinated (Me = 64.5) and non-vaccinated (Me = 57.5) groups (p < .01), indicating that older individuals were more likely to receive influenza immunization. Age difference between those who received flu vaccines regularly (Me = 67) and only sporadically (Me = 54) was also statistically significant (p < .001). Similarly, those who received flu vaccines five or more times were on average older (Me = 72.5) than individuals who received vaccines up to three times, as shown in **Table 3**.

A larger percentage of unemployed participants were vaccinated compared to the group of employed (75% vs. 59.1%) and this difference was statistically significant according to the χ^2 test (p < .05). It is also noteworthy that 66.1% of the unemployed received vaccines regularly, compared to only 46.7% of the employed participants. This difference is also statistically significant (p < .05). Similarly, those that were immunized against influenza five or more times were statistically significantly more likely to be unemployed (68.5% vs. 40.4%, p < .01), as shown in **Table 4**.

Discussion

Seasonal influenza is an important cause of substantial morbidity, mortality and socioeconomic burden and therefore it is subject to monitoring systems for infectious diseases [17, 18]. Seasonal influenza vaccination coverage among at-risk groups remains suboptimal in most developed countries [19–22] despite longstanding recommendations of public health organizations [23]. Awareness of the vaccine availability does not always guarantee vaccine uptake in a particular population [24]. The available evidence shows that individual vaccination decisions against seasonal influenza are governed by personal and social [23], as well as other factors [22]. Our study sample (N = 160) included 53.8% women and 46.2% men, with average age of

Table 3. Distribution of given responses by age groups
Tabela 3. *Varijable u odnosu na starosno doba ispitanika*

	Age (years)/*Starost (godine)*	p
Prior flu immunization, ever/*Vakcinacija protiv gripa, ikada*		
Yes/*Da*	64.5 (19−91)	<.01[a]
No/*Ne*	57.5 (21−81)	
Regular influenza immunization/*Redovna vakcinacija protiv gripa*		
Yes/*Da*	67.5 (19−91)	<.001[a]
No/*Ne*	54 (21−90)	
Number of previously received flu vaccines/*Koliko ste puta do sada primili vakcinu protiv gripa*		
One/*Jednom*	69 (22−90)	<.01[b]
Two/*Dva puta*	46 (29−82)	
Three/*Tri puta*	62 (26−82)	
Five or more/*Pet i više puta*	72.5 (19−91)	
Attitude toward immunization/*Stav o vakcinaciji*		
Positive/*Za*	64 (19−91)	>.05[b]
Negative/*Protiv*	59 (22−90)	
Undecided/*Neodlučan/na sam*	58 (21−81)	
Your motives for immunization/*Šta je doprinelo odluci za vakcinaciju*		
Fear of illness/*Strah od bolesti*	67 (29−86)	>.05[b]
Information provided by healthcare professionals/*Informacija od lekara*	63 (19−90)	
Information received through media/*Informacija od medija*	61 (22−91)	
Information provided by friends/*Informacija od prijatelja*	65 (64−72)	
Previous flu experiences/*Preležan grip prethodnih godina*	73 (56−84)	

Legend: [a]Mann-Whitney U test; [b]Kruskal-Wallis test; p - statistical significance
Legenda: Mann-Whitney U test; Kruskal-Wallis test; p - statistička značajnost

63 years, which is comparable to the sample (N = 700) characteristics (54.6% vs. 45.4%, 58.7 years) reported by Bertoldo et al. [5] as well as other authors [4, 15]. However, more than half of our examinees (88, 55%) were employed individuals, whereas only 30.6% of subjects who took part in Bertoldo et al.'s investigation were economically active [5]. It is worth noting that 55.5% of our respondents regularly received seasonal influenza vaccines, and 54.7% of them did so at least five times. Positive attitude toward vaccination prevailed (113, 72.4%), with the remaining 23 (14.7%) and 20 (12.8%) participants who were undecided or had a negative attitude, respectively. Statistically significant differences in attitudes to flu vaccination were not found between men and women. Information provided by healthcare professionals were the most influential reason for seeking influenza immunization (47.8%), followed by fear of illness (31%), previous flu experiences (7.1%), information provided through the media (11.5%) and advice offered by friends (2.7%). In another study, although participants reported many sources of information as important in their decision to get vaccinated (brochures, medical websites, other relevant websites, family, and friends) they regarded healthcare workers as the most reliable source of information [16]. In their 2017 study, Güvenç et al. surveyed 566 individuals, 21.75% of whom reported that they received influenza immunization in the preceding year, but the vaccination rate was higher among those aged 65 and older, individuals suffering from at least one chronic disease, and those that received a vaccine every year [4]. In 2019, Bertoldo et al. found that 42.1% of their sample received influenza vaccine in the last season (66.4%, the percentage was much higher among those older than 64 years), with 39.4% respondents stating that this was their fifth immunization, as recommended by physicians (74.9%) or specialists (6.4%) [5]. The authors also noted that individuals with insufficient knowledge or with a negative perception of immunization were less likely to be vaccinated. Inadequate knowledge and negative attitude toward influenza vaccination also decreased the likelihood of voluntary vaccination in the study conducted by Ermenlieva NM et al. [15]. Our investigation revealed higher immunization rate among older participants, whereby those who received vaccines regularly were on average older than individuals who did so sporadically (67 vs. 54 years), which is in line with the results reported by other authors [4, 22]. Bertoldo et al. similarly noted a significantly higher likelihood of vaccination among the elderly, those with greater awareness of vaccine utility and safety, participants with chronic respiratory diseases, and those who were on multiple medications [5]. In a study including 1,519 subjects, conducted in Germany, vaccination coverage was found to increase with age and

Table 4. Distribution of given responses by employment status
Tabela 4. *Distribucija dobijenih odgovora prema statusu zaposlenosti*

	Employed *Radno aktivni* (N = 88) (%)	Unemployed *Radno neaktivni* (N=72) (%)	p	Total sample *Ukupan uzorak* (N=160) (%)
Prior flu immunization, ever/*Vakcinacija protiv gripa, ikada*				
Yes/*Da*	52 (59.1%)	54 (75%)	<.05[a]	106 (66.3%)
No/*Ne*	36 (40.9%)	18 (25%)		54 (33.8%)
Regular influenza immunization/*Redovna vakcinacija protiv gripa*				
Yes/*Da*	35 (46.7%)	41 (66.1%)	<.05[a]	76 (55.5%)
No/*Ne*	40 (53.3%)	21 (33.9%)		61 (44.5%)
Number of previously received flu vaccines/*Koliko ste puta do sada primili vakcinu protiv gripa*				
One/*Jednom*	4 (7.7%)	8 (14.8%)		12 (11.3%)
Two/*Dva puta*	14 (26.9%)	3 (5.6%)	<.01[a]	17 (16%)
Three/*Tri puta*	13 (25%)	6 (11.1%)		19 (17.9%)
Five or more/*Pet i više puta*	21 (40.4%)	37 (68.5%)		58 (54.7%)
Attitude toward immunization/*Stav o vakcinaciji*				
Positive/*Za*	59 (68.6%)	54 (77.1%)		113 (72.4%)
Negative/*Protiv*	13 (15.1%)	7 (10%)	>.05[a]	20 (12.8%)
Undecided/*Neodlučan/na sam*	14 (16.3%)	9 (12.9%)		23 (14.7%)
Your motives for immunization/*Šta je doprinelo odluci za vakcinaciju*				
Fear of illness/*Strah od bolesti*	16 (29.1%)	19 (32.8%)		35 (31%)
Information provided by healthcare professionals *Informacija od lekara*	30 (54.5%)	24 (41.4%)		54 (47.8%)
Information received through media *Informacija od medija*	6 (10.9%)	7 (12.1%)	>.05[a]	13 (11.5%)
Information provided by friends *Informacija od prijatelja*	1 (1.8%)	2 (3.4%)		3 (2.7%)
Previous flu experiences/*Preležan grip prethodnih godina*	2 (3.6%)	6 (10.3%)		8 (7.1%)

Legend: N - sample size; [a]χ^2 - chi-square test; p - statistical significance
Legenda: N - broj ispitanika; [a]χ^2 - hi-kvadrat test; p - statistička značajnost

was the highest in persons aged 70 – 79 years [25]. Our investigation showed that vaccination rate among unemployed individuals was higher than among employed participants (75% vs. 59.1%; p <.05). In addition, 66.1% of unemployed subjects received vaccines regularly, compared to only 46.7% of those who were employed (p < .05). Similar difference was found when these two groups were compared in terms of having five or more prior immunizations (68.5% vs. 40.4%; p < .01). Empirical evidence shows that vaccine availability at a competent health center, in accordance with valid instructions [12], can significantly contribute to greater immunization uptake, especially among older individuals. Nonetheless, individual perceptions regarding vaccine risks and benefits are crucial in the decision-making process [25]. In general, members of at-risk groups and those who get vaccinated regularly tend to be better informed about influenza and are thus more likely to get immunized each season [4]. A survey of young workers in southern China revealed that a belief that they were strong enough not to require immunization was the primary reason (42.19%) for ignoring the public campaigns about the importance of vaccination [26]. Available data also show that employed individuals tend to perceive seasonal influenza immunization as a burden [17], especially if their employer does not recognize its importance or they lack access to free immunization through the primary healthcare system [4, 15, 16].

Conclusion

The results of our study indicate that the majority of examined adults have positive attitudes toward immunization and get vaccinated on the recommendation of healthcare professionals. Nonetheless, vaccine uptake is higher among the elderly and unemployed individuals. When interpreting these findings, it should be pointed out that our sample was relatively small and the study duration was short. Still, our results show that immunization coverage can be increased by better promotion strategies and health education of the population on the benefits of immunization. In particular, the working-age population should be targeted by immunization campaigns to increase seasonal influenza vaccination coverage.

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ASSOCIATION BETWEEN MICROVASCULAR COMPLICATIONS AND GLYCATED HEMOGLOBIN IN PATIENTS WITH DIABETES

POVEZANOST MIKROVASKULARNIH KOMPLIKACIJA I NIVOA GLIKOZILIRANOG HEMOGLOBINA KOD PACIJENATA SA DIJABETESOM

Biljana LAKIĆ[1, 2], Verica PETROVIĆ[1, 2], Kosana STANETIĆ[1, 2] and Suzana SAVIĆ[1, 2]

Summary

Introduction. The aim of this study was to determine the prevalence of microvascular complications in type 1 and type 2 diabetes mellitus patients in relation to glycated hemoglobin. **Material and Methods**. This cross-sectional study analyzed the prevalence of microvascular complications in patients with diabetes mellitus registered at the Primary Health Center Banja Luka. Demographic data, duration of diabetes, blood pressure, glycated hemoglobin, dyslipidemia, type of therapy, presence of retinopathy, neuropathy and nephropathy were analyzed. Data collection was done from December 2017 to November 2018. **Results**. The study included 228 patients, 132 (57.9%) men and 96 (42.1%) women. The most common microvascular complication was diabetic neuropathy (24.2%). The mean glycated hemoglobin level in patients with diabetic complications was 7.75 ± 1.66%. Although all participants with complications had unregulated diabetes mellitus (glycated hemoglobin > 7%), a statistically significant difference was found in regard to microalbuminuria (> 30 mg/24 h) and/or proteinuria (> 0.15 g/24 h) and/or decreased creatinine clearance (< 1.5 ml/sec) and their mean glycated hemoglobin (p = 0.025), while for other complications (neuropathy and retinopathy) the same was not confirmed. Multivariate logistic regression analysis confirmed that microalbuminuria and/or proteinuria and/or decreased creatinine clearance (odds ratio = 2.174; 95% confidence interval: 1.040 - 4.543; p = 0.039) as well as elevated diastolic blood pressure (odds ratio = 1.09; 95% confidence interval: 1.024 - 1.162; p = 0.007) were factors associated with glycated hemoglobin > 7%. **Conclusion**. The most common microvascular complication in patients with both types of diabetes mellitus is diabetic neuropathy with a prevalence of 24.2%. The presence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance were associated with glycated hemoglobin > 7% and elevated diastolic blood pressure.

Key words: Diabetes Mellitus; Diabetes Complications; Glycated Hemoglobin A; Diabetic Neuropathies; Diabetic Nephropathies; Diabetic Angiopathies; Primary Health Care; Cross-Sectional Studies

Sažetak

Uvod. Cilj ovog rada je bio ispitivanje učestalosti mikrovaskularnih komplikacija kod pacijenata sa dijabetesom melitus tipa 1 i tipa 2 u odnosu na glikozilirani hemoglobin. **Materijal i metode**. Studijom preseka ispitivana je učestalost mikrovaskularnih komplikacija kod pacijenata sa dijabetesom melitus, koji su registrovani u Domu zdravlja u Banjoj Luci. Analizirani su: demografski podaci, trajanje dijabetesa, krvni pritisak, glikozilirani hemoglobin, dislipidemija, vrsta terapije, prisustvo retinopatije, neuropatije i nefropatije. Podaci su prikupljani u periodu od decembra 2017. do novembra 2018. godine. **Rezultati.** U istraživanje je bilo uključeno 228 pacijenata i to 132 (57,9%) muškarca i 96 (42,1%) žena. Najčešća mikrovaskularna komplikacija je bila dijabetesna neuropatija (24,2%). Prosečna vrednost glikoziliranog hemoglobina kod pacijenata sa komplikacijama dijabetesa bila je 7.75±1.66%. Iako su svi ispitanici sa komplikacijama imali neregulisan dijabetes melitus (glikozilirani hemoglobin>7%), utvrđena je statistički značajna razlika u prisustvu mikroalbuminurije (>30 mg/24 h) i/ili proteinurije (>0,15 g/24 h) i/ili sniženog klirensa kreatinina (<1,5 ml/sec) i njihovog prosečnog glikoziliranog hemoglobina (p=0,025), dok za ostale komplikacije (neuropatiju i retinopatiju) isto nije potvrđeno. Multivarijantna logistička regresija je potvrdila da su mikroalbuminurija i/ili proteinurija i/ili snižen klirens kreatinina (odnos verovatnoća=2.174; 95% interval poverenja:1.040-4.543; p=0.039) kao i povišen dijastolni krvni pritisak (odnos verovatnoća=1.09; 95% interval poverenja:1.024-1.162; p=0.007) faktori povezani sa glikoziliranim hemoglobinom>7%. **Zaključak**. Najčešća mikrovaskularna komplikacija kod pacijenata sa oba tipa dijabetesa je dijabetesna neuropatija sa prevalencijom od 24,2%. Prisustvo mikroalbuminurije i/ili proteinurije i/ili sniženog klirens kreatinina su povezani sa glikoziliranim hemoglobinom>7% i povišenim dijastolnim krvnim pritiskom.

Ključne reči: dijabetes melitus; komplikacije dijabetesa; glikozilizirani hemoglobin A; dijabetička neuropatija; dijabetička nefropatija; dijabetička angiopatija; primarna zdravstvena zaštita; studija preseka

Introduction

Diabetes mellitus (DM) is a chronic non-communicable disease which has become a global epidemic. It is characterized by a condition of chronic hyperglycemia that may last for years and lead to a series of complications that slowly and quietly endanger the patient's health [1, 2]. The most common microvascular complications of DM are neuropathy, retinopathy and nephropathy. The International Expert Committee and the International Diabetes Federation (IDF) have introduced glycated hemoglobin

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Abbreviations

DM – diabetes mellitus
HbA1c – glycated hemoglobin A
OR – odds ratio
CI – confidence interval
ICD – International Classification od Diseases
T2DM – type 2 diabetes mellitus
T1DM – type 1 diabetes mellitus
BP – blood pressure
PHC – Primary Health Center
BiH – Bosnia and Herzegovina

A (HbA1c) in 2009 for glycemic control, and now as a diagnostic parameter for DM with all its advantages over other diagnostic procedures [1, 2]. Many studies have provided valuable evidence that early diagnosis and intensive glycemic control is linked to reduction in microvascular complications and possibly macrovascular complications over a long period of diabetes duration [3–11].

The HbA1c was found to be a direct product of post-translational glucose binding to hemoglobin molecules and that there was an association between HbA1c concentration and average blood glucose concentration over the previous 3 months, which is the average lifespan of erythrocytes [12, 13]. An intriguing possibility that one single measurement provides objective insight into mean glycemia over a long period has added a new dimension to the control and monitoring DM [14, 15].

Recent research has established a connection between glycemic variability and the development of microvascular complications, indicating that long-term fluctuations in glycemia contribute to the development of retinopathy and nephropathy in type 1 diabetes mellitus (T1DM) [16, 17].

The optimal HbA1c target is less than 7% for all adults, although it may be more strict of less than 6.5% in special patients who can achieve this without significant hypoglycemia or in those with shorter duration of diabetes [3, 18]. Current researches individualize HbA1c goals between 6.5% and 7% for both types of DM to improve the quality of life and prevent diabetic complications, which is what we must strive for [19, 20]. However, data regarding the prevalence of microvascular complications related to glycemic control and HbA1c among diabetic patients in Bosnia and Herzegovina (BiH) are scarce.

The primary goal of this study was to determine the frequency of microvascular complications in patients with T1DM and type 2 diabetes mellitus (T2DM), primarily with reference to HbA1c levels. The secondary goal of this study was to determine the factors associated with the occurrence of microvascular complications in patients with diabetes.

Material and Methods

A cross-sectional study included patients with both types of DM (T1DM and T2DM), who were registered at the Primary Health Center (PHC) Banja Luka. With a population size of 15,617, an error of 5%, 95% level of confidence, and a confidence interval of 6.44, the estimated sample size of patients with DM was 228. Participants were randomly selected from 20 families with T1DM and T2DM, according to International Classification of Diseases (ICD) [21]. Every third patient was selected from the medical records of patients with DM in accordance with the inclusion criteria.

Inclusion criteria were age 18 to 70, diagnosis of DM according to ICD (T1DM and T2DM), duration of diabetes at least 5 years, and a written consent to participate in the study. Data collection took place from December 2017 to November 2018.

Patients with DM and frequent hypoglycemic episodes who were previously diagnosed with macrovascular complications of diabetes were excluded from the study. The study was approved by the Ethics Committee of the PHC Banja Luka.

For the purpose of the research, a checklist was developed for each participant individually. Age, sex, duration of diabetes, blood pressure (BP), HbA1c, dyslipidemia, type of therapy, presence of retinopathy, neuropathy, and nephropathy were analyzed. With regard to age, the participants were divided into 5 groups: 20 to 30 years, 31 to 40 years, 41 to 50 years, 51 to 60, and 61 to 70 years. According to the duration of diabetes, they were divided into 4 groups: duration of diabetes from 5 years to 10 years, from 10 to 15 years, from 15 to 20 years, and over 20 years.

All the participants underwent baseline assessment. Control measurements of BP were performed every 2 months. Control measurements of HbA1c in participants with T1DM were performed every 3 months (a total of 4 measurements), and in participants with T2DM every 6 months (a total of 2 measurements).

The BP was measured three times during each visit to the family doctor using a mercury manometer according to World Health Organization recommendations. The final value of BP was recorded, and it was the mean of the second and third measurement.

The HbA1c and lipids were measured in the central laboratory of the PHC Banja Luka (bioanalyzer Arhitekt c 8000). According to the HbA1c level at the end of follow-up, participants were classified into two groups: participants with HbA1c < 7% and participants with HbA1c ≥ 7%. Dyslipidemia was diagnosed if total cholesterol value was > 4 mmol/l, and/or low-density lipoprotein (LDL) cholesterol > 2.6 mmol/l and/or triglyceride > 1.7 mmol/l [20].

The screening was performed for three basic microvascular complications (retinopathy, neuropathy and nephropathy). The screening for diabetic retinopathy was done by fundus examination performed by an ophthalmologist. A 10 g monofilament Semmes-Weinstein nylon was used to detect neuropathy. The monofilament handling procedure was done in the following way: the examiner first demonstrated the strength of the monofilament touch on each participant's hand, then told him to close his eyes and proceeded testing the sensations on both

feet. The examined points of pressure are the first metatarsophalangeal joint of the great toe, the dorsum of the great toe, the plantar side of the great toe, and the plantar side of the heel. The participants were asked to say "yes" when they felt the touch. The maximum score was eight. More than four incorrect answers indicated the existence of neuropathy [22]. To confirm neuropathy, the findings of a neurologist during the follow-up period or earlier were taken as well as the findings of electroneurography (ENG).

The presence of nephropathy was detected using microalbuminuria, proteinuria and creatinine clearance in 24-hour urine in the central laboratory of the PHC Banja Luka (biochemical analyzer AU 480). Microalbumin values of 30 – 300 mg/24 h were considered to be the phase of incipient nephropathy-microalbuminuria, and values greater than 300 mg/24 h defined the phase of manifest proteinuria-macroalbuminuria [23]. The value of protein in urine > 0.15 g/24 h and the value of creatinine clearance <1.5 ml/sec, according to the reference values of the central laboratory of the PHC Banja Luka, represented the limit value for diabetic nephropathy. During the research, only 38 participants presented with microalbuminuria, which was not valid for further analysis and for diagnosing nephropathy. Because of that, one of three positive values (microalbuminuria and/or proteinuria and/or decreased creatinine clearance) was monitored.

All analyses were performed using the Statistical package for the social sciences version 25 (SPSS Inc., Chicago, IL, USA). The results were analyzed and presented using descriptive statistics (absolute and relative numbers, measures of central tendency, standard deviation).

Levene's test was used to assess the equality of variances. Demographic data were analyzed using two samples of the independent Student's t-test and the Mann-Whitney U test. The Hi square (χ^2) test was used to compare categorical variables. Logistic regression was used to identify all factors (microvascular complications, blood pressure, type of therapy) associated with unregulated diabetes (HbA1c greater than 7%). The Kruskal-Wallis test was used to assess the differences in the risk of microvascular complications between the groups based on duration of diabetes. A probability level of $p < 0.05$ was considered statistically significant.

Table 1. Presence of microvascular complications in patients with diabetes in relation to the HbA1c level
Tabela 1. *Prisutnost mikrovaskularnih komplikacija kod pacijenata s dijabetesom u odnosu na vrednost HbA1c*

			Presence of neuropathy/*Prisutnost neuropatije*						p
			YES n, %/*DA n, %*		NO n, %/*NE n, %*		Total n, %/*Ukupno n, %*		
HbA1c, (%)		≤ 7.00	20	(36.4)	64	(37.4)	84	(37.2)	0.887
		7.01+	35	(63.6)	107	(62.6)	142	(62.8)	
		Total/*Ukupno*	55	(100)	171	(100)	226	(100)	
			Presence of retinopathy/*Prisutnost retinopatije*						p
			YES n, %/*DA* n, %		NO n, %/*NE* n, %		Total n, %/*Ukupno* n, %		
HbA1c, (%)		≤ 7.00	11	(28.9)	73	(39.2)	84	(37.5)	0.232
		7.01+	27	(71.1)	113	(60.8)	140	(62.5)	
		Total/*Ukupno*	38	(100)	186	(100)	224	(100)	
			Microalbuminuria and/or Proteinuria and/or decreased CCr *Mikroalbuminurija i/ili proteinurija i/ili snižen CCr*						p
			YES n, %/*DA n, %*		NO n, %/*NE n, %*		Total n, %/*Ukupno n, %*		
HbA1c, (%)		≤ 7.00	29	(26.6)	33	(42.3)	62	(33.2)	0.025
		7.01+	80	(73.4)	45	(57.7)	125	(66.8)	
		Total/*Ukupno*	109	(100)	78	(100)	187	(100)	
Sex *Pol*	Male *Muški*	≤ 7.00 HbA1c	19	(31.7)	20	(40.8)	39	(35.8)	0.322
		7.01+	41	(68.3)	29	(59.2)	70	(64.2)	
		Total/*Ukupno*	60	(100)	49	(100)	109	(100)	
	Female *Ženski*	≤ 7.00 HbA1c	10	(20.4)	13	(44.8)	23	(29.5)	0.022
		7.01+	39	(79.6)	16	(55.2)	55	(70.5)	
		Total/*Ukupno*	49	(100)	29	(100)	78	(100)	

Legend: HbA1c - glycated hemoglobin; CCr - creatinine clearance; Microalbuminuria (> 30 mg/24 h) and/or Proteinuria (> 0.15 g/24 h) and/or CCr (< 1.5 ml/sec); p - statistical significance
Legenda: HbA1c – glikozilirani hemoglobin; CCr – klirens kreatinina; Mikroalbuminurija (>30 mg/24 sata) i/ili proteinurija (>0,15 g/24 sata) i/ili CCr (<1,5 ml/sek); p – statistička značajnost

Results

The study included 228 patients, 132 (57.9%) men and 96 (42.1%) women. The average age of our participants was 55.8 ± 9.2 years.

The most common microvascular complication was diabetic neuropathy. This study determined the prevalence of diabetic neuropathy in 24.2% and retinopathy in 17% of participants with a statistically significant difference ($\chi^2 = 16.770$; $p < 0.001$). Out of the total number of participants, 109 had at least one parameter consistent with nephropathy. According to microalbuminuria (> 30 mg/24 h), 11.9% of participants had a positive result, 67% had a positive proteinuria test (> 0.15 g/24 h), and 45% had a decreased creatinine clearance (< 1.5 ml/sec). The mean HbA1c in patients with diabetic complications was 7.75 ± 1.66% with a statistically significant difference between patients with T1DM and T2DM (U = 3060.500; z = 1.977; p = 0.048).

The participants with unregulated glycemia showed higher incidence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance (p = 0.025), while the same was not confirmed for other complications (neuropathy and retinopathy) **(Table 1)**.

We analyzed demographic characteristics (sex) in relation to HbA1c and the presence of all microvascular complications and found that there was a statistically significant difference only in patients with microalbuminuria and/or proteinuria and/or decreased creatinine clearance and in women statistically significantly more in the group with HbA1c > 7% (p = 0.022) **(Table 1)**, while there was no statistical significance in regard to other complications. Analyzing microvascular complications in relation to sex, age, duration of diabetes and type of therapy, neuropathy was more frequent among the patients with longer duration of diabetes (p < 0.001), and retinopathy in patients using insulin therapy (p = 0.019) **(Table 2)**.

The parameters of diabetic nephropathy (microalbuminuria and/or proteinuria and/or decreased creatinine clearance) were tested in relation to the duration of diabetes using the Kruskal-Wallis test. The duration of diabetes affected the occurrence of incipient diabetic nephropathy (microalbuminuria) in our participants (p = 0.042) **(Table 3)**.

The univariate regression models showed associations between HbA1c > 7% and the following variables: presence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance (OR = 2.492), insulin therapy (OR = 2.215), elevated BP > 130 mmHg and > 80 mmHg (OR=1.833). Multi-

Tabela 2. The incidence of microvascular complications with respect to sex, age, duration of diabetes and type of therapy
Tabela 2. *Učestalost mikrovaskularnih komplikacija s obzirom na pol, doba, trajanje dijabetesa i vrstu terapije*

		Microvascular complications/*Mikrovaskularne komplikacije*								
		Neuropathy *Neuropatija*			Retinopathy *Retinopatija*			Microalbuminuria and/or Proteinuria and/or CCr *Mikroalbuminurija i/ili Proteinurija i/ili CCr*		
Variable *Promenljiva*		YES/*DA* (n, %)	NO/*NE* (n, %)	p	YES/*DA* (n, %)	NO/*NE* (n, %)	p	YES/*DA* (n, %)	NO/*NE* (n, %)	p
Sex/*Pol*	Male/*Muški*	38 (69.1)	94 (54.7)	0.059	26 (68.4)	104 (55.9)	0.155	60 (55)	72 (60.5)	0.404
	Female/*Ženski*	17 (30.9)	78 (45.3)		12 (31.6)	82 (44.1)		49 (45)	47 (39.5)	
Age/*Doba* (Years/*Godine*)	18 - 30	1 (1.8)	6 (3.5)		2 (5.3)	5 (2.7)		4 (3.7)	3 (2.5)	
	31 - 40	2 (3.6)	10 (5.8)		1 (2.6)	11 (5.9)		7 (6.4)	5 (4.2)	
	41 - 50	4 (7.3)	21 (12.2)	0.712	6 (15.8)	19 (10.2)	0.674	12 (11)	13 (10.9)	0.929
	51 - 60	25 (45.5)	73 (42.4)		15 (39.5)	82 (44.1)		46 (42.2)	53 (44.5)	
	61 - 70	23 (41.8)	62 (36.0)		14 (36.8)	69 (37.1)		40 (36.7)	45 (37.8)	
Duration of diabetes *Trajanje dijabetesa*	5 - 10 yr./*god*	19 (34.5)	106 (61.6)		15 (39.5)	110 (59.1)		60 (55.0)	66 (55.5)	
	10 - 15 yr./*god*	11 (20)	41 (23.8)		10 (26.3)	40 (21.5)		23 (21.1)	29 (24.4)	
	15 - 20 yr./*god*	13 (23.6)	18 (10.5)	0.000	8 (21.1)	22 (11.8)	0.127	15 (13.8)	16 (13.4)	0.790
	> 20 yr./*god*	12 (21.8)	7 (4.1)		5 (13.2)	14 (7.5)		11 (10.1)	8 (6.7)	
Type of therapy *Vrsta terapije*	Oral antidiabetic therapy/*Oralna antidijabetesna terapija*	20 (36.4)	89 (52)		11 (28.9)	98 (53)		49 (45.4)	61 (51.3)	
	Insulin therapy *Insulinska terapija*	23 (41.8)	44 (25.7)	0.056	17 (44.7)	48 (25.9)	0.019	36 (33.3)	31 (26.1)	0.479
	Combined therapy *Kombinovana terapija*	12 (21.8)	38 (22.2)		10 (26.3)	39 (21.1)		23 (21.3)	27 (22.7)	

Legend: CCr - creatinine clearance; Microalbuminuria (> 30 mg/24 h) and/or Proteinuria (> 0.15 g/24 h) and/or CCr (< 1.5 ml/sec); p - statistical significance
Legenda: CCr – klirens kreatinina; Mikroalbuminurija (> 30 mg/24 h) i/ili Proteinurija (>0,15 g/24 h) i/ili CCr (< 1,5 ml/s); p – statistička značajnost

Table 3. Individual parameters of diabetic nephropathy in relation to diabetes duration
Tabela 3. *Pojedinačni parametri dijabetesne nefropatije u odnosu na trajanje dijabetesa*

	Duration of diabetes *Trajanje dijabetesa*	N	Mean value *Srednja vrednost*	Kruskal-Wallis H	df	p
Microalbuminuria (> 30 mg/24 h) *Mikroalbuminurija (> 30 mg/24 sata)*	5 - 10 yr./*god*	66	64.08	8.211	3	0.042
	10 - 15 yr./*god*	29	51.47			
	15 - 20 yr./*god*	18	67.44			
	> 20 yr./*god*	14	85.18			
	Total/*Ukupno*	127				
Proteinuria (> 0.15 g/24 h) *Proteinurija (> 0,15 g/24 h)*	5 - 10 yr./*god*	96	84.49	2.351	3	0.503
	10 - 15 yr./*god*	38	83.84			
	15 - 20 yr./*god*	24	97.77			
	> 20 yr./*god*	16	98.81			
	Total/*Ukupno*	174				
CCr (< 1.5 ml/sec)	5 - 10 yr./*god*	87	85.22	2.671	3	0.445
	10 - 15 yr./*god*	35	72.67			
	15 - 20 yr./*god*	23	72.48			
	> 20 yr./*god*	15	83.70			
	Total/*Ukupno*	160				

Legend: CCr - creatinine clearance; df - degrees of freedom; p - statistical significance
Legenda: CCr – klirens kreatinina; ss – stepeni slobode; p – statistička značajnost

Table 4. Univariate and multivariate logistic regression of unregulated diabetes-related variables (HbA1c > 7%)
Tabela 4. *Univarijatna i multivarijantna logistička regresija varijabli povezanih s neregulisanim dijabetesom* (HbA1c>7%)

	OR *OV*	95% CI/*95%/IP*		p	OR *OV*	95% CI/*95%/IP*		p
		Lower *Niži*	Upper *Viši*			Lower *Niži*	Upper *Viši*	
Level of education/*Nivo obrazovanja*	0.592	0.421	0.833	0.003	0.457	0.275	0.758	0.002
Insulin therapy/*Insulinska terapija*	2.215	1.266	3.876	0.005	1.419	0.574	3.510	0.448
Oral antidiabetic therapy – metformin *Oralna antidijabetesna terapija – metformin*	0.446	0.244	0.814	0.009	0.309	0.111	0.862	0.025
Triglycerides/*Trigliceridi*	1.159	0.946	1.42	0.155	1.105	0.842	1.449	0.472
Microalbuminuria (> 30 mg/24 h) and/or Proteinuria (> 0.15 g/24 h) and/or CCr (< 1.5 ml/sec) *Mikroalbuminurija (> 30 mg/24 sata) i/ili proteinurija (> 0,15 g/24 sata) i/ili CCr (<1,5 ml/sek)*	2.492	1.427	4.352	0.001	2.174	1.040	4.543	0.039
High diastolic BP (> 80 mmHg) *Visoki dijastolni KP (> 80 mmHg)*	1.085	1.031	1.142	0.002	1.091	1.024	1.162	0.007
High BP (> 130 and > 80 mmHg) *Visok KP (> 130 i > 80 mmHg)*	1.833	0.979	3.435	0.058	0.989	0.383	2.557	0.982

Legend: HbA1c - glycated hemoglobin; p – statistical significance; OR – odds ratio; CI – confidence interval; CCr - creatinine clearance; BP - blood pressure
Legenda: *HbA1c – glikolizilirani hemoglobin;* p – statistička značajnost; *OV – odnos verovatnoće; IP – interval poverenja; CCr – klirens kreatinina; KP– krvni pritisak*

variate logistic regression analysis confirmed that microalbuminuria and/or proteinuria and/or decreased creatinine clearance (OR = 2.174; 95% CI: 1.040 - 4.543; p = 0.039) as well as elevated diastolic BP (OR = 1.09; 95% CI: 1.024 - 1.162; p = 0.007) were associated with HbA1c > 7% **(Table 4)**.

Discussion

This study determined that the most common microvascular complication in correlation with HbA1c > 7% was diabetic neuropathy with a prevalence of 24.2%. The second microvascular complication in correlation with HbA1c greater than 7% in patients with both types of DM was diabetic retinopathy with a prevalence of 17%. The main predictors of microvascular complications (individual parameters of diabetic nephropathy) were HbA1c > 7%, elevated diastolic BP, duration of diabetes, and insulin therapy.

A recent study conducted in Shanghai, China, found a prevalence of diabetic nephropathy and diabetic retinopathy of 27.97% and 11.33%, respec-

tively, in patients with T2DM with longer disease duration, elevated HbA1c, also high body mass index, high BP and triglyceride levels as possible independent risk factors [24].

A Hussein et al. study of patients with T2DM in Sudan found a prevalence of nephropathy, retinopathy and neuropathy with an incidence of 38.8, 23.9 and 22.5%, respectively, with HbA1c of 7.85% and the most common comorbidity – hypertension [25].

A 12-year longitudinal study from Karachi, Pakistan [26] confirmed that all microvascular complications were significantly high among diabetic patients with duration of diabetes > 10 years, and HbA1c > 7%. A study of Chui et al. in South China revealed a lot of independent risk factors for diabetic retinopathy in patients with T2DM (male gender, higher education level, longer duration of diabetes, higher systolic BP and HbA1c) [27].

This study showed that had HbA1c > 7% was more common in women, so one of the parameters of diabetic nephropathy with statistical significance was present. Also, a statistical connection was established between the duration of diabetes and presence of neuropathy, as well as between the duration of diabetes and microalbuminuria. Therefore, the duration of DM longer than 10 years may be considered as a possible predictor of these two diabetic microvascular complications.

Studies have shown that in addition to HbA1c and its reduction, that is important for delaying and preventing microvascular complications, BP and its good regulation is also an important parameter [28].

Of the analyzed risk factors, high BP was associated with microalbuminuria and/or proteinuria and/or decreased creatinine clearance as well as unadjusted diabetes or HbA1c > 7%. This finding confirms that in patients with diabetes the already established therapy of diabetic nephropathy is at the same time the therapy of hypertension. Among other risk factors (dyslipidemia, age) that were followed in relation to the presence of microvascular complications, showed no statistical significance.

Meta-analysis of Gorst et al. found an association between HbA1c variability with renal and cardiovascular disease in both types of diabetes [29]. The Diabetes Control and Complications Trial found that retinopathy is associated with HbA1c variability in T1DM, while in T2DM it is still debatable depending on the study and diabetic complications [30–32]. Otherwise, many studies have found a strong association between retinopathy and renal outcomes in patients with T2DM and that retinopathy is an independent risk factor for kidney disease in these patients [33, 34]. In T1DM, as many as 95% of patients with diabetic nephropathy also have diabetic retinopathy [23].

The limitation of this study is that only one sixth of our participants had a 24-hour urine analysis for the presence of microalbuminuria and therefore nephropathy could not be diagnosed, so individual parameters (microalbuminuria and/or proteinuria and/or decreased creatinine clearance) were monitored. Even though we followed participants from one PHC, that is the largest in our country, our results could not be applied in general for patients in the Republic of Srpska. Our study showed poor glycemic control in diabetic patients with already present microvascular complications. All healthcare professionals, especially in primary care, should work with diabetic patients to try to prevent or delay the complications of diabetes.

Conclusion

In conclusion, this study confirmed that the most common microvascular complication in patients with both types of diabetes mellitus was diabetic neuropathy with a prevalence of 24.2%. In these patients, the presence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance was associated with glycated hemoglobin > 7% and elevated diastolic blood pressure. Family physicians should perform regular microvasular complications screening tests according to the official clinical guidelines. Futhermore, longitudinal studies exploring the causal relationship between glycemic control and development of microvascular complications are needed.

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STRUCTURAL AND FUNCTIONAL MACULAR CHANGES AFTER CATARACT SURGERY IN DIABETIC PATIENTS

STRUKTURALNE I FUNKCIONALNE PROMENE MAKULE NAKON OPERACIJE KATARAKTE KOD PACIJENATA OBOLELIH OD DIJABETESA

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Summary

Introduction. In recent years, the number of diabetic patients requiring cataract surgery has been on the rise. The aim of this study was to examine the effects of cataract surgery on visual acuity and changes in the central retinal thickness in diabetic patients with and without retinopathy, in relation to the duration of the disease, type of therapy, and the level of glycated hemoglobin and serum lipids. **Material and Methods.** The prospective study included 51 eyes of 34 patients divided into three groups. Preoperatively, all patients underwent best-corrected visual acuity evaluation with Snellen chart, cataract grading using lens opacities classification system III, as well as fundus examination and optical coherence tomography. Postoperative follow-up visits were scheduled after the first, fourth, sixth, eighth, and twelfth weeks after which the patients underwent best-corrected visual acuity evaluation and optical coherence tomography. The obtained values were statistically processed and analyzed in relation to the duration of the disease, the type of therapy, and the level of glycated hemoglobin and serum lipids. **Results.** Of 51 eyes, 5.9% developed macular edema during the fourth postoperative week with central retinal thickness > 310 μm. Subclinical central retinal thickness changes were registered in all groups with the highest values in group I (diabetics with retinopathy) in the sixth postoperative week. The average value of central retinal thickness in group I was 256 ± 11 μm at baseline and 273 ± 11 μm in week 6. The best-corrected visual acuity improved in all groups, without changes in central retinal thickness. **Conclusion.** Good visual acuity and absence of significant changes in macular thickness are helpful when making the decision to perform cataract surgery in patients with diabetes. Postoperative follow-up visits should include optical coherence tomography in addition to standard procedures.

Key words: Cataract; Macular Edema; Diabetes Complications; Cataract Extraction; Diabetic Retinopathy; Tomography, Optical Coherence; Visual Acuity; Glycated Hemoglobin A

Sažetak

Uvod. Danas se sve veći broj pacijenata koji imaju dijabetes melitus javljaju se na operaciju katarakte. Cilj ovog istraživanja bio je ispitivanje uticaja operacije katarakte na vidnu oštrinu i promene centralne retinalne debljine kod dijabetičara u odnosu na dužinu trajanja oboljenja, vrstu terapije dijabetesa, visinu glikoziliranog hemoglobina i serumskih lipida. **Materijal i metode.** Prospektivna studija je obuhvatila 51 oko 34 pacijenta podeljena u tri grupe. Preoperativno svim ispitanicima je određena najbolje korigovana oštrina vida prema Snelenu, vrsta katarakte po sistemu klasifikacije zamućenosti sočiva, pregled očnog dna i optička koherentna tomografija. Postoperativne kontrole su zakazane nakon prve, četvrte, šeste, osme i dvanaeste nedelje, kada je određena najbolje korigovana oštrina vida i optička koherentna tomografija. Dobijene vrednosti su statistički obrađene i analizirane u odnosu na dužinu trajanja dijabetesa melitus, vrstu terapije, vrednosti glikoziliranog hemoglobina i serumskih lipida. **Rezultati**. U četvrtoj postoperativnoj nedelji, 5,9% ispitanika je razvilo makularni edem centralne retinalne debljine >310 μm. Supkliničke promene centralne retinalne debljine su registrovane u svim grupama ispitanika pri čemu su najviše vrednosti bile u grupi ispitanika sa dijabetesom melitus i prisutnom dijabetesnom retinopatiom u šestoj nedelji. Srednja vrednost centralne retinalne debljine je u grupi I na dan operacije iznosila 256 ± 11 μm, dok je u šestoj nedelji vrednost bila 273 ± 11 μm. Najbolje korigovana vidna oštrina je poboljšana u svim grupama i nije pratila promenu centralne retinalne debljine postoperativno. **Zaključak.** Dobra vidna oštrina i odsustvo značajnih promena debljine makule olakšavaju donošenje odluke o izvođenju operacije katarakte kod pacijenta obolelih od dijabetesa melitus. Postoperativne kontrole ovih pacijenata bi trebalo da pored standardnog pregleda, uključe i optičku koherentnu tomografiju.

Ključne reči: katarakta; makularni edem; dijabetesne komplikacije; ekstrakcija katarakte; dijabetesna retinopatija; optička koherentna tomografija; oštrina vida; glikozilizirani hemoglobin A

Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic metabolic diseases affecting millions of people in the world [1]. Diabetic macular edema (DME) is defined as retinal thickening within 1 disc diameter of the foveal center, along with microaneurysms and/or retinal hemorrhages. Recently, the most

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Abbreviations

DM – diabetes mellitus
DME – diabetic macular edema
DR – diabetic retinopathy
OCT – optical coherence tomography
CRT – central retinal thickness
BCVA – best corrected visual acuity
HbA 1c – serum glycosylated hemoglobin
VEGF – vascular endothelial growing factor
ICAM-1 – intercellular adhesion molecule-1 activation
LOCS III– lens opacities classification system
NSAID – nonsteroidal anti-inflammatory drug
ANOVA – analysis of variance

important characteristic of DME has become whether it involves the fovea or not. Central DME involves the center of the macula, with a central subfield thickening of at least 310 μm on optical coherence tomography (OCT) using a time domain device [2]. As diabetic patients are at increased risk of developing cataract and losing visual acuity, they are likely to need surgery. Unfortunately, surgery may lead to macular edema as well as to long term deterioration of visual functions. Furthermore, it can exacerbate diabetic retinopathy in patients with long term type 2 DM, patients with insulin dependence, patients with high level of glycated hemoglobin (HbA 1c) and serum lipids, patients with hypertension, poor nuclear transparency and longer ultrasound exposure, as well as patients with kidney dysfunction. These are important risk factors for DME [3–6].

Hyperglycemia induces several biochemical processes which contribute to the pathogenesis of diabetic retinopathy. Retinal neurons and glial cells increase their production of vascular endothelial growing factor (VEGF), even with no ophthalmoscopic evidence of diabetic retinopathy. Increased inflammation, characterized by leukostasis, accumulation of macrophages, and intercellular adhesion molecule-1 (ICAM-1) activation are associated with capillary nonperfusion and damage of the blood-retinal barrier. Patients with DME have elevated vitreous levels of VEGF, ICAM-1, interleukin-6 (IL-6), and monocyte chemoattractant protein-1 compared with non-diabetic patients.

High lipid levels may cause endothelial dysfunction and increased vascular permeability through a local inflammatory response. Decrease in subfoveal choroidal blood flow in type 2 diabetic patients with retinopathy may be relevant in the pathophysiology of macular edema. Eyes with macular edema have been reported to have a greater decrease in choroidal blood flow than eyes without macular edema, suggesting relative hypoxia of the retinal pigment epithelium (RPE) and outer retina which can worsen during the surgery [7, 8].

Surgical trauma and subsequent inflammation following cataract surgery may increase the levels of VEGF and other cytokines more in diabetic patients than patients without diabetes. These factors can compromise the retinal vasculature and can lead to macular changes [9, 10].

The OCT is a non-contact, non-invasive ophthalmic diagnostic technique for retinal imaging and therefore has a significant place in detection of retinal thickness changes in diabetic patients after cataract surgery [10]. This technique provides high resolution and allows close study of retinal layers and cells in different diseases [11].

This clinical study was designed to compare visual functions and structural retinal changes between a group of diabetic patients with diabetic retinopathy and a group of diabetic patients without diabetic retinopathy in comparison to non-diabetic population, before and after cataract surgery, taking into consideration the following parameters: diabetes type and duration, type of treatment, HbA 1c levels, serum lipids, cataract type and phacoemulsification (PHACO) ultrasound time.

Material and Methods

This prospective study was conducted at the Eye Clinic of the University Clinical Center of Republic of Srpska from January to December 2019. The study was approved by the Ethics Committee of the University Clinical Center of Republic of Srpska, Bosnia and Herzegovina, and it was conducted in accordance with the Declaration of Helsinki (1964). A fully informed written consent was obtained from all patients prior to the study.

The inclusion criteria were as follows:

– Patients with cataract best corrected visual acuity (BCVA) ≤ 0.5 due to cataract)
– Patients with type 2 DM.
– The exclusion criteria were:
– Patients with severe cataract and high nuclear density where OCT could not be performed preoperatively
– Patients with severe diabetic retinopathy
– Patients with preoperative macular edema history
– Patients with previous panretinal photocoagulation treatment
– Patients with previous intravitreal drug injection
– Patients with epiretinal membrane or vitreoretinal traction
– Patients with glaucoma, uveitis and any other ocular pathology except cataract
– Patients with intraocular surgery within 6 months prior to the study
– Patients with intraoperative cataract complications (capsular tear, iris lesions).

A total of 51 eyes of 34 participants were included in this study and divided into 3 groups:

– Group I: Diabetic patients with diabetic retinopathy (mild, moderate) (17 eyes)
– Group II: Diabetic patients without diabetic retinopathy (17 eyes)
– Group III: Healthy patients undergoing cataract surgery (17 eyes).

All patients underwent a thorough preoperative ophthalmological examination including BCVA evaluation using Snellen chart, Goldmann applanation tonometry, slit lamp and fully dilated fundus examination. Posterior segment diagnostic procedures were performed including color fundus photography and autofluorescence (Zeiss Visucam 500) and OCT of the macula (Zeiss Cirrus HD-OCT). The scanning protocol for OCT used in this study was Macular Cube 512 x 128 A-scan pattern with the centre of 6 x 6 mm scanning area at the centre of the macula, creating 3 annular rings further divided into 9 zones: central circular zone of fovea with 1 mm diameter, 4 parafoveal zones with 3 mm diameter, and 4 parafoveal zones with 6 mm diameter. Presence of macular edema was defined as central retinal thickness (CRT) > 310 μm in central foveal pit assessed by OCT. In some patients both eyes were examined.

Lens opacities classification system III (LOCS III) was used for cataract classification. Early Treatment Diabetic Retinopathy Study (ETDRS) and International Clinical Diabetic Retinopathy Disease Severity Scale were used for diabetic retinopathy classification.

The following parameters were preoperatively examined: age, gender, diabetes type and duration, type of treatment, levels of HbA 1c and serum lipids.

All patients underwent cataract surgery by the same trained surgeon (S. S.) using topical anesthesia. A 2.75 mm clear corneal (small) incision was made followed by capsulorhexis and phacoemulsification (Bausch & Lomb Stellaris 2016) after which a foldable one-piece hydrophilic acrylic intraocular lens (AKREOS ADAPT AO) was implanted. Intracameral antibiotic was injected at the end of the surgery. Postoperatively, topical corticosteroid was administered to all patients while topical nonsteroidal anti-inflammatory drug (NSAID) was not prescribed due to our study protocol and in order to avoid NSAID effect on cystoid macular edema prevention.

Postoperative follow-up visits were scheduled in 1 week, 4 weeks, 6 weeks, 8 weeks, and 12 weeks, after which all patients underwent BCVA evaluation, slit lamp and fundus examination and OCT assessment.

Main outcome measures, BCVA and OCT were compared within and between the 3 groups in regard to the examined parameters.

A statistic analysis was performed using IBM SPSS Version 23. Student's t-test was used to analyze the difference between two samples, analysis of variance (ANOVA) was used to analyze differences between more than two samples. Spearman's rank correlation was used to measure the correlation between research variables. Data were statistically processed and the threshold of statistical significance was 0.05.

Results

This study included 51 eyes of 34 patients of which 13 (38%) were men and 21 (62%) women. The average age was 65 ± 6 years with no difference between the groups. All participants had a clinical diagnosis of cataract. Twenty-three participants (68%) had type 2 DM; of these, 29.4% had DM for more than 10 years with average duration of 11 ± 1.6 years; at baseline, 22% of participants received insulin treatment. Regarding the diabetic retinopathy, 35.3% of diabetic patients had non-proliferative diabetic retinopathy, out of whom 20.6% had a mild and 14.7% moderate form. In regard to the HbA 1c status, in the group of patients with HbA 1c > 7%, the mean HbA 1c levels were 7.75 ± 0.64%. Patient characteristics at the time of surgery, as well as the parameters of accompanying systemic diseases are presented and summarized in **Table 1.**

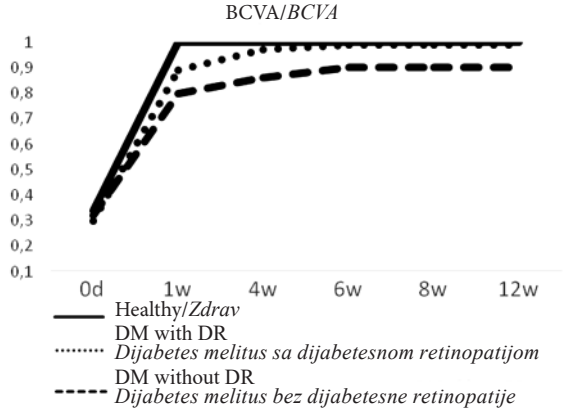
A standard phaco surgery was performed in all eyes. According to LOCS III system, 25 eyes had N2 grade of nuclear density, 10 eyes N1 grade, and 16 eyes P2 grade. The average phacoemulsification time was 5.13 seconds without statistically significant difference between the groups. Two eyes (3.9%) were excluded due to the intraoperative complications.

Visual acuity-functional outcomes

Graph 1 and **Table 2** show mean BCVA in all 3 study groups at baseline, 1 week, 4 weeks, 6 weeks, 8 weeks, and 12 weeks after the cataract surgery. Postoperative BCVA was increased in all groups with its maximum 6 weeks after surgery, and no change was reported during further follow-up. There was a statistically significant difference in BCVA within groups at baseline and 4 weeks after the surgery (p = 0.00, Student's t-test). BCVA changes did not follow CRT changes in the postoperative period **(Graphs 1** and **2).**

Structural outcomes - optical coherence tomography measurements

Graph 2 and **Table 2** show the results of OCT examination, average retinal thickness in central field at baseline, 1 week, 4 weeks, 6 weeks, 8 weeks, and 12 weeks after the cataract surgery.



Graph 1. Postoperative best corrected visual acuity (BCVA) changes

Grafikon 1. *Promene najbolje korigovane oštrine vida (BCVA) tokom postoperativnog perioda*

BVCA - *Najbolje korigovana oštrina vida*

Table 1. Demographic characteristics at baseline
Tabela 1. *Demografske karakteristike ispitanika preoperativno*

		Number (n) *Broj (n)*	Percentage (%) *Procenat (%)*	Mean ± Standard Deviation (SD) *Prosek ± Standardna devijacija (SD)*
Gender/*Pol*	Male/*Muški*	13/11	38/41	
	Female/*Ženski*	21/16	62/59	
Age/*Starost*		34/27		65 ± 5/67 ± 5
Diabetes mellitus/*Dijabetes melitus* (DM)	Yes/*Da*	23/20	68/74	
	No/*Ne*	11/7	32/26	
DM duration *Dužina trajanja DM*	>10 years/*>10 godina*	10/9	44/45	11 ± 1.6/11 ± 1.7
	<10 years/*<10 godina*	13/11	56/55	6 ± 2.7/6 ± 2.8
Treatment type *Vrsta terapije*	Oral antidiabetic drugs *Oralni antidijabetici*	18/15	78/75	
	Insulin/*Insulin*	5/5	22/25	
HbA 1c/*Glukozilirani hemoglobin*	>7%	13/11	38/41	7.75 ± 0.64/7.57 ± 0.51
	<7%	21/16	62/59	5.76 ± 0.83/5.99 ± 0.74
Cholesterol *Holesterol*	>5.2 mmol/l	10/7	29/26	5.99 ± 0.56/5.91 ± 0.33
	<5.2 mmol/l	24/20	71/74	4.37 ± 0.46/4.41 ± 0.49
High-density lipoprotein *Lipoprotein visoke gustine*	>1.55 mmol/l	17/11	50/41	1.80 ± 0.12/1.76 ± 0.11
	<1.55 mmol/l	17/16	50/59	1.11 ± 0.17/1.09 ± 0.16
Low-density lipoprotein *Lipoprotein niske gustine*	<2.6 mmol/l	14/10	41/37	1.67 ± 0.59/1.86 ± 0.58
	>2.6 mmol/l	20/17	59/63	3.57 ± 0.60/3.48 ± 0.54
Triglycerides *Trigliceridi*	<1.7 mmol/l	23/19	68/70	1.35 ± 0.20/1.37 ± 0,21
	>1.7 mmol/l	11/8	32/30	2.38 ± 0.80/2.53 ± 0.91

Legend/*Legenda*: DM – Diabetes mellitus/*Dijabetes melitus*

Table 2. Central retinal thickness (CRT) changes
Tabela 2. *Promene centralne retinalne debljine (CRT)*

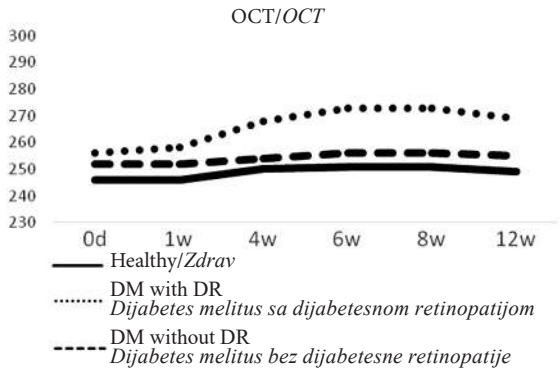
Mean CRT ± SD (μm)/*Prosečna CRT ± SD (μm)*							
	Number of eyes (n)/*Broj očiju (n)*	Day 0 *0. dan*	1 week *1. nedelja*	4 week *4. nedelja*	6 week *6. nedelja*	8 week *8. nedelja*	12 week *12. nedelja*
Group I (DM with DR) *Grupa I (DM sa DR)*	13	256 ± 11	258 ± 9	268 ± 8	273 ± 11	273 ± 11	269 ± 14
Group II (DM without DR) *Grupa II (DM bez DR)*	13	252 ± 13	252 ± 13	254 ± 14	256 ± 13	256 ± 13	255 ± 14
Group III (Healthy population) *Group III (Zdravi)*	13	246 ± 8	246 ± 8	250 ± 8	251 ± 8	251 ± 7	249 ± 8
ANOVA P < 0.05		F = 2.66 (p = 0.084)	F = 4.39 (p = 0.02)	F = 10.91 (p = 0.000)	F = 13.36 (p = 0.000)	F = 13.9 (p= 0.000)	F = 9.14 (p= 0.001)

Legenda: CRT – Centralna retinalna debljina; DM sa DR – Dijabetes melitus sa dijabetesnom retinopatijom; DM bez DR - Dijabetes melitus bez dijabetesne retinopatije; ANOVA – Analiza varijanse

Three eyes (5.9%) developed CRT > 310 μm after 4 weeks and they were excluded according to study protocol due to presence of intraretinal cysts on OCT scans. The other eyes had subclinical changes in OCT measurements after the surgery with the largest deviations after 6 weeks in comparison to baseline OCT values. Before statistical data processing, the number of eyes in groups was matched in order to get valid statistical results.

There was no difference in average baseline CRT values between the groups (group I: 256 ± 11 μm; group II: 252 ± 13 μm; group III: 246 ± 8 μm, respectively (p = 0.084, F = 2.66, ANOVA). A statistically significant difference in mean CRT values between groups was observed in postoperative follow-up period (p < 0.05, ANOVA) with major significant difference in diabetic patients with DR and after 6 weeks (group I: 273 ± 11 μm; group II: 256 ± 13 μm; group III: 251 ± 8 μm respectively, p = 0,000, F = 13.36, ANOVA).

Also, subgroup analyses were performed in regard to correlation of CRT changes and preoperatively recorded parameters: duration of diabetes, type of treatment, HbA 1c and lipid serum levels. There



Graph 2. Postoperative optical coherence tomography (OCT) changes
Grafikon 2. *Postoperativne promene optičke koherentne tomografije (OCT)*

nondiabetic patients. The BCVA increased in all groups postoperatively and showed that cataract was the main reason of visual acuity loss at the time of surgery.

In previous studies, the prevalence of postoperative macular edema varied from 0.2% to 20.4%. Advance of modern phacoemulsification as well as application of NSAID drops in combination with steroids postoperatively, has reduced the rates of macular edema which was between 0.2% and 2.35%. In diabetic patients it may be as high as 22% [14, 15]. The prevalence of subclinical macular edema in diabetic patients varies from 31% to 81% due to many confounding factors [9].

In our study, 3.8% (3 eyes of 51) developed central involved macular edema (CRT > 310 μm, SD OCT) in the 4th postoperative week. According to Kown et al. [17] macular edema occurs one month after surgery. The prevalence of macular edema among the diabetic patients was lower than expected and found

Table 3. Subgroup analysis of CRT correlated with systematic parameters 6 weeks after surgery
Tabela 3. *Analiza centralne retinalne debljine među grupama u korelaciji sa sistemskim parametrima u 6. postoperativnoj nedelji*

	Group I (DM with DR) *Grupa I (DM sa DR)*			Group II (DM without DR) *Grupa II (DM bez DR)*		
	Mean/*Srednja vrednost* ± SD	T	p	Mean/*Srednja vrednost* ± SD	T	p
DM > 10 years/*DM > 10 godina*	274 ± 12.3 μm	-0.442	0.667	262 ± 2.2 μm	-1.202	0.255
DM < 10 years/*DM < 10 godina*	271 ± 10.4 μm			253 ± 16.4 μm		
Insulin/*Insulin*	273 ± 11.0 μm	-0.075	0.941	250 ± 12.3 μm	1.079	0.304
OAD/*Oralni antidijabetici*	272 ± 11.9 μm			259 ± 13.6 μm		
HbA1c > 7%/*Glikozilirani hemoglobin*	271 ± 12.4 μm	0,427	0.678	258 ± 9.3 μm	-0.534	0.604
HbA1c < 7%/*Glikozilirani hemoglobin*	274 ± 10.2 μm			254 ± 16.6 μm		
LDL > 2.6 mmol/l/*Lipoprotein niske gustine*	274 ± 8.3 μm	-0,673	0.515	260 ± 12.4 μm	-2.41	0.035
LDL < 2.6 mmol/l/*Lipoprotein niske gustine*	269 ± 17 μm			242 ± 2.3 μm		

Legenda: DM – Dijabetes melitus, DR – Dijabetesna retinopatija

was no statistically significant difference in mean CRT in the 6th postoperative week between diabetic subgroups in regard to duration of diabetes, type of treatment, HbA 1c and lipid serums levels **(Table 3).**

Discussion

Diabetes can adversely affect all ocular tissues, including the natural crystalline lens. Diabetic patients develop cataract earlier and it matures to visual significance more quickly due to hyperglycemia. Beside the loss of visual acuity, cataract formation can mask the level of retinopathy and makes adequate treatment of retinopathy with laser photocoagulation difficult. Such patients require cataract surgery at an earlier age than nondiabetic patients [12, 13]. Phacoemulsification is a common surgical procedure applied in diabetic patients.

In this prospective study we demonstrated the influence of cataract surgery on visual acuity and macular changes in diabetic patients with and without DR and in the literature. The reason could be a higher rate of diabetic patients without retinopathy or mild form of retinopathy. Several authors reported CRT changes in patients with diabetic retinopathy after uncomplicated cataract surgery. The risk for macular thickening after cataract surgery depends on the severity of retinopathy and/or preexisting diabetic macular edema [16–18]. At our clinic, patients with severe diabetic retinopathy and/or diabetic macular edema undergoing cataract surgery were considered for anti-VEGF treatment preoperatively to avoid worsening of DR, development of DME, and improvement of visual function.

In our study, CRT measurement by OCT was the same in the three groups. Comparing the average CRT values, we found a statistically significant difference between the groups. Subclinical CRT changes (CRT < 300 μm) were detected postoperatively with the maximum value in group I (diabetics with DR) 6 weeks after surgery. Sarao et al. [10] found that the peak of CRT changes or development of macular edema was 5 – 6 weeks after uncomplicated cataract surgery. Dia-

betics without DR and nondiabetic patients showed minimal CRT changes postoperatively. This was also confirmed by the study of Kim et al. [19] reporting changes in central point thickness on OCT after cataract surgery in patients with different status of retina due to DM.

In 25% to 50% of diabetic eyes, subclinical macular changes can progress to DME and compromised visual acuity during one year, according to the DCRC protocol G [20].

In this study, analysis of subgroups did not show that hyperglycemia affected CRT changes. There was a difference in mean CRT value between the group with HbA 1c > 7% and group with HbA 1c < 7%, but it was not statistically significant. In a study including 1,002 participants, Yang et al. [5] reported > HbA 1c as a risk factor for developing macular edema in diabetic patients after cataract surgery. This was not established in our study, and the only reason could be the small number of patients included in the study without previous episodes of macular edema.

Our study did not show that the duration of diabetes and insulin dependence was a risk factor for macular edema after cataract surgery in diabetic patients. Although Kim et al. [19] showed that the group of patients with diabetes duration longer than 10 years had a postoperative increase of center point thickness of 83 μm, Flesner et al. [20] concluded that duration of diabetes longer than 10 years was not a risk factor for CRT changes after cataract surgery. In our population fewer patients receive insulin treatment and diabetic patients, particularly those who visit internal medicine specialist rarely, present with fear from insulin therapy.

We concluded that high level of low-density lipoprotein cholesterol was not a risk factor for postoperative CRT changes in diabetic patients and it is in contrast with previous studies [21]. There are, unfortunately, some limitations in this study. It included a small number of patients compared to large-scaled studies. Among the diabetic patients more than 50% had DM < 10 years and in groups with HbA 1c > 7% mean HbA 1c value was 7.75 which showed good metabolic control. Twenty-two percent of patients received insulin therapy. The study needs more patients and longer follow-up period to identify predictive factors of postoperative macular edema in diabetic population in order to be useful for prevention, diagnosis and adequate treatment of this condition.

Conclusion

In conclusion, we found that cataract surgery had a good impact on visual function in diabetic and nondiabetic patients. The impact on central retinal thickness in diabetic population without previous macular edema was mild and it was not connected with hyperglycemia, hyperlipidemia, insulin treatment and duration of diabetes.

Good visual function and improvement of the best visual acuity with minimal structural macular changes are helpful when making the decision to perform cataract surgery in diabetic patients. However, these patients should postoperatively be treated with topical nonsteroidal anti-inflammatory drugs in combination with steroids. Follow-up visits should include routine procedures to measure macular morphology and function.

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THE INCIDENCE OF NEUROPATHIC PAIN SYMPTOMS IN PATIENTS WITH KNEE OSTEOARTHRITIS

UČESTALOST SIMPTOMA NEUROPATSKOG BOLA KOD PACIJENATA SA OSTEOARTRITISOM KOLENA

Josip IVAČIĆ[1], Enis GARIPI[2], Aleksandar KNEŽEVIĆ[2, 3] and Nikola BOŠKOVIĆ[4]

Summary

Introduction. Pain is the most common symptom of knee osteoarthritis. Until recently, this pain was referred to as nociceptive pain. However, the difficulties of pain management in knee osteoarthritis indicate the possible presence of a neuropathic component. The objective of this study was to determine how often neuropathic component is part of chronic pain in knee osteoarthritis. **Material and Methods.** The study included 417 patients with knee osteoarthritis. The patients were tested using the Neuropathic Pain (Douleur Neuropathique) 4 Questions and a Numeric Pain Rating Scale. Patients were divided into 2 groups. The first group included patients with a Neuropathic Pain 4 Questions score ≥ 4, and the second group with a score < 4. **Results.** The majority of patients included in this study were females (301, 72.2%), and most of the patients scored less than 4 in the questionnaire (231, 55.4%). Among the patients with a score ≥ 4, 144 (77.4%) were female, which is significantly higher compared to the group of patients who scored < 4, 157 (68%) (p = 0.037). There was no statistically significant difference in age between the two groups (p = 0.231). The current pain intensity, average pain, and maximum pain during the last 4 weeks were significantly higher in the group with a score ≥ 4 (p < 0.001). **Conclusion.** A significant number of patients with knee osteoarthritis had a neuropathic component of pain. There were significantly more women in the group with score ≥ 4, and this group also reported significantly higher current, as well as average and maximum pain during last 4 weeks than the other group.

Key words: Osteoarthritis, Knee; Neuralgia; Nociceptive Pain; Pain Measurement; Surveys and Questionnaires; Chronic Pain

Sažetak

Uvod. Vodeći simptom osteoartritisa kolena je bol. Do sada se smatralo da je ovaj bol u osnovi nociceptivni. Ipak, njegova česta rezistencija na terapiju ukazuje na eventualno prisustvo neuropatske komponente. Cilj ovog istraživanja bio je da utvrdi koliko često je prisutna neuropatska komponenta u hroničnom bolu kod osteoartritisa kolena. **Materijal i metode.** U ovu studiju uključeno je 417 pacijenata sa osteoartritisom kolena. Pacijenti su testirani putem upitnika Neuropatski bol (*Douleur Neuropathique)* u 4 pitanja i numeričkom skalom bola. Pacijenti su podeljeni u dve grupe. Prvu grupu činili su pacijenti sa rezultatom na upitniku ≥ 4, a drugu grupu sa skorom < 4. **Rezultati.** Većina pacijenata uključenih u ovu studiju bile su žene – 301 (72,2%), takođe, većina naših pacijenata postigla je skor < 4 – 231 (55,4%)). Među pacijentima sa skorom ≥ 4, 77,4% bilo je ženskog pola (144), što je značajno više u odnosu na grupu sa skorom < 4 (p = 0,037). Nije bilo statistički značajne razlike u starosti između dve grupe (p = 0,231). Trenutni intenzitet bola, prosečan i maksimalan bol tokom poslednje četiri nedelje bili su značajno veći u grupi sa skorom ≥ 4 (p < 0,001). **Zaključak.** Značajan broj pacijenata sa osteoartritisom kolena ima neuropatsku komponetnu bola. U grupi pacijenata sa skorom ≥ 4 ima značajno više žena, a ova grupa prijavljuje i značajno viši trenutni, kao i prosečan i maksimalan bol tokom poslednje četiri nedelje.

Ključne reči: osteoartritis kolena; neuropatski bol; nociceptivni bol; merenje bola; istraživanja i upitnici; hronični bol

Introduction

Knee osteoarthritis (KO) is a common chronic, degenerative disease characterized by progressive cartilage damage, thickening of the bone beneath it, formation of new bone and capsular fibrosis [1–3]. The prevalence of this degenerative disease increases with age and is more common in women [2, 3]. The KO is the leading cause of impaired mobility in elderly people, and pain is one of its most common symptoms [1, 3, 4]. Pain in KO is currently referred to as nociceptive [3, 5, 6], where stimulation of nociceptive receptors by inflammatory agents due to chronic inflammation represents the main pathophysiological mechanism [5, 7]. However, a great number of patients showed characteristics of neuropathic pain in KO (e.g. burning, tingling etc.) [7, 8]. The etiology of this type of pain in the clinical picture of KO is not sufficiently elucidated. The subchondral bone, which suffers extensive damage and changes in this degenerative disease, is richly innervated and lesions of the

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Abbreviations
KO – knee osteoarthritis
DN4 – Neuropathic Pain 4 Questions

nerve endings may be the reason for neuropathic pain development [5, 6]. Some of the studies have shown that the joint bones of patients with osteoarthritis compared with healthy patients have a higher number of inflammatory cells, increased degree of angiogenesis, and increased growth factor receptor expression [5]. These changes can affect the sensory nervous system and in certain cases lead to sensitization and dysfunctions in intrinsic pain modulation [9]. The synovial inflammation level correlates with the amount of knee pain, and synovial joint is one of the best innervated structures of the knee [5]. Neuropathic pain often responds poorly to standard analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) that are frequently used in patients with KO [10]. Patients with neuropathic pain more often respond to non-standard pain therapy such as tricyclic antidepressants, reuptake inhibitors of norepinephrine or gabapentinoids [5, 11]. A small correlation was found between the extent of pathological changes in the knee joint and the level of pain. About 40% of patients with confirmed changes on radiological images do not have pain, while patients with minimal changes may report extremely severe pain [7]. Dilemmas like these, as well as the existence of various symptoms related to the existence of neuropathic pain in patients with KO, speak in favor of the fact that the pain in this disease is both nociceptive and neuropathic [6, 8]. Correct differentiation of pain is an important step in the therapeutic approach. Accompanying symptoms to neuropathic pain are most often abnormal sensations, feeling pain on non-painful stimuli (allodynia), prickling, stinging sensation, tingling and itching [5]. Sensory abnormalities, such as mechanical hyperalgesia and allodynia have been observed in patients with KO [12]. To confirm that neuropathic pain contributes the clinical picture is challenging. Several questionnaires have been developed to measure the proportion of neuropathic pain, such as: PainDETECT score, Leeds Assessment of Neuropathic Symptoms and Sings (LANSS) pain scale, Neuropathic Pain 4 Questions (Douleur Neuropathic) (DN4), Identification Pain (ID Pain) and Neuropathic Pain Questionnaire [7, 13–17].

We believe that detection of neuropathic pain in patients with KO is of great importance for symptom control and it can improve the quality of patients' lives. Therefore, the main goal of the present study is to determine the incidence of neuropathic pain symptoms in KO patients.

Material and Methods

The study included 417 patients with KO who were treated at the General Hospital "Senta" in the period from 2017 to 2020. The study was conducted according to the criteria set by the declaration of Helsinki and each subject signed an informed consent before participating in the study. The inclusion criteria were as follows: patients older than 18 years with the diagnosis of KO which was made according to criteria set by the American Rheumatology Association [18]. Each patient underwent a knee radiograph. The exclusion criteria were diabetes mellitus, cerebrovascular stroke, polyneuropathy or a psychiatric disorder.

In order to establish symptoms of neuropathic pain, DN4 questionnaire was used. It consists of 10 items, 7 questions related to pain characteristics and the 3 items related to physical examination. Physical examination was performed by the physician who investigated the presence of hypoesthesia and allodynia. All items are scored based on "Yes" (1 point) or "No" answers (0 point). Patients with a total score ≥ 4 were defined as having neuropathic pain symptoms [16, 19].

The patients were divided into two groups, based on the values determined by the DN4 questionnaire. The first group included patients with DN4 less than 4, and the second patients with DN4 equal or greater than 4.

To assess the intensity of current, the maximum and averagw pain intensity in the last 4 weeks, a numerical rating scale was used. In the Numerical Rating Scale (NRS) for pain, patients were asked to rate their level of pain from 0 to 10. On the scale from 0 to 10, 0 score indicates patients without pain; 1, 2 and 3 scores indicate mild pain; 4, 5 and 6 indicate moderate pain; 7, 8 and 9 indicate severe pain, while 10 score indicates the worst possible pain [18, 20].

For statistical analysis, the Statistical package for the social sciences version 20.0 was used. Descriptive statistics were calculated for the study variables. For comparison between two groups, the Student's t-test was used for numerical variables, while Chi-square test was used for categorical variables. P values < 0.05 were considered significant.

Results

For the purpose of this study, 417 patients (average age 68.03 ± 12.74 years) were recruited and divided into two groups. There was no age difference between the tested groups (67.35 ± 12.73 vs. 68.86 ± 12.74, $p = 0.231$).

Of the total sample, the majority were female respondents (72.2%). There was a significantly higher percentage of women in the DN4 ≥ 4, compared to DN4 < 4 group (77.4% vs. 68%, $p = 0.037$) **(Table 1)**. We also found that out of the total number of respondents, 144 (47.8%) women and 42 (36.2%) men scored ≥ 4 on the DN4 questionnaire.

Pain intensity was significantly higher in the group of patients with DN4 ≥ 4 for all three examined items: at the time of measurement ($p < 0.001$), maximum pain intensity in the past 4 weeks ($p < 0.001$), and the average pain measured in the past 4 weeks ($p < 0.001$). More details are given in **Table 1**.

Discussion

Osteoarthritis is one of the leading causes of disability in the modern world [3]. The most common

Table 1. Differences between DN4 < 4 and DN4 ≥ 4 groups
Tabela 1. *Razlike između DN4<4 i DN4≥4 grupa*

	DN4 < 4*	DN4 ≥ 4*	Total/*Ukupno*	χ^2/t	p
No/*Broj* (%)	231 (55.4)	186 (44.6)	417 (100)	/	/
Female (%)/*Žene (%)*	157 (68)	144 (77.4)	301 (72.2)	$\chi^2 = 4.586$	0.037
Age (Mean ± SD) years *Starost (srednja vrednost±SD) godine*	67.35 ± 12.73	68.86 ± 12.74	68.03 ± 12.74	t = -1.200	0.231
Present pain intensity (Mean ± SD) *Trenutni intenzitet bola (srednja vrednost±SD)*	6.36 ± 2.012	7.30 ± 1.999	5.92 ± 2.18	t = -4.743	< 0.001
Maximum pain intensity in the last 4 weeks (Mean ± SD)/*Maksimalni intenzitet bola u poslednje 4 nedelje (srednja vrednost±SD)*	8.50 ± 1.474	9.23 ± 1.036	8.85 ± 1.40	t = -5.909	< 0.001
Average pain intensity in the last 4 weeks (Mean ± SD)/*Prosečan intenzitet bola u poslednje 4 nedelje (srednja vrednost±SD)*	5.69 ± 1.918	6.69 ± 1.874	6.01 ± 1.95	t = -2.441	< 0.001

Legend: *DN4 - Neuropathic Pain Questionnaire with 4 questions; SD - standard deviation
*Legenda: *DN4 - Neuropatski bol u 4 pitanja; SD – standardna devijacija*

form of this disease affecting the lower extremities is KO [21]. It poses a problem for more than half of the elderly population. Increased longevity of human population and increase in frequency of risk factors, such as obesity, may be the explanation for further increasing prevalence of this disease [11]. The leading symptom of KO, as well as the most common reason for seeking help, is chronic pain [7, 12, 22, 23].

Chronic pain in KO is currently characterized as nociceptive chronic pain [7]. Inadequate response of chronic osteoarthritis pain to standard analgesics opened the question of the existing neuropathic pain being the possible component in chronic pain in general [5, 7, 11, 12, 22, 23]. Earlier researches also indicate the existence of neuropathic pain in chronic knee pain [7, 11, 22–25]. The exact mechanism of neuropathic pain is not elucidated completely, though a hypothesis of cellular and molecular mechanisms is proposed [3, 6, 10]. The complexity of changes that occur in KO and their long-term development, usually several decades time frame, are the result of various genetic and environmental factors [11].

In our study, the presence of neuropathic pain in patients with osteoarthritis was evaluated by DN4 questionnaire. According to our results, 44.6% of patients had a score greater than 4, and such a result indicates the existence of neuropathic pain. Power et al. [12] as well as French et al. [22] demonstrated that 23% of patients experience neuropathic pain, while the research of Ohtori et al. from 2012 confirmed the existence of neuropathic pain in 5.4% of patients and probable neuropathic pain in 15.2% of patients with KO [7]. The 2011 Hochman et al. survey indicated that 19% of patients had symptoms indicative of neuropathic pain [25]. The possible explanation for higher percentage in our study may be longer duration of symptoms in our sample. Another reason may be the fact that subjects from our study live in rural parts without nearby hospitals, so they tend to postpone their visit to the doctor until advanced stages of osteoarthritis. A previous research found that longer duration of pain was associated with higher rate of central sensitivity symptoms which can be interpreted as neuropathic pain by DN4 [26, 27].

The proportion of female patients in our study was 72.2% which coincides with the earlier researches that confirmed that this condition is more frequent in women [7, 12, 25]. In the group of patients with a DN4 equal or higher than 4, i.e. group with a probability of suffering from neuropathic pain, there were 77.4% of female participants. Our research showed that there is a statistically significant difference in the percentage of female patients in the group of patients with suspected neuropathic pain. The above-mentioned finding is in agreement with Power's research from 2018 [12], who found that 36% of female subjects and 28% of male subjects had scores in the likely or possibly neuropathic range, but differs from the 2012 Ohtori et al. survey that found no significant correlation between the PainDETECT score and sex [7].

The results of our study indicate that there is no statistically significant difference in age between the groups; the group with a DN4 score lower than 4, and the group with score equal or greater than 4, meaning that age does not contribute to the onset of neuropathic pain. These results coincide with the results obtained by Hochman et al. from 2011 [25] and Ohtori et al. from 2012 [7].

Our research shows that patients with DN4 score equal or higher than 4 had significantly more severe pain scores. This was the case for present, average and maximum pain intensity in the past 4 weeks. Higher pain intensity in neuropathic pain patients was in line with previous studies [7, 22, 25].

Conclusion

The neuropathic component of pain has a large share in the overall chronic pain in patients with knee osteoarthritis. The results of our research support the findings of previous studies and altogether may change the diagnostic prospects and improve pain treatment in this group of patients. The complexity of chronic pain in osteoarthritis and its treatment

remains a question which needs to be answered. The complex pathophysiological mechanism of pain and its adequate diagnosis are a major dilemma for clinicians, especially in making the decision on therapeutic approach to these patients. We believe that we should actively look for signs and symptoms of neuropathic pain in patients with knee osteoarthritis, even in cases when the pathological changes are minimal. Special attention should be paid to diagnostics and therapeutic approaches to chronic pain, in order to improve the quality of life of patients.

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CHRONIC SUBDURAL HEMATOMA – DIAGNOSIS, TREATMENT AND PERSPECTIVES

HRONIČNI SUBDURALNI HEMATOM – DIJAGNOZA, LEČENJE I PERSPEKTIVE

Mirela JUKOVIĆ[1, 2] and Viktor TILL[1, 2]

Summary

Introduction. Chronic subdural hematoma has become an important entity in radiological, neurological and neurosurgery practice. **Classification.** The classification of chronic subdural hematoma is most often done in relation to the time of the disease onset (acute, subacute and chronic), whereas the second classification is based on hematoma density using computed tomography. **Clinical presentation.** The clinical presentation may mimic a spectrum of various diseases and chronic subdural hematoma can be easily overlooked without radiological verification. **Diagnosis.** The diagnosis of chronic subdural hematoma is partly clinical and partly radiological. In most cases, computed tomography is the initial diagnostic method for detection of this disease. Many studies point to different management strategies in the diagnosis and treatment of the disease. **Therapy.** The therapy of chronic subdural hematoma depends on the patient's neurological deficit, but generally it is divided into conservative and surgical treatment. **Conclusion.** The aim of this paper is to review chronic subdural hematomas with reference to their clinical and radiological characteristics for better understanding of these phenomena.

Key words: Hematoma, Subdural, Chronic; Tomography, Spiral Computed; Radiology; Diagnosis; Signs and Symptoms; Treatment Outcome; Trauma Severity Indices

Sažetak

Uvod. Hronični subduralni hematom postaje značajan entitet u radiološkoj, neurološkoj i neurohirurškoj praksi. **Klasifikacija subduralnog hematoma** se vrši najčešće u odnosu na vreme nastanka bolesti (akutni, subakutni i hronični) i druga klasifikacija je zasnovana na denziteu hematoma korišćenjem kompjuterizovane tomografije. **Klinička prezentacija** može imitirati različit spektar oboljenja i hronični subduralni hematom se lako može prevideti bez radiološke verifikacije. **Dijagnoza** je delom klinička i delom radiološka. Kompjuterizovana tomografija je u najvećem broju slučajeva incijalna metoda za dijagnostiku ovog oboljenja. Mnoge studije ukazuju na različitu strategiju u dijagnostici i tretmanu ovog oboljenja. **Terapija** hroničnog subduralnog hematoma se sprovodi u odnosu na neurološki deficit pacijenta i generalna podela obuhvata konzervativni ili hirurški tretman. Cilj ovog rada je revijalni prikaz hroničnog subduralnog hematoma sa osvrtom na njegove kliničke i radiološke karakteristike zbog boljeg razumevanja ovog fenomena.

Ključne reči: hronični subduralni hematom; CT; radiologija; dijagnoza; znaci i simptomi; ishod lečenja; ocena težine traume

Introduction

Subdural hematomas are extra axial, semilunar accumulations of blood located between the dura and arachnoid. They are caused by stretching of very thin cortical bridging veins because of acceleration/deceleration forces [1]. There are several hypotheses and data in literature that explain formation and progression of chronic subdural hematoma (CSDH) such as inflammatory process, bridging vein trauma, osmotic pressure gaps, conversion of acute subdural hematoma to CSDH, and membrane neovascularization in the subdural space [2].

Depending on the timing of presentation and symptoms duration, subdural hematomas are classified as acute (to 7 days after trauma), subacute (8 - 22 days) and chronic type (over 22 days after injury) [3]. This type of classification was made without clear criteria and consensus in literature [4]. Another classification of subdural hematomas was made based on the texture of the hematoma on plain computed tomography (CT) scan as hyperdense, mixed, isodense and hypodense [5] **(Figure 1. 1.1. - 1.6)**. The CSDHs mostly occur in the elderly whose number is increasing every year. The index of demographic aging in 2010, in the North part of Serbia (Vojvodina Province) was 1.06, according to Petrović et al. 2011 [6]. As the population is aging rap-

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Abbreviations

CSDH – chronic subdural hematoma
CT – computed tomography
GCS – Glasgow coma scale
GOS – Glasgow outcome scale
MRI – magnetic resonance imaging
MLS – midline shifts
HW – hematoma width
DTI – diffusion tensor imaging

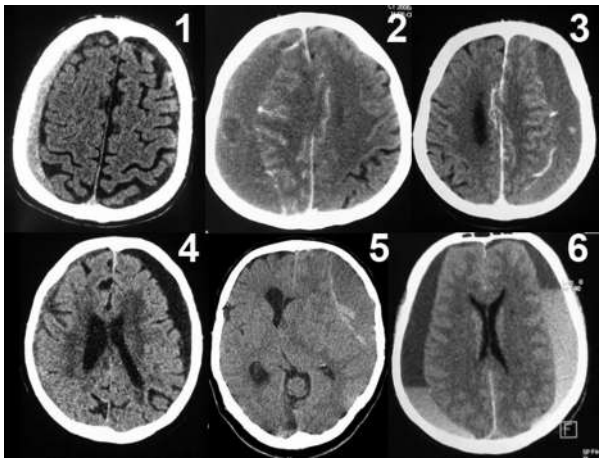

Figure 1. Classification of subdural hematomas (SDH)
1: Hyperdense subdural hematoma on the right side; 2: Unilateral isodense CSDH on the right side; 3: Unilateral isodense CSDH on the left side; 4: Hypodense CSDH on the left side; 5: Unilateral mixed density of CSDH on the left side; 6: Mixed bilateral CSDH
Slika 1. *Klasifikacija subduralnog hematoma (SDH)*
1: Hiperdenzni subduralni hematom sa desne strane; 2: Jednostrani izodenzni hronična subduralni hematom (HSDH) sa desne strane; 3: Jednostrani izodenzni HSDH sa leve strane; 4: Hipodenzni HSDH sa leve strane; 5: Jednostrani HSDH mešovitog denziteta sa leve strane; 6: Bilateralni HSDH mešovitog denziteta

idly, according to the literature [7] it is more likely to expect an increasing incidence rate of CSDH in this popullation. Consequently, a higher incidence of mortality is possible if the prevention, diagnosis and treatment strategies are not improved as well. Prevention of CSDH includes reduction of falls and traumatic injuries and future research should be directed towards prevention and identification of intrinsic and extrinsic risk factors for falls in elderly people [8]. Optimal therapy and constant monitoring are recommended for patients with comorbidities such as alcohol consumption, coagulopathy, liver and kidney diseases and seizures with clinical reference to older patients with sudden neurological deficit, behavioral disorders and mental changes. The reduction of postoperative complications in hospitals is also important and patients need special nursing care. Nursing knowledge, and practice about care of patients with CSDH should be improved through educational and training programs [9].

The aim of this paper is to review CSDHs with reference to their clinical and radiological characteristics for better understanding of these phenomena in order to improve diagnosis, therapy and clinical outcome.

Radiological classification of CSDHs

The CSDHs may mimic various neurological diseases. When we are dealing with elderly patients with CSDH, sometimes it cannot be recognized by clinicians alone, because many symptoms and signs in patients may be consequences of atherosclerotic changes and degenerative brain diseases, so CSDH can be overlooked without additional radiological diagnosis [10]. Classification of CSDH was made by Nakaguchi et al. based on internal architecture, density, and hematoma expansion on CT [11]. However, density of the hematoma on brain CT is not strictly connected to older age, namely, hyperdense hematoma on CT is usually acute, but isodense hematoma is not only subacute, and hypodense is not strictly chronic [5]. Acute subdural hematomas are usually caused by traumatic events, but CSDHs can appear without previous trauma (in 30 – 50% of patients) [12]. The CSDHs may be unilateral and bilateral with the assumption that the cranial morphology plays an important role in determination of the site [13, 14]. Potentially, repeated hemorrhage is connected to different density of the subdural hematoma on CT, and it depends on coagulation status and other risk factors and comorbidity in older patients. Extravasation of blood and cerebrospinal fluid into the subdural space causes local aseptic inflammation and inflammatory induced angiogenesis. Consequently, dura mater produces granulation tissues and inflammatory cells leading to neomembrane production i.e. the capsule of the hematoma [15]. Fibrinolytic activities cause microhemorrhage and increase the subdural hematoma [16].

Clinical features

The clinical course of this type of disease includes three phases: initial phase, which includes formation of subdural hematoma presenting with several symptoms and episodes; the second phase involves biochemical mechanisms of subdural hematoma growth with clinically asymptomatic period (or latent period) lasting from a few days to several weeks; and the third phase with expanding hematoma and disturbance of compensatory mechanism which leads to symptomatic period of the disease [2]. Also, the interval from trauma to clinical presentation of CSDH is different in younger and older patients. Younger patients may have promoting factors for CSDHs such as ventriculoperitoneal shunts, intracranial hypotension, and history of coagulopathy, alcohol consumption, vascular malformation or arachnoid cyst and have shorter duration from trauma to surgery treatment [17, 18]. Delayed clinical presentation of CSDH in elderly occurs due to wideness of extra axial liquor spaces, as a result of cortical atrophy [17, 19]. The literature data show numerous different symptoms and signs in patient with CSDH [10]. In the thesis of Juković, which included 83 patients with CSDHs treated at the Clinical Center of Vojvodina in

the period of three years, the following symptoms were found: headache, dizziness, seizures, vomiting, hemiparesis, mental changes, confusion, speech and visual disturbances or facial paresis. According to Juković, the highest percentage of patients with CSDH in Vojvodina had comorbidities such as high blood pressure (33%) and heart diseases (16%). Alcohol consumption was recorded in 16.9% of patients and coagulability disorders in 13.2%. A previous trauma was found in 67.5% of patients, but 32.5% of patients had no traumatic event, or they did not remember prior head injury [13]. Falls and fall-induced injuries are the most important injuries in elderly people and represent one of the major causes of disability and morbidity and about 20% need medical attention [20].

On admission, Glasgow Coma Scale (GCS) is the most widely used scoring system used in assessing level of consciousness and neurological deficit [21]. The patient's clinical outcome is based on Glasgow Outcome Scale (GOS) [22]. Although the history of trauma is the major cause of subdural hematoma, non-traumatic subdural hematomas can be diagnosed after lumbar puncture causing intracranial hypotension, after long term usage of antiplatelet or anticoagulant drugs or due to coagulation disorders [23].

Diagnosis

Computed tomography and magnetic resonance imaging (MRI) play an important role in the diagnosis of subdural hematoma. The MRI has a higher sensitivity for evaluation of internal structure and neomembrane of CSDH that is important for optimal surgery treatment [23]. As a rapid, non-invasive and widely available method, CT is the first line modality of choice in diagnosis of subdural hemorrhage [24]. Some dural and leptomeningeal metastases, sarcoidosis, histiocitosis and subdural empyema [25, 26] may mimic or may be associated with CSDHs, therefore the use of contrast CT is justified in such cases.

In the thesis of Juković, clinical and CT parameters are used to give more information about the prognosis and outcome of patients with CSDH [13, 17, 27–30]. Isolated CT parameters - midline shifts (MLSs) and hematoma width (HW) fail to show a high prognostic value for the outcome. However, MLS and hemiparesis show a high prognostic value when MLS exceeds the threshold level [27]. Clinical parameters included the age of patients and neurological state on hospital admission evaluated using GCS. The GCS showed to be most significant for the outcome estimated by GOS. The combination of these parameters using multiple regression analysis is used for predicting unknown values to a certain extent ($R^2 = 0.33$).

GOS = 0.166-0.018 x A+0.013 x W+0.313 x GCS+0.040 x MLS

Although only about one third of outcomes can be explained by the created model, more cases and application of advanced statistical models could lead to improved treatment and outcome of patients with CSDH.

The newest techniques, such as MR, MR spectroscopy, MR perfusion, diffusion tensor imaging (DTI) and 18F-fluorodeoxyglucose positron emission tomography have an important role in the diagnosis of traumatic brain injuries. Although not all of these techniques are routinely implemented in daily radiological practice, their relevance is growing, and they are given importance due to the possibility of individual approach to each patient and thus better diagnosis and treatment [31–33].

Therapy

The treatment of subdural hematoma depends on the type of hematoma and clinical presentation. Acute subdural hematoma is more common in younger patients and requires urgent treatment because of brain edema, existence of MLSs diagnosed by CT and more severe clinical symptoms and signs. The CSDH requires prompt surgical treatment in cases of significant neurological deficit, after the latent period has passed. Surgical treatment of CSDH includes different principles of evacuation **(Figure 2)** such as one or two burr hole drainage, twist drill craniotomy, craniotomy and the subdural evacuating port system [34, 35]. Santarius et al. showed that burr hole is the superior method than twist drill craniotomy [36]. Patients that were treated with burr hole had lower risk for recurrence of hematoma and small percentage of complications after surgery [36, 37]. Craniotomy is a more invasive method and it requires an extended time of surgery and recovery period [38]. According to Juković, the average hospital stay of patients who were treated with craniotomy was 13.3 days and in patients treated with burr hole it was about 10 days [13]. In exceptional cases, the surgical treatment of patients with CSDH is postponed, although there are positive radiological parameters. If the general clinical status of the patient is poor, due to comorbidities (liver disease, chronic pulmonary obstructive disease, cardiac decompensation) or there are risk factors for surgical treatment (thrombocytopenia, coagulation disorder) the surgery is delayed with constant monitoring [39]. Mori and Maeda showed that patients with surgical treatment had good clinical recovery and that surgical

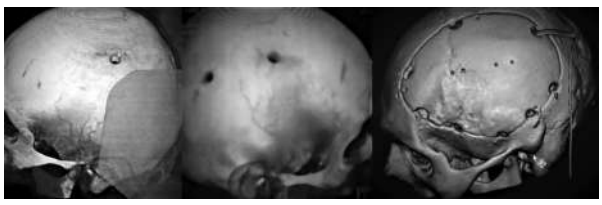

Figure 2. Types of surgical treatment in patients with CSDHs (single burr hole drainage/left side, two burr holes drainage, craniotomy/right side)
Slika 2. *Tipovi hirurškog tretmana kod pacijenata sa HSDH (jedan ovalni trepanacioni drenažni otvor/leva strana slike; dvostruki ovalni trepanacioni otvor, kraniotomija/desna strana slike)*

therapy is safe even in patients above 90 years if their clinical and physical condition is appropriate [19]. The recurrence of CSDH after surgery is possible and factors that contribute to recurrence of CSDH are multi-factorial involving independent predictors, such as laminar type of hematoma, thicker hematoma, and larger post-operative drainage amounts of CSDH [23, 40]. Stanišić et al. showed that hematoma volume before surgery, laminar and separated types of CSDH and residual CSDH post-surgery on the CT scan were independent predictors for recurrence of CSDH [41]. Ohba et al. showed that pneumocephalus after surgery treatment had a tendency to be associated with recurrence of CSDH [42]. Postsurgical complications may be related to tension pneumocephalus, anesthesia, cerebral inflammation, intraparenchymal hemorrhage or neurological deficits, more frequently in recurrent CSDH [43, 44].

In Juković's research, the postoperative complication rate was low. One of the patients had ischemic stroke, one had intraparenchymal hemorrhage. Extracranial complication in the form of pneumonia was noted in one patient [13]. According to literature records, the data about spontaneous resolution of CSDH [39, 45] and nonsurgical treatment are isolated cases [46, 47]. Asymptomatic patients, mild headache or patients without neurological deficits are candidates for conservative treatment. It is considered that small volume of the CSDH without significant mass effect on brain parenchyma, MLS below 5 mm on the CT scan or frontal localization of CSDH have tendency to resolve spontaneously. The "wait and see" approach is justified in patients with a low volume of CSDH and in patients without neurological deficit [48]. Hemiparesis and speech disturbance in elderly patients with large midline shifts and unilateral CDSH were most common signs that required surgery [49].

Trends in diagnostic radiology and clinical outcome of CSDH

Neuroimaging modalities, supported by computer technology, are becoming more and more significant in healthcare [50]. The CT modality has a remarkable role in fast preoperative diagnosis of CSDH as well as in follow-up. The MRI and DTI could be implemented as additional imaging techniques, because of detailed evaluation of internal characteristic of CSDH and determining the significance of mass effect on corticospinal tracts and other brain structures which could be potentially involved in the manifestation of neurological symptomatology. Clinical signs and symptoms, GCS on admission, biochemical and laboratory analysis, and neuroimaging data provide precise information about every patient. The clinical and radiological input data about patients with CSDH may be the basic information for optimal strategies in individual clinical treatment protocols. Today, machine learning techniques, based on computer softwares, can optimize protocols and improve patient treatment and outcome [51, 52]. The implementation of advanced methods for neuroimaging data analysis could contribute to better diagnosis and give overall performance of outcome. Literature suggests the use of computer assisted system, which is integrated with a medical imaging machine, provides a quick diagnosis and reduces the number of diagnostic errors [53]. New technical and statistical methods can be implemented in radiological imaging analysis for better detection and expanded diagnosis systems [54].

Conclusion

Chronic subdural hematoma is a disease of the elderly, but it has a great potential to become one of the most common diseases in radiological, neurological and neurosurgery practice due to the increase of the aging population. Recognition of this disease is essential for proper treatment and reduction in mortality. Clinical evaluation associated with radiological imaging allows better understanding of this phenomenon providing correct diagnosis and better prognosis of the patients. We strongly believe that a larger sample of patients, together with a comprehensive database of clinical and radiological signs evaluated through the prism of modern data mining techniques and predictive models, may significantly improve the treatment and final outcome of various types of brain diseases in the future.

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ALLERGIC RHINITIS, PART OF THE ALLERGIC RESPIRATORY SYNDROME

ALERGIJSKI RINITIS, DEO RESPIRATORNOG ALERGIJSKOG SINDROMA

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Summary

Introduction. Diseases associated with immunoglobulin E hypersensitivity, such as allergic rhinitis, may have different clinical expressions. Patients with allergic rhinitis often have associated diseases, comorbidities, which supports the concept of allergy as a systemic disease. The aim of this study was to evaluate the incidence and types of comorbidities in allergic rhinitis. We also evaluated the possible effects of certain clinical and demographic parameters on the onset of comorbidities. **Material and Methods.** This retrospective, observational, and cross-sectional study included patients with a clinical diagnosis of allergic rhinitis treated at the Department of Ear, Nose and Throat in the period from October 2011 to April 2013. The collected data were analyzed using the Statistical Analysis System (Institute Inc. NC, USA) program, version 9.1.3. **Results.** The study included 319 patients with allergic rhinitis. Allergic rhinitis was intermittent in 30.7% of cases, persistent in 37.9%, and persistent with seasonal exacerbation in 31.3% of patients. We found that 86.8% of patients had some form of comorbidity. The most common were conjunctivitis (50.2%), almost equal percentage of asthma (29.8%) and chronic rhinosinusitis (28.8%), followed by otitis media with effusion (8.8%), atopic dermatitis (5.2%), urticaria (4.1%), and laryngitis (3.8%). Persistent allergic rhinitis, with persistent nasal obstruction as the dominant symptom, was significantly associated with chronic rhinosinusitis. Positive family history was significantly associated with the occurrence of asthma and allergic rhinitis. **Conclusion.** The results of our study showed that allergic rhinitis is rarely an isolated condition and it should always be observed in the context of the allergic respiratory syndrome.

Key words: Rhinitis, Allergic; Respiratory Hypersensitivity; Comorbidity; Signs and Symptoms; Sinusitis; Asthma

Sažetak

Uvod. Oboljenja udružena sa imunoglobulin E preosetljivošću kao što je alergijski rinitis mogu imati različitu kliničku ekspresiju. Pacijenti sa alergijskim rinitisom često imaju i udružena oboljenja, komorbiditete, što ukazuje na to da je alergija sistemsko oboljenje. Postavili smo cilj da procenimo učestalost i tipove komorbiditeta alergijskog rinitisa. Takođe smo ispitivali mogući uticaj određenih kliničkih i demografskih parametara na pojavu komorbiditeta. **Materijal i metode.** Pacijenti sa kliničkom dijagnozom alergijskog rinitisa uključeni su u prospektivnu, opservacionu, studiju preseka na Odjelu za bolesti uha, grla i nosa Univerzitetskog kliničkog centra Republike Srpske u Banjaluci, tokom perioda od oktobra 2011. godine do aprila 2013. godine. Prikupljeni podaci analizirani su statističkim sistemom analize (*Institute Inc. NC, USA*), verzija 9.1.3. **Rezultati.** U studiju je uključeno 319 pacijenata sa alergijskim rinitisom. Alergijski rinitis je bio intermitentni kod 30,7% slučajeva, perzistentni kod 37,9% slučajeva i perzistentni sa sezonskim egzacerbacijama kod 31,3% pacijenata. Utvrdili smo da 86,8% pacijenata ima neki oblik komorbiditeta. Najčešći je bio konjunktivitis (50,2%), gotovo je bio jednak procenat astme (29,8%) i hroničnog rinosinuzitisa (28,8%); slede sekretorni otitis medija (8,8%), atopijski dermatitis (5,2%), urtikarija (4,1%) i laringitis (3,8%). Perzistentni alergijski rinitis sa perzistentnom nazalnom opstrukcijom kao dominantnim simptomom, značajno je bio povezan sa hroničnim rinosinuzitisom. Pozitivna porodična anamneza je bila značajno povezana s pojavom astme i alergijskog rinitisa. **Zaključak.** Prema rezultatima naše studije, alergijski rinitis je retko izolovano oboljenje i treba ga uvek posmatrati u kontekstu respiratornog alergijskog sindroma.

Ključne reči: alergijski rinitis; respiratorna hiperosetljivost; komorbiditet; znaci i simptomi; sinusitis; astma

Introduction

Respiratory allergies, including allergic rhinitis (AR), are complex disorders due to the heterogeneity of symptoms that vary in terms of localization, time of onset, co-occurrence of other conditions, response to treatment and prognosis [1]. They are associated with complex interrelationships with different expres-

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Abbreviations
AR – allergic rhinitis
IgE – immunoglobulin E
ARIA – Allergic Rhinitis and its Impact on Asthma
OME – otitis media with effusion
SPT – skin prick test

sions. The unity of the respiratory tract is confirmed both from a morphological and from a functional point of view. Knowledge that AR, rhinosinusitis, and asthma are manifestations of an inflammatory process within a continuous airway, has led to the introduction of a new concept of "united airway disease". This concept is widely appreciated and is supported by findings from numerous studies [2, 3]. The AR is a common inflammatory chronic disease induced by an immunoglobulin E (IgE)-mediated reaction after allergen exposure in the nasal mucosa. Current estimates suggest that up to 30% of Europeans may be suffering from allergic rhinoconjunctivitis [4–6]. It is rarely isolated, so it should be considered in the context of upper and lower airway disease.

Clinical expression of AR may be viewed through the severity or presence of comorbidities. Moreover, in our daily practice, we can recognize different clinical entities of AR, from patients with mild symptoms to severe forms of the disease. In some patients AR is an isolated disease, while others have one or more comorbidities. To date, we have not been able to recognize the factors that contribute to the severity of symptoms or the onset of comorbid disorders in AR patients. However, AR needs to be considered in the context of systemic allergic disease associated with numerous comorbid disorders, including asthma, chronic middle ear effusions, sinusitis, and lymphoid hypertrophy with obstructive sleep apnea, sleep disorders, and consequent behavioral and educational effects [4].

The aim of this study was to evaluate the incidence and types of AR comorbidities in our clinical practice. We also evaluated the possible impacts of some clinical and demographic parameters on the onset of comorbidities.

Material and Methods

A retrospective, cross-sectional observational study included 319 adults and children with AR, diagnosed and treated as outpatients at our Rhinology Department during a study period of 19 months. All children were under the age of 18. Demographic data and place of residence were collected and AR was identified if patients were exposed to aeroallergens and showed a positive allergen skin prick test (SPT). Detailed medical history data, complete physical examination, and SPT were performed. A standard SPT was performed using a panel of standardized allergen extracts [7]. The recommended method of prick testing included appropriate use of specific allergen extracts, positive and negative controls, interpretation of the tests after 15 – 20 minutes of application, with a positive result defined as a wheal ≥ 3 mm diameter. Sensitization to two or more allergens indicated polysensitization. Duration of AR was classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines with some modifications. Intermittent AR was defined by symptoms that occur for 4 or less days per week or not more than 4 consecutive weeks. Persistent AR was defined by symptoms occurring for more than 4 days/week and more than 4 consecutive weeks. We also took into consideration a group of subjects with persistent symptoms with seasonal exacerbation. The classification of AR severity was based on symptom intensity according to the ARIA guidelines as mild or moderate/severe [8].

The presence of comorbidities was also evaluated. The presence of asthma was obtained from the medical records. Evidence of otitis media with effusion (OME) was collected from medical visits to Audiology Department during the previous 3 months. Patients were considered to suffer from allergic conjunctivitis if they complained of ocular symptoms accompanying rhinitis. The criteria for diagnosis of rhinosinusitis were a history of > 2 nasal symptoms and either positive nasal endoscopy and/or positive sinus radiography based on the definition from the European position paper on rhinosinusitis and nasal polyps 2012 [9].

Formal ethical approval to conduct the study was obtained from the Ethics Committee before the commencement of the study. Informed consent was sought from each patient before being enrolled into the study.

A descriptive analysis of the study population was performed. The analysis was carried out using the Statistical Analysis System (Institute Inc. NC, USA) program, version 9.1.3. All variables were described for the total sample. The number of valid cases was used in all tables and graphs, and when calculating percentages or any other statistical data. Continuous variables were summarized based on the number of valid cases, mean, standard deviation, median, and extreme values; categorical variables were described by means of number of valid cases and percentages in every category, while variables with an asymmetric frequency distribution were described using the medians and their 25th to 75th percentiles. Other appropriate tests (chi-squared, Mann–Whitney, or Kruskal–Wallis) were used in each case for other comparisons. Statistical significance was set at a p value of < 0.05.

Results

There were 319 patients, both adults and children, with AR; 153 (48.0%) were male and 166 (52%) were female **(Table 1)**. The median age was 17.0 years (min. 3.0 - max. 58.0). A particularly high proportion of patients (over 40%) were 8 - 19 years of age. According to the duration of AR, persistent allergic rhinitis was the most common type of AR (37.9%), followed by persistent AR with seasonal exacerbation (31.3%), and intermittent AR (30.7%). Almost all patients were in the moderate/severe group (92%) of AR due to the fact that data were collected from patients at a tertiary healthcare department. There were no

Table 1. Incidence of some demographic characteristics in patients with allergic rhinitis
Tabela 1. *Učestalost određenih demografskih parametara na alergijski rinitis*

	n	%	p-value/*p vrednost**
Gender/*Pol*			
Male/*Muški*	153	48	.467
Female/*Ženski*	166	52	
Age, years/*Uzrast, godine/*(median, min – max)/(*prosek, min. – maks.*)	17	3 - 58	
Place of residence/*Mesto stanovanja*			
Rural/*Selo*	39	12.2	
Suburban/*Predgrađe*	122	38.2	< .001
Urban/*Grad*	158	49.5	
Family history of allergies/*Porodična istorija alergija*	164	51.4	.614
Polysensitization/*Polisenzibilizacija*	268	84	< .001
Type of allergic rhinitis/*Tip alergijskog rinitisa*			
Intermittent/*Intermitentni*	98	30.7	
Persistent/*Perzistentni*	121	37.9	.217
Persistent with seasonal exacerbation/*Perzistentni sa sezonskim pogoršanjima*	100	31.3	

Legend/*Legenda*: *Based on chi-square test of equal distribution of categories/**Bazirano na x^2 test jednake distribucije kategorija*
Total N = 319/*Ukupno n = 319;* p value was set at 0.05/*p < 0,05 vrednosti su imale statistički značaj*

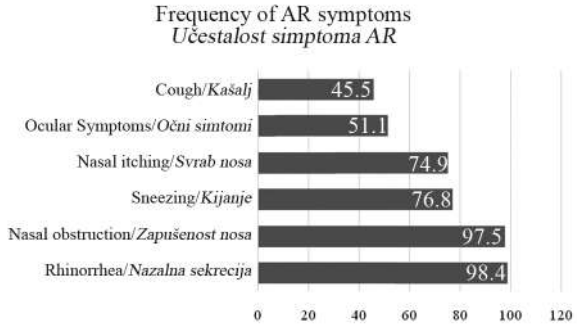
significant differences between gender, age, average age (median, min – max), place of residence and type of AR **(Table 2)**.

There were significantly more positive medical histories of allergies and poly-sensitized patients in the group of persistent AR with seasonal exacerbation. Distribution of allergen sensitization corre-

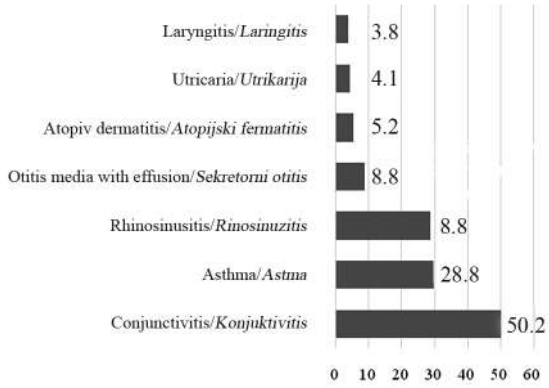
Table 2. The incidence of certain demographic characteristics related with the duration of allergic rhinitis
Tabela 2. *Učestalost određenih demografskih parametara na trajanje alergijskog rinitisa*

	AR type/*Tip alergijskog rinitisa*			p-value* *p vrednost*
	Intermittent *Intermitentni*	Persistent *Perzistentni*	Persistent with seasonal exacerbation/*Perzistentni sa sezonskim pogoršanjima*	
Gender/*Pol* (%)				
Male/*Muški*	42.9	52.9	47	.325[1]
Female/*Ženski*	57.1	47.1	53	
Age, median, years/*Uzrast, prosek, godine*)	14	20	17	.162[2]
Place of residence/*Mesto stanovanja* (%)				
Rural/*Selo*	14.3	10.7	12	
Suburban/*Predgrađe*	36.7	40.5	37	.682[3]
Urban/*Grad*	49	48.8	51	
Family history of allergies *Porodična istorija alergija* (%)	45.9	47.1	62	.039[1]
Polysensitization/*Polisenzibilizacija* (%)	81.6	76	96	< .001[1]
Allergens/*Alergeni* (%)				
House dust/*Kućna prašina*	68.4	93.4	84	< .001[1]
Grass pollen/*Polen trava*	72.4	50.4	76	< .001[1]
Tree pollen/*Polen drveća*	29.6	20.7	46	< .001[1]
Weed pollen/*Polen korova*	62.2	53.7	68	.091[1]
Mould/*Buđ*	5.1	7.4	3	.345[1]
Pet dander/*Životinjski derivati*	5.1	6.6	10	.429[1]

Legend: *p - values obtained through different procedures depending on predictor's level of measurement: 1 = exact chi-square test; 2 = multinomial logistic regression; 3 = chi-square test for linear trend; p value was set at 0.05
*Legenda: *p - vrednosti dobijene različitim postupcima, zavisno od nivoa merenja: 1 = x^2 test sa egzaktnim proračunima, 2 = multinomininalna logistička regresija; 3 = x^2- test za linearni trend; p < 0,05 vrednosti su imale statistički značaj*



Graph 1. The incidence of allergic rhinitis symptoms
Grafikon 1. *Učestalost simptoma alergijskog rinitisa*



Graph 2. The incidence of comorbidities of allergic rhinitis
Grafikon 2. *Učestalost komorbiditeta alergijskog rinitisa*

sponded to the type of AR. Approximately half the patients had positive parental history of allergies, (n = 164/319, 51.4%). Most of the patients lived in urban locations (49.5%, CI [44.1, 55.0]). One in eight patients were from rural (12.2%, CI [9.0, 16.3]) areas. Mites (82.8%) were the most common allergen, followed by grass pollen (65.2%), weed pollen (60.8%), tree pollen (31.3%), pet dander (7.2%) and molds (5.3%). Most of the patients were poly-sensitized (n = 68/319, 84%, CI [79.6, 87.6], p < .001) **(Table 1)**. The most frequent symptoms were nasal obstruction (97.5%) and rhinorrhea (98.4%) **(Graph 1)**.

We found that 86.8% of patients had some comorbidity (p < .001). The most frequent were conjunctivitis (50.2%), almost equal percentage of asthma (29.8%) and chronic rhinosinusitis, (28.8%), followed by otitis media with effusion (8.8%), atopic dermatitis (5.2%), urticaria (4.1%) and laryngitis (3.8%) **(Graph 2)**.

Conjunctivitis was most common in patients with intermittent and persistent with seasonal exacerbation type of AR, while rhinosinusitis was most common in patients with persistent AR. There was a significant difference (p < .001) between presence of conjunctivitis and intermittent or seasonal occurrence of AR, as well as between sinusitis and persistent (43%) or persistent with seasonal exacerbation AR (35%). There were no significant differences between other comorbidities and type of AR **(Table 3).**

The **Table 4** shows the incidence or influence of some clinical and demographic parameters on the onset of comorbidities. Asthma was significantly more frequent (p < .001) in patients with positive history of allergies. The probability of rhinosinusitis as a comorbidity significantly increases (p < .001) with age. Persistent nasal obstruction or persistent symptoms of AR rather than intermittent symptoms were significantly associated with rhinosinusitis (p < .001). Cough, deviated septum and polyps were significantly associated with rhinosinusitis (p < .001).

Discussion

The prevalence of allergic diseases worldwide has dramatically increased over the last 20 - 30 years, which calls for the need to monitor allergies in general. Complex allergies are on the rise, resulting in increased demand for healthcare services, due to polysensitization and multiple organ system involvement. Recent studies show increasing trends of allergic diseases in developing countries [4]. Environmental changes, including the presence of

Table 3. The incidence of different comorbidities in regard to the type of allergic rhinitis
Tabela 3. *Učestalost različitih komorbiditeta u odnosu na tip alergijskog rinitisa*

Comorbidity/*Komorbiditeti*	AR type/*Tip alergijskog rinitisa*			
	Intermittent *Intermitentni* (%)	Persistent *Perzistentni* (%)	Persistent with seasonal exacerbation *Perzistentni sa sezonskim pogoršanjima* (%)	p-value* *p vrednost*
Conjunctivitis/*Konjunktivitis*	65.3	24.8	66	<.001
Asthma/*Astma*	28.6	28.9	32	.831
Rhinosinusitis/*Rinosinuzitis*	5.1	43	35	<.001
Otitis media with effusion *Sekretorni otitis*	10.2	10.7	5	.274
Urticaria/*Urtikarija*	5.1	1.7	6	.280
Laryngitis/*Laringitis*	2	5	4	.539

* Based on exact chi-square test of equal distribution of categories; Total = 319; p value was set at 0.05

** Bazirano na x^2 testu jednake distribucije kategorija. Ukupno = 319; p < 0,05 vrednosti su imale statistički značaj*

Table 4. The incidence and influence of some clinical and demographic parameters on the onset of allergic rhinitis comorbidities
Tabela 4. *Učestalost i uticaj određenih kliničkih i demografskih parametara na pojavu komorbiditeta alergijskog rinitisa*

	Comorbidity/*Komorbiditeti*		P - value[1]
Variable/*Varijable*	Positive/*Pozitivno*	Negative/*Negativno*	*P*
Asthma/*Astma*			
Family history of allergies/*Porodična istorija alergija* (%)	65.3	45.4	**.001***
Cough/*Kašalj* (%)	84.2	29.0	**<.001***
Otitis media with effusion/*Sekretorni otitis*			
Age, years, average/*Uzrast*, *godine*, *prosek*)	9.0	19.0	**<.001***
Rhinosinusitis/*Rinosinuzitis*			
Age, years, average/*Uzrast*, *godine*, *prosek*	24.0	16.0	**<.001***
Nasal obstruction/*Zapušenost nosa* (%)			
Intermittent/*Intermitentni*	9.8	44.1	**<.001***
Persistent/*Perzistentni*	90.2	52.4	
Rhinorrhea/*Sekrecija iz nosa* (%)			
Intermittent/*Intermitentni*	51.1	77.1	**<.001***
Persistent/*Perzistentni*	47.8	21.1	
Nasal itching/*Svrab nosa* (%)			
Intermittent/*Intermitentni*	57.6	74.4	**.009***
Persistent/*Perzistentni*	8.7	4.0	
Sneezing/*Kijanje* (%)			
Intermittent/*Intermitentni*	55.4	77.5	**<.001***
Persistent/*Perzistentni*	10.9	3.5	
Ocular symptoms/*Očni simptomi* (%)			
Intermittent/*Intermitentni*	39.1	55.5	**.006***
Persistent/*Perzistentni*	1.1	0.0	
Cough/*Kašalj* (%)	66.3	37.0	**<.001***
Deviated septum/*Devijacija septuma* (%)	83.7	33.9	**<.001***
Nasal polyps/*Nazalni polipi* (%)	19.6	1.3	**<.001***

*p < .05. Based on chi-square test of association except for age (Kruskal-Wallis test)/*p<,05. *Bazirano na x^2-testu, osim za godine (Kruskal-Wallis test)*
p < 0.05 value was accepted as significant level and the significant differences between the groups are shown in bold
p < 0,05 vrednosti su prihvaćene kao signifikantne, značajna razlika između grupa je prikazana boldovano

outdoor pollution and urban lifestyle are a likely cause of the increase of allergies in developing countries, including ours. We are still unable to identify endophenotypes of AR which develop from complex genetic and epigenetic interactions. The concept of precision medicine in allergic diseases requires higher efficiency in conducting diagnostic procedures and personalized management.

Results of this study validate these trends, since almost all patients from the study were in the moderate/severe group (92%) of AR. This finding is clearly influenced by the fact that data were collected from patients at a tertiary department, although the evidence from a previous survey showed that the majority or approximately 75% of AR patients reported moderate/severe forms of rhinitis [10].

In this study, patients from urban and suburban areas came somewhat more frequently for examination, but there were no significant differences in terms of the prevalence of AR in patients from a particular area. This confirms the results of previous studies according to which people from rural areas, including ours, are increasingly adopting urbanized Western lifestyle, and so it is not possible to determine whether the place of residence is the factor that modifies the clinical manifestations of AR [11].

In regard to the age of patients, these results are in agreement with the previous ones which show that AR is most prevalent in the pediatric and adolescent population [5, 12].

A study performed in Spain reported that AR was the most frequently diagnosed allergic disease (44.9%) in patients under the age of 14 [13].

There were almost equal types of AR in our study, but the majority of patients suffered from persistent symptoms, taking into account the total number of patients with persistent and persistent with seasonal exacerbation AR. Similar findings were also reported in other studies. Results of a survey conducted in the United States show that the majority of patients with AR reported perennial symptoms [14]. Results of a survey conducted by

Canonica et al. found that 42.5% of the AR patients had persistent symptoms [15]. A study by Bachert et al. reported that approximately 40% of patients with AR compared with 23.5% of patients with non-allergic rhinitis had persistent symptoms [10].

According to our results, the incidence of patients with positive history of allergies was much higher in the group of patients with persistent AR with seasonal exacerbation and in the group of patients with asthma. Positive family history is mentioned as a predictive factor in the development of asthma and AR. Earlier results show that positive family history of asthma or rhinitis increases the risk of developing asthma and AR compared to persons with no family history [16].

Nasal congestion and rhinorrhea were identified as the most frequent symptoms and that is consistent with previous studies. Intermittent and persistent presence of symptoms reported by patients corresponded to the type of AR [15]. Moreover, most patients were likely to be sensitized to both pollen and house dust mites. Other perennial allergens, such as mould and pet dander, were less present. Distribution of allergen sensitization corresponded to the type of AR. Most of our patients were polysensitized, which is in agreement with earlier studies according to which polysensitization is highly prevalent in patients with AR. Different studies found different results in terms of the frequency of polysensitization [17, 18].

Immunoglobulin E associated diseases such as AR may have several clinical expressions. Respiratory allergy can be considered as a global disorder of the airways. Therefore, AR, asthma, and rhinosinusitis frequently coexist, and are considered as part of a common syndrome, for which different terms, including chronic respiratory allergy have been proposed [19–21].

We found that 86.8% of patients had some concomitant disease. This was in agreement with previous studies which found that patients with AR were at a higher risk of other comorbidities compared with a large number of adults without AR [22].

In a previous study, it was reported that sinusitis and conjunctivitis were frequent past or current comorbidities, and that coexistence of otitis media and nasal polyposis was less frequent. The same study estimated that asthma was present in 32.7% of cases [23].

We found that the most frequent was conjunctivitis (50.2%) in patients who were sensitized to outdoor allergens. A recent study found that about 75% of AR patients complained of the symptoms of allergic conjunctivitis [24].

We also found that 29.8% of patients had asthma. It was in agreement with previous studies which found that up to 40% of patients with AR suffered from asthma [20, 22].

Several studies have reported a strong association between asthma and AR, which is why these two diseases, which have been considered separate entities until recently, are now considered a single entity, for which different terms, including "chronic respiratory allergy", "united airway disease" have been proposed [2, 25]. The AR is associated with asthma in 40% of patients, whereas 80% to 95% of patients with allergic asthma also have rhinitis [4]. There were no significant differences in terms of the presence of asthma in different types of AR, which is in disagreement with earlier studies which found that asthma was more prevalent among AR patients with more severe and persistent disease [26]. In this study, asthma was significantly more frequent ($p < .001$) in patients with positive history of allergies.

We found that 8.8% of patients had otitis media with effusion. Evidence suggests epidemiologic and pathophysiological links between allergy and OME. One of the contributing factors to the development of OME is allergic inflammatory response. The prevalence of AR in patients with OME ranges from 24% to 89%, usually around 23% [27]. According to a study by Kreiner-Møller et al., OME was closely associated with AR presumably caused by allergic inflammation, but not mechanical nasal mucosal swelling [28]. In a recent study, Passali et al. showed significant association between OME and persistent allergic rhinitis [29].

A causal mechanism between allergic nasal inflammation and development of sinus disease is still unclear. Rhinosinusitis is a heterogeneous group of diseases with different underlying etiologies and the pathophysiological mechanism involved in its development is complex [30]. The survey also documents a strong relationship between nasal allergies and sinus conditions, with 66% of AR patients reporting that they also suffer from rhinosinusitis or sinus conditions. In contrast, only 20% of adults without nasal allergies suffer from rhinosinusitis or sinus problems [22].

Due to a very similar presentation, it is very difficult to distinguish AR and rhinosinusitis. In this study, sneezing, itchy nose and/or eyes, obstruction and rhinorrhea were symptoms related to AR, whereas adults and children with sinus disease complained of headache, facial pressure, cough, postnasal drip, and/or smell disorder. According to our results, rhinosinusitis was found in 28.8% of patients. Increasing number of studies have found a significant correlation between AR and rhinosinusitis and one of them revealed that 50% of adults and 43% of children with nasal allergies reported having chronic rhinosinusitis [31].

Several mechanisms could explain the link between allergic inflammation and sinus disease. Allergic inflammation of the nasal mucosa may give rise to mucosal congestion, leading to impaired mucus drainage at the ostiomeatal complex in predisposed patients. Allergy is considered to be a predisposing factor for developing rhinosinusitis, although the theory is still controversial. Many studies have suggested that allergic inflammation could affect acute or chronic rhinosinusitis. However, epidemiologic studies have suggested that the incidence of rhinosinusitis is not significantly higher in AR patients than in healthy subjects. The observation that asthma and rhinosinusitis coexist in patients at a higher frequency than would be expected from

the prevalence of each in the general population provides a strong connection between the upper and lower airways [21, 32].

In this study, there was a significant difference between sinusitis and persistent (43%) or persistent with seasonal exacerbation AR (35%) as shown in **Table 2**. Cough, deviated septum and polyps were significantly associated with rhinosinusitis ($p < .001$) as shown in **Table 4**.

The previous studies confirmed that rhinosinusitis was more prevalent in cases with perennial AR [33] and that rhinosinusitis was associated with sinonasal anatomical variants [34, 35]. There is no strong evidence for a correlation between nasal anatomical variations in general and the incidence of chronic rhinosinusitis [9].

There is a well established relationship between atopic dermatitis and airway allergic diseases and its progression over time is well known as atopic march. Patients with extrinsic atopic dermatitis with specific IgE antibodies to common environmental allergens, present in early childhood, are at a higher risk for progressing in the atopic march to allergic rhinitis and asthma [36]. The prevalence of atopic dermatitis in this study was 5.2% and there was no significant relationship between other comorbidities. In this study, another less common comorbidity associated with AR was laryngitis with prevalence of 3.8%. It is still controversial whether AR may be a causative mechanism of laryngeal inflammation and symptomatology [37].

The reasons for differences in the clinical presentation of comorbid diseases in patients with AR are still unknown. One of the possible explanations why there is no definite answer is the overlapping of hereditary, physiological and clinical characteristics of patients, which affects variety of conditions. In order to fully respond to these challenges, AR should be understood as a part of chronic allergic respiratory syndrome, not as an isolated allergic disease.

Conclusion

This study is in agreement with others in regard to the presence of comorbidities in patients with allergic rhinitis. Although these relationships are well established from a clinical and epidemiologic point of view, the mechanism of how allergic rhinitis predisposes comorbidities or affects their course, remains unclear. This continues to be a subject of investigation and debate.

Due to cross-sectional nature of this study, the results should be interpreted with caution, and the variability of results, regarding the incidence of some clinical and demographic parameters, may be related to regional differences, selection methodology and definition used. These results point to presence of comorbidities in many patients with allergic rhinitis, which corresponds to the fact that allergic rhinitis is part of a systemic disease. In spite of all the limitations, this study indicates that allergic rhinitis is a major health problem in the region. The aim of further studies will be to understand the complexity of the mechanisms underlying the varieties in the clinical phenotype of allergic rhinitis and predisposition to the onset of comorbidities.

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ANALYSIS OF COLORIMETRIC PARAMETERS OF INTERNATIONAL COMMISSION ON ILLUMINATION L*A*B* SYSTEM IN THE COLOR OF MAXILLARY CENTRAL INCISORS

*ANALIZA KOLORIMETRIJSKIH PARAMETARA CIEL*A*B* SISTEMA BOJE CENTRALNOG GORNJEG SEKUTIĆA*

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Summary

Introduction. Tooth color can be represented in a three-dimensional color system by applying L* (lightness), a* (red-green color tone) and b* (yellow-blue color tone) coordinates. Clinically significant color difference, Delta-E, can be expressed in units that are correlated with visual perception using the International Commission on Illumination L*a*b* system. The aim of the study was spectrophotometric analysis of the natural maxillary central incisor color, and to establish any gender-related differences in lightness, red-green tone, and yellow-blue tone coordinates. **Material and Methods.** The study included 80 students (40 male and 40 female, with an average age of 22 years). The color of the maxillary right central incisor was determined using an intraoral spectrophotometer and VITAPAN Classical and VITA 3D-Master color shade guides. Lightness, red-green tone, and yellow-blue tone values were recorded for each result. The obtained data were processed by using χ^2, Student's t-test and Mann-Whitney test. **Results.** Results showed no statistically significant gender-related difference in color according to the VITApan Classical and VITA 3D-Master color key. No difference was found in the lightness of the central maxillary incisor between genders, or in terms of red-green tone ($p = 0.860573$). A statistically significant difference was found when observing the sex-related yellow-blue tone of the color of the central maxillary incisor. **Conclusion.** The analysis of colorimetric parameters of the International Commission on Illumination L*a*b* system provides useful information about the tooth color in the examined population, while potentially revealing differences in lightness, red-green tone and yellow-blue tone between genders.

Key words: Color; Tooth; Spectrophotometry; Incisor; Sex Characteristics

Sažetak

Uvod. Boja zuba se primenom L* (svetlina), a* (crvenozeleni ton boje) i b* (žutoplavi ton boje) koordinata može predstaviti u trodimenzionalnom sistemu boja. Razlika u boji (ΔE) se primenom *International Commission on Illumination L*a*b** sistema može izraziti u jedinicama koje su kliničke značajne. Cilj rada bio je spektrofotometrijska analiza boje prirodnog centralnog gornjeg sekutića kao i utvrđivanje razlike u vrednostima L*, a* i b* koordinata u zavisnosti od pola ispitanika. **Materijal i metode.** U istraživanju je učestvovalo 80 studenata (40 ispitanika muškog pola i 40 ispitanika ženskog pola, prosečne starosti 22 godine). Boja desnog centralnog gornjeg sekutića određivana je primenom intraoralnog spektrofotometra kroz VITAPAN *Classical* i VITA 3D-master boje. L*, a* i b* vrednosti prikazane su za svaki rezultat određivanja boje. Dobijeni podaci obrađeni su primenom χ^2, Studentov t-testa i Man-Vitnjevog testa. **Rezultati.** Rezultati pokazuju da nema statistički značajne razlike u boji prema VITAPAN *Classical* i VITA *3D-master* ključu boja u zavisnosti pola ispitanika. Nije utvrđena razlika u svetlini centralnog gornjeg sekutića među polovima, kao ni po pitanju crvenozelenog tona ($p = 0.860573$). Statistički značajna razlika uočena je kod posmatranja vrednosti žutoplavog tona boje centralnog gornjeg sekutića. **Zaključak.** Analiza kolorimetrijskih parametara *International Commission on Illumination L*a*b** sistema obezbeđuje korisne informacije o boji zuba ispitivane populacije kao i postojanje razlike u svetlini, crvenozelenom tonu i žutoplavom tonu boje u zavisnosti od pola ispitanika.

Ključne reči: boja; zub; spektrofotometrija; sekutić; razlike u polu ispitanika

Introduction

One of the main goals of restorative dentistry is to achieve optimal morphological, optical and biological forms of restoration, which includes satisfactory reproduction of the color/shade of the natural teeth [1]. In restorative dentistry, tooth color is usually determined visually using a shade guide, which is the most widely accepted and most commonly used method [2].

For a long time, the VITApan Classical shade guide was the gold standard in the tooth color determination. However, it has several disadvantages, such as insufficient range of available colors, distribution of color with respect to two parameters

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Abbreviations

CIE L*a*b*	– International Commission on Illumination L*a*b*
ΔE	– Delta-E (color difference)
3D	– three-dimensional
L*	– lightness
a*	– red-green balance
b*	– yellow-blue balance

(lightness and saturation) only, and lack of dispersion of color samples in the three-dimensional (3D) color space [3]. As a result, several more advanced shade guides have been developed.

In 1991, Hall emphasized the need to include all three color parameters (lightness, hue and saturation) in the color determination process [4]. His pioneering work on the subject was the basis for the development of the VITA 3D-Master shade guide in 1998. Thus, VITA 3D-Master is the first three-dimensional commercial color determination and reproduction system based on the colorimetric classification principles. In the selection and organization of samples in the shade guide, all three parameters affecting color perception were taken into account, and the color selection procedure was adapted to the visual perception mechanisms [5]. Owing to its design, wider color range and uniform color distribution, VITA 3D-Master is superior to all classic shade guides [2, 6]. However, for those with less clinical experience or insufficient knowledge related to this system based on lightness-saturation-hue concept, it may be difficult to understand and apply it in practice [7]. As individual aptitude and conditions in which color determination is performed affect the reliability and accuracy of the tooth color determination procedure, the visual method is considered highly unreliable [6, 8].

The instrumental tooth color determination method offers the potential for eliminating all the aforementioned shortcomings. Numerous devices for instrumental determination of tooth color are available today, such as three-stimulus colorimeters, spectroradiometers, digital cameras and spectrophotometers [1, 2, 9–11].

Nonetheless, due to their accuracy, simplicity and ease of application, spectrophotometers remain the most popular devices in clinical practice [12]. When using a spectrophotometer, tooth color is determined by measuring the amount and spectral composition of light reflected from the surface of the observed tooth. In the class of clinical spectrophotometers, the VITA Easyshade Compact stands out due to its superior performance, since the device can determine not only the base color of the whole tooth and its thirds, but verify the color of the restoration [11]. As spectrophotometers are designed for application on smooth surfaces, their use in dentistry is hindered by the convex tooth exterior, which complicates the correct placement of the probe tip. In vivo colorimeter measurements of the color of permanent maxillary teeth show that the middle third segment best represents the overall tooth color and hue [13, 14]. Following the measurement, the color from the VITApan Classical shade guide and the VITA 3D-Master shade guide is displayed along with the L*C*h* a*b* coordinates in the CIE L*a*b* color space for the measured tooth area [15].

In 1976, the International Commission on Illumination (Commission Internationale de l'Eclairage) (CIE) introduced the CIE L*a*b* system based on opponent process theory of color. In this three-dimensional space, color can be represented by L*, a* and b* coordinates on their respective axes. Coordinate L* (vertical axis) represents the lightness of the color (with L* = 0 denoting pure black and L* = 100 pure white, i.e., a perfect diffuser). On the other hand, coordinate a* represents the chromaticity of the color, i.e., red-green color balance (+a indicates redness and –a greenness), whereas coordinate b* represents the yellow-blue color balance (+b indicates yellowness and –b blueness) [16]. For natural colors, the values of these coordinates are close to 0 and they increase for more intensive (i.e., more chromatic) colors. A clinically significant color difference, Delta-E (ΔE) can be expressed in units that are correlated with visual perception using the CIE L*a*b* system [1, 3, 4, 8, 11, 14]. In experimental conditions, the $\Delta E > 1$ is visible to the naked eye, while in clinical conditions, the difference must exceed 3.7 to be noticeable [2, 5]. As far back as 1900, Munsell wrote about the 3D aspect of color, which can be captured via parameters such as hue, chroma (saturation) and value (lightness) [17].

A vast research on the topic of tooth color is focused on the dentition in the upper jaw, especially the frontal region, i.e., central incisors, lateral incisors, and canines due to their visual exposure and extremely high esthetic requirements [18]. In several studies, only the maxillary incisors [4] or canines [16] were considered.

Age and gender are also important factors in tooth color [14], whereby several studies have shown that women have lighter teeth than men [19–21]. On the other hand, tooth form and shape are not affected by gender [22].

There are many available studies where spectrophotometric analysis of color parameters was used based on the CIE L*a*b* system [23, 24].

There is a paucity of studies focusing on student (and generally younger) population examining tooth color parameters, as majority of such investigations were based on samples aged 30 and older. This results in lack of generalization, given that due to various age-related physiological changes and the development of secondary dentin, the tooth color becomes darker as we get older [24, 25].

Therefore, the aim of our study was to determine if there are any gender-related differences in the natural maxillary central incisor color in the student population by conducting spectrophotometric analysis of relevant color parameters using the CIE L*a*b* system.

Material and Methods

This prospective study included 80 dental students (40 males and 40 females, aged 20 - 24 years) attending the Faculty of Medicine of the University of Novi Sad. Students meeting any of the following criteria were

excluded from the study: tooth discoloration due to smoking or certain medications, presence of direct or indirect restorations of the natural maxillary central incisors, and previous endodontic treatments involving these teeth. The color of maxillary right central incisor was determined using VITA Easyshade Compact intraoral spectrophotometer (VITA Zahnfabrik, Bad Säckingen, Germany). At the start of the study, all participants received a professional dental cleaning. Prior to selecting the color, the spectrophotometer was subjected to manual calibration involving the application of protective foil, followed by choosing the appropriate function from the menu in order to assess the overall tooth color. When performing the measurements, the probe tip was set vertically at an equal distance from the surface of the tooth, no less than 2 mm away from both the incisal and the gingival edge, in the middle segment of the maxillary central incisor, as the most representative of the natural tooth color. Each measurement by VITApan Classical and VITA 3D-Master color provided L*, a* and b* values to be recorded. The obtained results were processed using χ^2, Student's t-test and Mann-Whitney test.

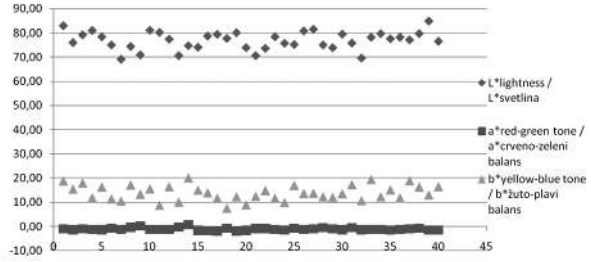
Results

According to the values obtained by intraoral spectrophotometer, in the male subsample, the brightness parameter (L*) ranged from 70.2 to 83.7, with an average of 76.67 **(Graph 1)**, while values in the female subjects ranged from 69.0 to 84.8, with an average of 76.81 **(Graph 2).** The difference between values obtained in male and female subjects was not statistically significant, as shown in **Table 1.**

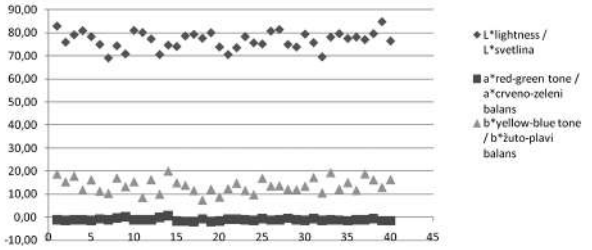
In 36 of 40 male participants, the red-green tone (a* coordinate) tended toward the red (negative) part of the scale (ranging from -0.1 to -2.3), while the remaining four participants had positive values (ranging from 0.0 to 0.3), as shown in **Graph 1.** Similar red-green tone distribution was noted in female students, with negative values in 37 cases (ranging from -0.2 to -2.0), as shown in **Graph 2.** Once again, the difference between obtained values in males and females was not statistically significant **(Table 1).**

In the male subsample, the value of the yellow-blue tone (b* coordinate) was strictly positive (8.4 - 21.9), indicating predominance of yellow color tone **(Graph 1).** Similarly, only positive values were recorded in the female participants, ranging from 7.4 to 20.1 **(Graph 2).** However, the difference between genders was statistically significant (p = 0.036402, **Table 1**).

Based on the analysis of the information presented in **Table 2** and the p-value of 0.0000178, it can be concluded that the tooth color of dental students established using VITAPAN Classical shade guide is not evenly distributed, as D color (p =



Graph 1. Distribution of colorimetric parameters (L* - lightness, a*- red-green tone, and b*- yellow-blue tone) of maxillary central incisor color values in male participants
Grafikon 1. *Distribucija kolorimetrijskih parametara (L*-svetlina, a* - crvenozeleni balans, i b* - žutoplavi balans boje) centralnog gornjeg sekutića kod ispitanika muškog pola*



Graph 2. Distribution of colorimetric parameters (L* - lightness, a*- red-green tone, and b* - yellow-blue tone) of maxillary central incisor color values in female participants
Grafikon 2. *Distribucija kolorimetrijskih parametara (L*-svetlina, a* - crvenozeleni balans, i b* - žutoplavi balans boje) centralnog gornjeg sekutića kod ispitanika ženskog pola*

Table 1. Analysis of the colorimetric parameters related to the maxillary central incisor (L* - lightness, a* - red-green tone, and b* - yellow-blue tone) with respect to gender
Tabela 1. *Analiza kolorimetrijskih parametara centralnog gornjeg sekutića (L*- svetlina, a* - crvenozeleni balans, i b* - žutoplavi balans boje) u zavisnosti od pola ispitanika*

Group 1 M//*Grupa 1 M* vs. Group 2 F/*Grupa 2 Ž*	Mean *Srednja*	Mean *Srednja*	t-value *t-vrednost*	df *df*	P *P*	Valid N *Validan broj*	Valid N *Validan broj*
Lightness M/*Svetlina M* vs. Lightness F/*Svetlina Ž*	76.67	76.81	-0.176226	78	0.860573	40	40
Red-green M/*Crvenozelena M* vs. Red-green F/*Crvenozelena Ž*	-0.9	-1.1075	1.564895	78	0.121656	40	40
Yellow-blue M/*Žutoplava M* vs. Yellow-blue F/*Žutoplava Ž*	15.365	13.8325	2.129084	78	0.036402	40	40

M/*M* – Male/*Muški pol,* F/*Ž* – Female/*Ženski pol*

Table 2. Z-test (VITAPAN Classical shade guide) and Mann-Whitney test (VITA 3D-Master shade guide)
Tabela 2. *Z-test (VITAPAN klasični ključ boja) i Man-Vitnijev test (VITA 3D-Master ključ boja)*

Sample Proportion/*Proporcija uzorka*	N/*Broj ispitanika*	Z	p-value/*p vrednost*
VITAPAN Classical/*VITAPAN klasični*	80	2.721443	0.00325
Vita 3D/*Vita 3D*	80	0.620652	0.534829

0.00325) is prevalent in more than 25% of the sample, as shown in **Table 2** and **Graph 3**.

Using the 3D-Master shade guide, lightness group 3 was identified in more than 20% of participants, as shown in **Table 2** and **Graph 4.**

Among the male students, A1 (i.e., 2M1) color had the highest lightness value (83.7) while C3 (i.e., 3.5M) color had the lowest (70.2), as shown in **Table 1**. As shown in **Table 2,** among the female students, C2 (i.e., 3M1) and A1 (i.e., 1.5M1) color had the lowest (69.0) and the highest (84.8) lightness value, respectively.

Discussion

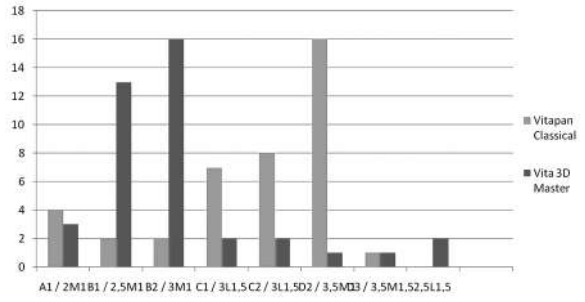
As part of this investigation, precise tooth color measurements were performed using the VITA Easyshade Compact optoelectronic device, which enables quick and accurate measuring and provides results that are completely independent of the conditions under which color selection is made or the person performing the procedure [5, 9, 26, 27]. The VITA Easyshade Compact device is considered the most reliable in both in vitro and in vivo settings [28] and is thus typically used as a reference for tooth color determination [29]. Available evidence indicates that, in comparison with the visual method, its color correspondence is 93.3%, with an increase in accuracy by 33% [30].

VITA Easyshade Compact is easy to use and it enables visualizing the L*C*h*a*b* coordinates for the measured tooth area in the CIE L*a*b* color space, while providing other useful information about the shade, such as the difference between the color of a measured tooth area and approximate VITAPAN Classical A1-D4 shade in the 3D color space [5].

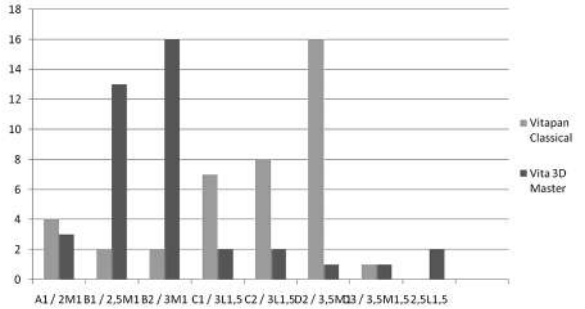
Moreover, as age has been shown to affect the color of natural teeth, to eliminate any age-related variations, the present study focused on individuals aged 20 – 24 years [31]. This is in line with other studies, given that older participants are rarely considered for this type of research [16]. Evidence reported in related literature indicates that teeth become darker with age [32].

In the CIE L*a*b* system, which is recognized as a universal system for color specification, both the light source and the observer are standardized. With this system, each color can be represented as a point in a spherical space and its position is determined by the distance between the point and each of the three (L*, a* and b*) axes. Therefore, knowledge about this system and its usage is recommended [1, 33]. Within the color space diagram, the color range of natural teeth occupies a small segment of a specific shape (akin to a vertically placed banana), located in the upper third of the diagram (representing the yellow-orange part of spectrum), and in the area of moderate saturation (related to lightness). Consequently, the lightest shades (which have lower saturation) are the closest to the vertical axis [34]. Still, it is worth noting that the distribution of natural tooth color in a Sudanese sample formed a parallelogram shape, while in American and German population it showed elongated oval and circular shape, respectively [19].

The average lightness values in our male (76.67) and female (76.81) subsamples are in accordance with the published results (77.1) [16]. However, the analysis of the L* coordinate values (i.e., the lightness of the



Graph 3. Maxillary central incisor color values in male participants according to the VITAPAN Classical and VITA 3D-Master shade guides
Grafikon 3. *Boja centralnog gornjeg sekutića kod ispitanika muškog pola u skladu sa VITAPAN klasičnim i VITA 3D-Master ključem boja*



Graph 4. Maxillary central incisor color values in female participants according to the VITAPAN Classical and VITA 3D-Master shade guides
Grafikon 4. *Boja centralnog gornjeg sekutića kod ispitanika ženskog pola u skladu sa VITAPAN klasičnim i VITA 3D-Master ključem boja*

maxillary central incisor) revealed no statistically significant difference between genders, opposite to the observations of other authors that women tend to have brighter teeth [19, 31]. In addition, in some studies, colorimetric measurements have shown that, even though maxillary teeth are more yellow compared to mandibular teeth, maxillary incisors are lighter than mandibular incisors [16]. The mean red-green tone value in our male and female subsample was -0.9 and -1.1075, respectively. For most participants, irrespective of gender, this parameter had a negative value and no statistically significant gender-related differences were found. As the literature search failed to reveal any studies in which analysis of the red-green or blue-yellow parameter was conducted, no comparison with the available data is possible. Yellow-blue tone was strictly positive and peaked at 15.365 and 13.8325 in males and females, respectively. Overall, the maxillary central incisors of female students exhibited less visible yellow tone.

The results yielded by this study have shown that, regardless of gender, the predominant tooth color corresponded to D2 in the VITAPAN Classical shade guide (i.e., 3M1 in the VITA 3D-Master shade guide). In the current study sample, colors from groups A and B according to the VITAPAN Classical shade guide were less represented in regard to those in the color groups C and D. In particular, using the intraoral spectrophotometer in accordance with the VITAPAN Classical shade guide, A3 and B1 colors were not detected in the male subsample and A2 was absent in the female group. In a study of tooth color in the Sudanese population aged 15 – 72, the most common color was A3, followed by A1. In the same study, 3M1 color according to the 3D-Master shade guide was determined in just over 5% of participants, while 1M2 was found in more than 30% of the sample [19]. In our study, the dominant color according to the 3D-Master shade guide was 3M1, which is in line with the results reported by Gómez-Polo, who analyzed tooth color in the Spanish population [35]. Thus, it can be presumed that tooth color is likely dependent on the ethnicity of the population being examined.

Conclusion

In restorative dentistry, in order to accurately determine the tooth color and reliably interpret the results of analysis, it is essential to master the basic principles of color science. In particular, the colorimetric parameters of the International Commission on Illumination L*a*b* system provide ample information about the tooth color in the examined population, while potentially revealing any differences in lightness, red-green tone and yellow-blue tone between genders.

Owing to the limitations of the present study, no statistically significant differences in the maxillary central incisor lightness and red-green color tone were noted between genders. However, yellow color tone was more prominent among male students. Within the VITAPAN Classical and 3D-Master shade guide, D2 and 3M1 color, respectively, was most prevalent in the studied sample. Moreover, A1 from the VITAPAN Classical shade guide has the highest and C1 the lowest lightness values irrespective of gender.

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PATTERNS OF ALCOHOL USE AMONG FIRST GRADE HIGH SCHOOL STUDENTS IN NOVI SAD

OBRASCI UPOTREBE ALKOHOLA MEĐU UČENICIMA PRVIH RAZREDA SREDNJIH ŠKOLA U NOVOM SADU

Sara PEKOVIĆ[1] and Olja NIĆIFOROVIĆ ŠURKOVIĆ[2, 3]

Summary

Introduction. Alcohol drinking habits are usually formed during adolescence. Adolescents most often drink alcohol to fit in with their peers, but genetics and social modeling are also of great importance. Adolescents who consume alcohol are more prone to mental disorders as well as risky and violent behavior. **Material and Methods.** A cross-sectional study was conducted among first grade high school students in Novi Sad in December 2017. The final sample included 1,067 participants. For the purpose of this study, the European School Survey Project on Alcohol and Other Drugs questionnaire was used. Data were analyzed using the Statistical Package for the Social Sciences program, version 11.0. **Results.** Beer is the easiest alcoholic beverage to obtain for young people in Novi Sad, followed by wine and spirits. A great number of participants have consumed alcohol at least once in their lifetime and more than half in the last 30 days, (83.5%) and (52.6%) respectively. More than a third of participants had an episode of excessive drinking during the last month. Early onset of drinking was found among one half of male and a third of female participants. **Conclusion.** These results indicate an unfavorable situation when it comes to alcohol consumption among young people in Novi Sad. Therefore, efforts of the society that encourage healthy development of adolescents are important, as well as taking preventive measures in order to reduce the risk of alcohol abuse among young people.

Key words: Alcohol Drinking; Underage Drinking; Adolescent; Surveys and Questionnaires; Binge Drinking; Health Risk Behaviors; Primary Prevention; Sex Characteristics

Sažetak

Uvod. Navike u vezi sa upotrebom alkohola se pretežno formiraju tokom adolescencije. Adolescenti najčešće konzumiraju alkohol da bi se uklopili u društvo, ali i genetski faktori i socijalno modelovanje imaju veliki uticaj. Adolescenti koji konzumiraju alkohol su skloniji mentalnim poremećajima, rizičnom i nasilnom ponašanju. **Materijal i metode.** Sprovedena je studija preseka među učenicima prvih razreda srednjih škola u Novom Sadu u toku decembra 2017. godine. U konačni uzorak za analizu ušlo je 1.067 ispitanika. Za potrebe ovog istraživanja korišćena su pitanja iz upitnika *European School Survey Project on Alcohol and Other Drugs.* Baza podataka je kreirana u kompjuterskom program SPSS, verzija 11.0. **Rezultati.** Najlakše dostupan alkohol mladima u Novom Sadu je pivo, zatim vino i žestoka pića. Veliki broj ispitanika je konzumirao alkohol bar jednom u životu (83,5%), a više od polovine u prethodnih mesec dana (52,6%). Više od trećine učenika (39,2%) imalo je epizodu ekscesivnog pijenja u prethodnih mesec dana. Rani početak konzumacije alkohola uočava se kod približno polovine mladića i trećine devojaka. **Zaključak.** Rezultati ukazuju na nepovoljnu situaciju kada je u pitanju konzumacija alkohola među mladima u Novom Sadu. Stoga su važni napori društva koji podstiču zdrav razvoj adolescenata kao i preduzimanje preventivnih mera u cilju smanjenja rizika od zloupotrebe alkohola kod mladih.

Ključne reči: upotreba alkohola; maloletničko konzumiranje alkohola; adolescenti; istraživanja i upitnici; opijanje; ponašanje rizično po zdravlje; primarna prevencija; razlike u polu ispitanika

Introduction

The first contact with alcohol usually occurs during adolescence and this is the period when drinking habits are mostly formed [1]. According to a research conducted in Serbia in 2008, the results of the European School Survey Project on Alcohol and Other Drugs (ESPAD) survey showed that as much as 89.1% of first grade high school students have consumed alcohol at least once in their lifetime [2].

According to the Cox-Klinger model, there are four core drinking motives: mood enhancement, avoidance of unpleasant emotions, better social adjustment, and avoidance of social rejection [3]. Some of the unpleasant emotions that motivate alcohol consumption are anxiety and stress, which are common in this period of life [4]. Avoidance of unpleasant emotions is the most common reason for alcohol consumption among younger adolescents coming from problematic families, while older adolescents often drink to fit in with their peers [5]. Genetics and upbringing also play an important part: up to

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Abbreviations
ESPAD – European School Survey Project on Alcohol and Other Drugs

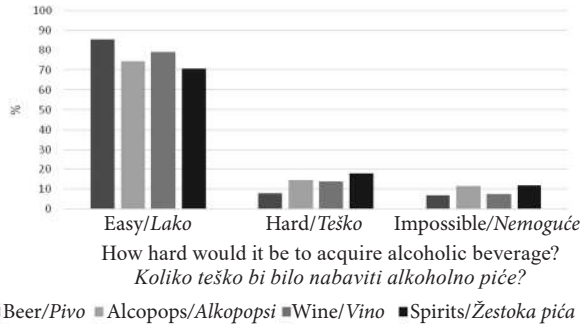
82% of children whose parents consume alcohol consume it as well, while 72% of children whose parents do not consume alcohol follow their example [6]. Furthermore, children of alcoholics are 4 times more likely to become alcoholics themselves [7].

As for the consequences of alcohol consumption among adolescents, acute intoxications are the most common [8]. Moreover, alcohol abuse is the most prevalent cause of acute poisoning among adolescents, while younger children most frequently get intoxicated with medications [9]. Chronic illnesses related to alcohol consumption take longer to appear and they are not that common at younger age [8]. Adolescents who consume alcohol are at greater risk of mental disorders such as depression, anxiety, attention deficit hyperactivity disorder and schizophrenia [10]. Also, they are more prone to accidents related to drunk-driving, which are the main reason for injuries in this age group [11]. Young people who frequently consume alcohol are at greater risk for risky sexual behavior than those who do not consume alcohol and even of those who use marijuana frequently [12]. Heavy episodic drinking is related to violent behavior among young people, especially those from lower socioeconomic groups [13].

The aim of this study is to determine the availability of alcoholic beverages, the prevalence of alcohol use, and patterns of alcohol use among first grade high school students in Novi Sad.

Material and Methods

This cross-sectional study was conducted among 1,236 first grade high school students attending 18 high schools in Novi Sad in December 2017 using the ESPAD questionnaire. After the exclusion of questionnaires with missing data (gender, date of birth, those filled by participants not born in 2002), the final sample included 1,067 participants.



Graph 1. Availability of different alcoholic beverages to first grade high school students
Grafikon 1. *Dostupnost različitih alkoholnih pića za učenike prvih razreda srednjih škola*

The survey was conducted on school premises during one class, as a self-administered questionnaire. The students were informed verbally and in writing that the survey was voluntary and anonymous. Signed consents were collected separately, to ensure anonymity of the participants.

Data were analyzed using the Statistical Package for the Social Sciences program, version 11.0 and presented with methods of descriptive statistics. Statistical significance between genders was tested with Pearson's chi-square test and Fisher's test. P-values < 0.05 were considered statistically significant.

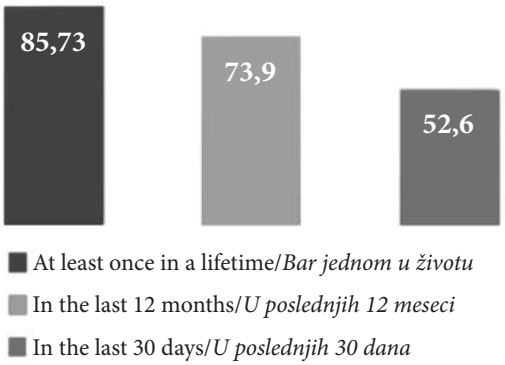
Results

The final sample included 1,067 students (55% female and 45% male). Most of the first grade high school students thought that alcohol was easy to get, with beer being the easiest (85.8% of students answered they found it easy to buy beer if they wanted to), followed by wine (79%), alcopops (74.2%) and spirits (70.7%) **(Graph 1)**.

A significant percentage of our participants have consumed alcohol at least once in their lifetime (83.5%). In the last year, 73.9% of the participants consumed alcohol and 52.6% of them in the last month **(Graph 2)**.

In the last 30 days, beer was consumed by 40.8% of students, spirits by 37.7%, wine by 37.2%, and alcopops by 29% of students. There is a significant statistical difference between male and female students, more male students have consumed beer (50.5% of boys versus 32.9% of girls) and spirits (40.1% of boys versus 35.8% of girls), while more female students have consumed wine (39.9% of girls versus 33.8% of boys). Binge drinking (consumption of 5 or more alcoholic beverages on one occasion) in the last 30 days was experienced by 39.2% of students and significant percentage of surveyed students (15.3%) reported that they had alcohol induced imbalance, amnesia or vomiting in the last month.

Early onset of alcohol use (13 years or less) is significantly more common among boys (49.9%) than girls (34.8%). First alcohol intoxication at the age under 13 years was reported by 13.2% of boys and 3.5% of girls.



Graph 2. Percentage of students who have consumed alcohol
Grafikon 2. *Procenat studenata koji su konzumirali alkohol*

Table 1. Reasons for alcohol consumption among first grade high school students
Tabela 1. *Razlozi za konzumaciju alkohola među učenicima prvih razreda srednjih škola*

Reasons for alcohol consumption *Razlozi za konzumaciju alkohola*	Never/*Nikad* (%)		Rarely/*Retko* (%)		Often/*Često* (%)	
	M/*M*	F/*Ž*	M/*M*	F/*Ž*	M/*M*	F/*Ž*
Drinking alcohol helps me having fun. *Konzumacija alkohola mi pomaže da uživam u zabavi.* *	57.5	59.5	22.3	27.2	20.3	12.7
I love the feeling of drinking alcohol./*Sviđa mi se osećaj konzumacije alkohola.*	65.5	66.4	19.6	21.1	14.9	12.5
Drinking alcohol makes parties better. *Konzumacija alkohola poboljšava proslave.**	64.0	67.7	19.2	23.7	16.8	8.6
Drinking alcohol cheers me up./*Konzumacija alkohola me oraspoloži.*	69.1	66.2	19.6	21.6	11.3	12.1
Drinking alcohol helps me forget about my problems. *Konzumacija alkohola mi pomaže da zaboravim na svoje probleme.*	74.2	75.9	13.7	14.5	12.1	9.6
Drinking alcohol helps me when I am depressed or nervous *Konzumacija alkohola mi pomaže kada sam depresivan/nervozan.*	76.2	76.2	15.8	15.4	8.0	8.4
I drink alcohol because I want people to like me. *Konzumiram alkohol jer želim da se dopadnem ljudima.**	82.3	89.7	10.5	8.8	7.4	1.5
I drink alcohol because I do not want to feel left out *Konzumiram alkohol jer ne želim da se osećam izostavljeno.**	82.9	92.3	12.1	6.4	5.0	1.3
I drink alcohol in order to fit in with the group of people I like. *Konzumiram alkohol da bi se uklopio/-la u grupu ljudi koja mi se dopada.**	78.7	91.0	13.5	7.9	7.8	1.1

Legend/*Legenda*: M/*M* - males/*muški pol*, F/*Ž* - females/*ženski pol*
statistically significant differences between genders ($p < 0.05$)/ *statistički značajne razlike među polovima ($p < 0,05$)*

Most of our participants drink alcohol for mood enhancement and less often because it helps them avoid unpleasant emotions. Only a small percentage drink because it helps them fit in with peers, but this reason is significantly more common among male students ($p < 0.05$). The most common reasons for alcohol consumption among our participants are shown in **Table 1**.

In the last year, risky behaviors and accidents under the influence of alcohol were common among both genders resulting in injuries, serious fights, and damage or loss of property. Male participants are also significantly more prone to get into fights, having problems with the police, driving intoxicated, swimming intoxicated in deep water (pool, river or sea), having sexual intercourse without protection, and having sex that they regretted the day after **(Table 2)**.

Table 2. Risky behaviors and accidents under the influence of alcohol in the last year among first grade high school students in Novi Sad
Tabela 2. *Rizična ponašanja i nezgode pod uticajem alkohola u poslednjih godinu dana među učenicima prvih razreda srednjih škola u Novom Sadu*

Risky behaviours and accidents under the influence of alcohol *Rizična ponašanja i nezgode pod uticajem alkohola*	Males *Muški pol* (%)	Females *Ženski pol* (%)
Getting injured/*Povreda*	21.5	17.1
Getting into serious quarrels/*Ozbiljna svađa*	19	17.4
Damage or loss of properties/*Oštećenje ili gubitak stvari*	16.7	14.2
Getting into fights/*Tuča**	19	7.4
Having problems with the police/*Problemi sa policijom**	12.9	4.3
Driving intoxicated/*Vožnja u pijanom stanju**	14	2.6
Swimming intoxicated in deep water/*Plivanje u dubokoj vodi u pijanom stanju**	19.9	6.2
Having sex without protection/*Seksualni odnos bez zaštite**	11	0.9
Having sex that they regret the day after/*Seksualni odnos zbog kog si se pokajao/-la sutradan**	6.8	0.9
Selfharming/*Samopovređivanje*	6.2	5
Being hospitalized because of intoxication/*Hospitalizacija zbog intoksikacije alkoholom*	3.6	0.9
Being robbed/*Bio/-la žrtva pljačke*	3.1	1.6
Getting into car accident while driving intoxicated/*Imao-/la saobraćajnu nesreću u pijanom stanju*	2.5	1.4

statistically significant differences between genders ($p < 0.05$)/ *statistički značajne razlike među polovima ($p < 0,05$)*

Discussion

In Europe, trends in alcohol use seem to be slightly decreasing among young people in the last 10 years. However, the percentage of minors who consume alcohol is still considerably high. According to our study, the percentage of the first year high school students who have consumed alcohol at least once in their lifetime and in the last month, is similar to the average in European countries (83.5% compared to 80% and 52.6% compared to 48%) [14]. The trends are more favourable in the United States, where 33% of same-age students have consumed alcohol at least once in their lifetime (Monitoring the Future survey, 2007) [15]. It can be attributed to strict regulations regarding selling alcohol to persons under the age of 21. Binge drinking was experienced by 39.2% of our participants in the last month which is higher than European average in 2008, accounting for 35% (from 8% in Island to 56% in Denmark) [14]. Young people who start drinking before the age of 13 are at considerably greater risk of developing alcohol addiction later in life [16]. Our results show that approximately one half of boys and one third of girls started drinking before they turned 13 years old. Similar results were obtained in European countries in 2015, with some exceptions where the situation is more favourable (Island, Norway) [14].

According to ESPAD report from 2011, most young people associate alcohol with having fun (64%), while half of them drink to forget about their problems (48%) [17]. Our participants have also chosen having fun as the main reason for alcohol consumption.

Alcohol consumption is the leading cause of homicide, suicide and lethal accidents among adolescents and more adolescents lose their lives because of alcohol use than due to all the other psychoactive substances combined [18]. According to the World Health Organization, alcohol is the leading risk factor for increase of disability adjusted life years in the 10 – 24 years age group [19]. According to our survey, 21.5% of boys and 17.1% of girls got injured in the last year while being under the influence of alcohol.

Adolescents who consume alcohol are more prone to risky behavior, such as drunk driving, unprotected sexual activity, and use of illicit drugs [20]. Driving intoxicated in the last year was more common in our male participants (14% compared to 2.6% in females), as was unprotected sexual activity (11% of males and 0.9% of females).

Conclusion

The results of our study indicate that the prevalence of alcohol use among young people in Novi Sad is unfavorable. Therefore, efforts of the society that encourage healthy development of adolescents are important, as well as taking preventive measures in order to reduce the risk of alcohol abuse and its consequences among young people. The most effective way of prevention is education about the consequences of alcohol consumption and strict regulations on alcohol availability to minors.

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Erratum

In the double issue of Medical Review, 73; 5 – 6, 2020, there is an error on page 183 in the section of article authors and their affiliations (data from the submitted manuscript). At the request of the author, here is a correction:

Instead of: Borislava NIKOLIN[1, 4], it should be Borislava NIKOLIN[1, 2], referring to the Oncology Institute of Vojvodina, Diagnostic Imaging Center, Sremska Kamenica[1], and University of Novi Sad, Faculty of Medicine, Novi Sad[2].

Eratum

U dvobroju 5-6/2020 na strani 183 kod afilijacija autora prisutna je greška (na osnovu podataka koji su pristigli u Redackiju) te na molbu autora donosimo ispravku:

Pored imena prof. Borislave NIKOLIN stoje brojevi [1,4], a treba da budu brojevi [1,2] (koji se odnose na Oncology Institute of Vojvodina, Diagnostic Imaging Center, Sremska Kamenica [1], University of Novi Sad, Faculty of Medicine Novi Sad [2]).

CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
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SEROUS ADENOCARCINOMA DETECTED IN THE CERVICAL SMEAR – A CASE REPORT

SEROZNI ADENOKARCINOM U CERVIKALNOM BRISU – PRIKAZ SLUČAJA

Ljiljana TADIĆ LATINOVIĆ[1], Ilija BAROŠ[1], Danijela BATINIĆ ŠKIPINA[2] and Slavica MARIĆ[3]

Summary

Introduction. Cytological smear tests of the cervix are routine diagnostic methods used for detection of precancerous lesions and tumors of the cervix; they are highly sensitive and specific in the detection of precancerous squamous intraepithelial lesions. Glandular lesions are much less frequently found in the cervical smear. The most common glandular lesions detected in the cervical smear are endocervical and endometrial adenocarcinomas. Cervical metastases are rare, although there are case reports in the literature. **Case Report.** In this case report, we present a 64-year-old woman with an abnormal cervical smear and postmenopausal metrorrhagia. Numerous accumulations, as well as individual atypical epithelial cells, were detected in the cervical smear and a cytological diagnosis of a high-grade squamous intraepithelial lesion was made based on cytomorphological features suspicious for invasion (Bethesda Classification, 2014) so a cervical biopsy and curettage of the endocervical canal were performed. A high-grade serous adenocarcinoma was diagnosed by histopathological examination of cervical biopsy and cervical canal curettage specimens, after which a transvaginal ultrasound examination was performed, which showed tumors on both ovaries and free fluid in the abdominal cavity. The patient underwent abdominal hysterectomy with bilateral salpingo-oophorectomy. Histological examination confirmed high-grade ovarian papillary serous adenocarcinoma with psammoma bodies. **Conclusion.** The cytological diagnostic features and criteria for serous adenocarcinoma in Papanicolaou smears are still vague and insufficiently defined in the literature, which is the reason for very common errors in the interpretation, so further research on the pathogenesis, diagnosis and therapy of this tumor is of great importance.

Key words: Adenocarcinoma; Ovarian Neoplasms; Vaginal Smears; Papanicolaou Test; Cervix Uteri; Diagnosis

Sažetak

Uvod. Citološki bris grlića materice je dijagnostička metoda koja se rutinski koristi za otkrivanje prekanceroznih lezija i tumora grlića materice; visoko je senzitivna i specifična metoda za otkrivanje prekanceroznih lezija iz skvamoznog epitela. Glandularne lezije u cervikalnom brisu se identifikuju znatno ređe. Najčešća glandularna lezija opisana u brisu grlića materice je endocervikalni adenokarcinom, a potom adenokarcinom endometrijuma. Metastaze u grliću materice se retko javljaju, mada u literaturi postoje prikazi sličnih slučajeva. **Prikaz slučaja**. Predstavljamo 64-godišnju ženu sa abnormalnim nalazom cervikalnog brisa i postmenopauzalnom metroragijom. U razmazu brisa cerviksa su otkrivene brojne nakupine, kao i pojedinačne atipične epitelne ćelije, te je na osnovu citomorfoloških karakteristika postavljena citološka dijagnoza skvamozne intraepitelne lezije visokog gradusa – ne može se isključiti invazija (H-SIL ne može se isključiti invazija, Betezda klasifikacija 2014), nakon čega je urađena biopsija grlića materice i kiretaža endocervikalnog kanala. Histopatološkim pregledom biopsije grlića materice i kiretaže cervikalnog kanala postavljena je dijagnoza seroznog adenokarcinoma visokog gradusa posle čega je urađen transvaginalni ultrazvučni pregled kojim je dokazano prisustvo tumorskih masa na oba jajnika i slobodna tečnost u trbušnoj duplji. Pacijentkinja je podvrgnuta abdominalnoj histerektomiji sa bilateralnom salpingo-ooforektomijom. Histološkim pregledom potvrđen je papilarni serozni adenokarcinom jajnika visokog gradusa sa prisutnim psamomskim telašcima. **Zaključak.** Opis citoloških karakteristika i kriterijumi za dijagnozu seroznog adenokarcinoma u Papanikolau razmazu još uvek su u literaturi neprecizno i nedovoljno definisani što je vrlo često razlog grešaka u interpretaciji, pa su dalja istraživanja patogeneze, dijagnoze i terapije ovog tumora od velikog značaja.

Ključne reči: adenokarcinom; tumori jajnika; vaginalni i cervikalni bris; PAPA test; grlić materice; dijagnoza

Introduction

The most common primary tumor of the cervix is squamous cell carcinoma, whereas primary adenocarcinomas originating from the endocervical epithelium occurring in the cervix are much less com-

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Abbreviations

Pap – Papanicolaou smear
WT1 – Wilms' tumor 1
ER – estrogen receptor

mon [1]). Uterine cervix is a rare site of metastatic tumors. It is somewhat more common for tumors from neighboring organs, such as the rectum and bladder, to directly infiltrate the cervix. Lobular breast cancer, lung cancer, gastrointestinal tumors, and melanoma, are also among the rare tumors known to metastasize to the cervix [2].

Serous adenocarcinomas of the cervix may be of primary origin, may spread directly from the endometrium, ovaries, fallopian tubes, or peritoneum, and may rarely be metastatic from the aforementioned primary locations [3, 4].

Primary serous adenocarcinomas of the cervix are extremely rare and account for about 1% of adenocarcinomas of the cervix. Histologically, they are identical to papillary serous adenocarcinomas of the ovary, endometrium, and peritoneum [5]. Before diagnosing primary serous cervical cancer, it is necessary to clinically exclude its origin from other parts of the female genital system.

Serous adenocarcinoma, regardless of whether it is primarily of cervical origin or has primarily originated from other organs, is rarely seen in Papanicolaou (Pap) cervical cytological samples. The history of the disease, data on previous primary tumors and cytomorphological characteristics help in making an accurate diagnosis of these tumors. In 36% of cases, serous carcinoma in Pap smear originates from the ovaries and/or fallopian tubes [6]. Regardless of the place of primary origin, serous carcinoma is histologically characterized by papillary formations that are composed only of serous epithelial cells, contain a connective base or atypical adenoid formations and groups of cells in solid clusters. Psammoma bodies are often found in the tumor tissue.

Serous adenocarcinomas in the Pap smear are characterized by papillary clusters with serrated edges and very often present with cell overlap and formation of three-dimensional clusters. The cells are large, the nuclei of the cells are large, round, they often have prominent nuclei, and the amount of cytoplasm is variable and may contain eccentrically placed vacuoles. Psammoma bodies are rarely present in cytological samples [7]. Most metastatic cancers are characterized by a clean background and absence of tumor diathesis, while the direct spread of the tumor to the cervix is characterized by tumor diathesis. Tumor cells of serous adenocarcinoma express Wilms' tumor 1 (WT1), p53, and estrogen receptor (ER) immunohistochemical markers.

Case Report

Due to postmenopausal vaginal bleeding, a routine cervical smear was taken from a 64-year-old woman. It was taken with a cervix brush and prepared by the conventional Pap staining method. Numerous cell clusters were detected in the smear, as well as individual atypical epithelial cells. Cell groups were arranged in the form of small clusters and hyperchromatic crowded groups **(Figure 1)**, papillary-like structures **(Figure 2),** while scattered individual cells were present in rare foci. The cells were mostly polygonal and round in shape, elongated in places, and spindle-shaped **(Figure 3)**. The nuclei of the cells were oval or round with a present pronounced nuclear pleomorphism, coarse-grained chromatin and one to two visible nucleoli. In most cells the cytoplasm was sparse, in rare cells it contained vacuoles, and in some cells it was orangeophilic in appearance, suggesting possible squamous differentiation. Abundant amount of nuclear debris, polymorphonuclear cells, and a lot of fresh erythrocytes in the background of the smear indi-

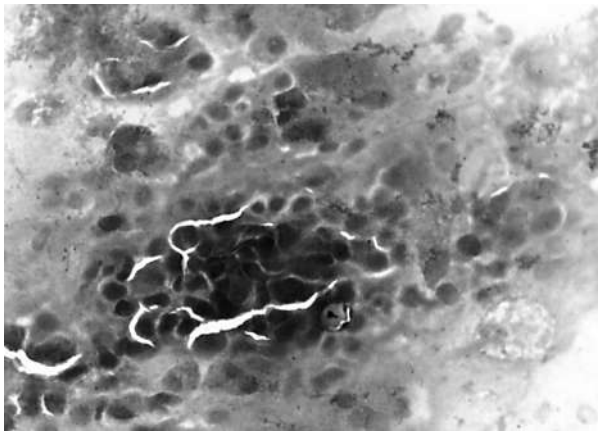

Figure 1. Cervical smear of atypical epithelial clusters of tumor cells with tumor diathesis (Papanicolaou staining x 200)
Slika 1. *Cervikalni bris atipičnih epitelnih ćelija u nakupinama sa tumorskom pozadinom (Papanikolau bojenje x 200)*

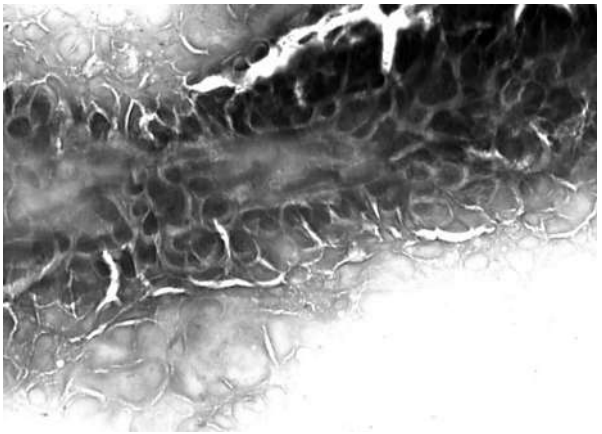

Figure 2. Cervical smear of atypical epithelial cells arranged in papillary structure (Papanicolaou staining x 200)
Slika 2. *Cervikalni bris atipičnih epitelnih ćelija aranžiranih u papilarnu strukturu (Papanikolau bojenje x 200)*

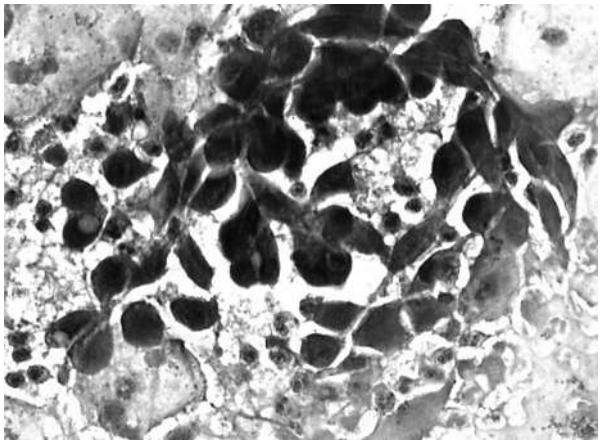

Figure 3. Cervical smear of atypical epithelial cells of polygonal and spindle shape with tumor background (Papanicolaou staining x 400)
Slika 3. *Cervikalni bris atipičnih epitenih ćelija poligonalnog i vretenastog oblika sa tumorskom pozadinom (Papanikolau bojenje x 400)*

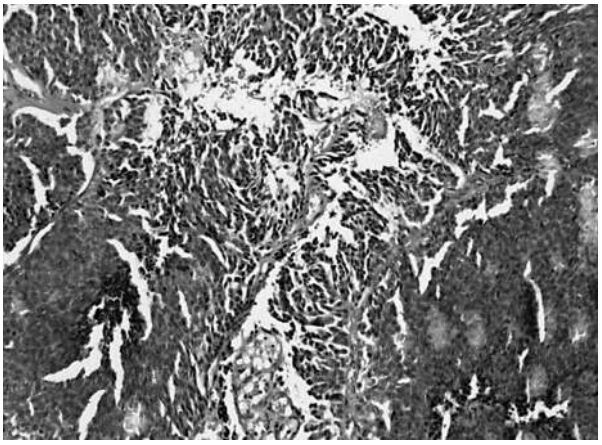

Figure 4. Solid groups and papillary structures of serous adenocarcinoma in a cervical biopsy sample (hematoxylin/eosin staining, x 200)
Slika 4. *Solidne grupe i papilarne strukture seroznog adenokarcinoma u bioptičkom uzorku grlića materice (hematoksilin/eozin bojenje, x 200)*

cated presence of pronounced tumor diathesis. Based on cytomorphological characteristics in the cervical smear, the diagnosis of high-grade squamous intraepithelial lesion suspicious for invasion was made (Bethesda classification, 2014).

Vaginal examination verified a tumor mass on ectocervix with contact bleeding. A biopsy of the cervix and curettage of the endocervical canal were performed. Histopathological examination of cervical biopsy and cervical canal curettage confirmed the presence of high-grade serous adenocarcinoma without clinical data on the primary location of the tumor. The tumor tissue was composed of polygonal epithelial cells with a pronounced degree of pleomorphism, and the cells were almost entirely arranged into solid groups with focally present, poorly formed glandular and sparse papillary formations **(Figure 4)**. An immunohistochemical analysis was performed on the cervical biopsy sample, which confirmed high positivity of ERs in tumor cell nuclei **(Figure 5A)**, low positivity of progesterone receptors, positive expression of WT1 **(Figure 5B)**, and high expression of Ca-125 in the cytoplasm of tumor cells **(Figure 5C)**. Immunohistochemical profile of the tumor indicated a high-grade serous adenocarcinoma.

After the diagnosis of serous adenocarcinoma in the biopsy sample of the cervix and endocervical canal curettage, a transvaginal ultrasound examination was performed. It confirmed the presence of tumor masses on both ovaries and free fluid in the abdominal cavity. The patient underwent laparotomy and abdominal hysterectomy with bilateral salpingo-oophorectomy. Multiple peritoneal biopsies were performed and ascites fluid was sent for cytological analysis. Omentectomy and lymphadenectomy were not performed due to extensive omental infiltration by the tumor. Macroscopically, the tumor mass in the right ovary was 6.8 cm x 4.9 cm x 5.3 cm, and in the left ovary 7.6 x 5.2 x 4.7 cm. Tumor tissue infiltrated the entire fimbriae and ampullary portion of both fallopian tubes. A cross-section revealed a solid tumor, grayish-white, and crumbly. The cervix in all four quadrants was invaded by a 2.3 x 1.8 x 1.3 cm tumor nodule. In cross-section, the tumor tissue in the cervix was grayish-white and crumbly, reaching to the lateral edges of the resection on the anterior lip of the cervix. In the tissue of the ovaries, fallopian tubes and cervix, microscopic examination confirmed a high-grade papillary serous adenocarcinoma with psammoma bodies. Immunohistochemical analysis was performed on ovarian tumor fragments, and the results were identical to those from the biopsy sample of cervical tumors. A simple cystic hyperplasia without atypia was present in the endometrium. The presence of numerous malignant cells originating from the adenocarcinoma was proved in the cytological sample of ascitic fluid.

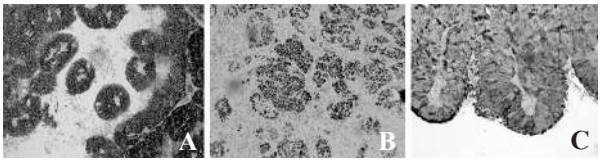

Figure 5. A - Positive ER in a cervical biopsy sample (IHH, x 100); B - Positive WT1 in a cervical biopsy sample (IHH, x 100); C- Positive Ca125 in a cervical biopsy sample (IHH, x 200)
Slika 5. *A − pozitivni ER u bioptičkom uzorku grlića materice (IHH x 100); B − pozitivan WT1 u bioptičkom uzorku grlića materice (IHH x 100); C − pozitivan CA 125 u bioptičkom uzorku grlića materice (IHH x 200)*
Legend: ER – estrogen receptor; *WT1* – Wilms' tumor 1; Ca 125 - Cancer antigen 125; IHH - immunohystochemistry
Legenda: ER – estrogenski receptor; WT1 – Vilmsov tumor 1; Ca 125 – antigen karcinoma 125; IHH – imunohistohemija

Discussion

Cervical carcinoma is one of the most common carcinomas in the female population [8]. Serous adenocarcinoma of the female genital tract is a type of tumor that is rarely diagnosed in the cervical smear [3]. The Pap test is not a sensitive test for the detection of serous adenocarcinoma, regardless of the primary site of this histological type of tumor [3].

The description of cytological characteristics and criteria for the diagnosis of serous adenocarcinoma in Pap smear are still inaccurate and insufficiently defined in the literature, which is the reason for very common errors in interpretation. The cytological diagnosis of papillary serous adenocarcinoma should be considered when the cervicovaginal smear contains short, three-dimensional papillary clusters of large atypical cells with prominent nucleoli, individual malignant cells, or naked nuclei with blood or necrosis in the background [9].

Tumor cells of primary adenocarcinoma of the endometrium, ovaries and fallopian tubes in cervicovaginal smears are identical to those in papillary serous adenocarcinoma of the uterus, but the background is clear (without tumor diathesis) unless it is a direct infiltration of the cervix [10].

Primary serous cervical carcinomas are the least frequently detected in the cervical smear because this histological variant of primary cervical adenocarcinoma is rather rare.

Serous adenocarcinomas of primary endometrial origin are most commonly found in Pap smears and serous adenocarcinoma tumor cells whose primary sites of origin are the ovaries, fallopian tubes, and peritoneum, are rarely found in cytological samples [11]. It is not possible to differentiate the primary place of origin of this type of tumor only based on the morphology in the cytological sample [10]. The differential diagnosis of primary serous cervical cancer includes primary serous carcinoma of the endometrium, ovaries, fallopian tubes, and peritoneum with spread to the cervix, with direct infiltration or metastasis, and it requires clinical correlation. If fractional curettage of the endometrium and endocervix does not prove cancer, it is necessary to exclude or confirm the existence of tumors of adnexal and peritoneal origin. The presence of ovarian and fallopian tube adenocarcinoma cells in the cervicovaginal smear varies from 6% to 36% [12]. The cytology of papillary serous adenocarcinoma may be difficult to distinguish from the cytology of primary endocervical carcinoma. Elongated overlapping nuclei, serrated edges of the nuclei ("feathered edges") in clusters are cytological characteristics that indicate endocervical adenocarcinoma [3].

The differential diagnosis of serous adenocarcinoma in the cervical smear includes squamous lesions (either invasive carcinoma or high-grade squamous intraepithelial lesion) because squamous cells occur individually or in clusters with tumor diathesis in the background [13]. Differential diagnosis can sometimes be very difficult if squamous intraepithelial neoplasia involves the endocervical glands. Squamous cells show hyperchromatic nuclei and condensed cytoplasm.

Endocervical adenosquamous carcinoma may be another diagnostic problem. Cervical adenosquamous carcinoma cytologically presents with syncytium-like cell arrangements and occasionally, as glandular structures consisting of large pleomorphic cells with abundant, dense cytoplasm and macronucleoli. Papillae and psammoma bodies are not a prominent feature of adenosquamous carcinoma [14].

The identification of this poor prognostic variant of female genital tract cancer may be clinically important and a preoperative Pap test may be useful in making a decision in the choice of treatment.

Conclusion

In this case report, poor differentiation of serous adenocarcinoma and technically poor cytological Papanicolaou smear resulted in misdiagnosis of a neoplasm of squamous epithelial origin. Immunohistochemical analysis of tumor tissue from a biopsy sample contributed to the accurate diagnosis of serous adenocarcinoma, that is not often found in the cervix, which is why it is much less often present in the cervical smear.

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IN MEMORIAM
IN MEMORIAM

Prim. mr sc. med. JOŽEFA JATIĆ (1944–2020)

Prim. mr sc. med. Jožefa Jatić, internista endokrinolog-dijabetolog rođena je 1944. godine u Republici Sloveniji. Diplomirala je na Medicinskom fakultetu u Ljubljani gde je obavila deo pripravnničkog staža, a potom deo na klinikama Medicinskog fakulteta u Novom Sadu. Po položenom stručnom ispitu radila je kao lekar opšte prakse u Domu zdravlja u Bačkoj Palanci. Radila je i kao lekar primarne zdravstene zaštite u seoskim i gradskim ambulantama, a dežurala je i u službi hitne medicinske pomoći. Na Medicinskom fakultetu u Novom Sadu položila je kurs iz Socijalne pedijatrije 1971. godine. Od 1974. godine radila je u Savetovalištu za dijabetes pri Domu zdravlja u Bačkoj Palanci. Specijalistički ispit iz interne medicine položila je na Medicinskom fakultetu u Novom Sadu 1978. godine. Naredne godine pohađala je dvosemestralne postdiplomske studije iz dijabetologije i endokrinologije na Medicinskom fakultetu u Novom Sadu. Sledeće godine završila je drugu godinu postdiplomskih studija, a 1985. godine uspešno je odbranila magistarski rad na istom fakultetu.

Od Ministarstva zdravlja Srbije dobila je 1996. godine zvanje primarijus.

Dr Jožefa Jatić učestvovala je 1999. godine u otvaranju prvog vanbolničkog centra za dijalizu u Domu zdravlja u Bačkoj Palanci, gde je nastavila da radi kao načelnik sve do penzionisanja 2009. godine. Od 1994. do 2014. godine radila je kao dijabetolog u Savetovalištu za dijabetičare Doma zdravlja u Baču. Bila je aktivni član DLV-SLD, član Internističke sekcije i Sekcije za endokirinološke i metaboličke poremećaje čiji je bila i predsednik. Obavljala je funkciju i člana Predsedništva DLV-SLD, kao i predsednika Podružnice DLV Bačka Palanka. U jednom mandatu je bila i delegat DLV u Skupštini SLD u Beogradu.

Zalaganjem dr Jožefe Jatić formirano je Društvo za borbu protiv šećerne bolesti u Bačkoj Palanci. U toku cele svoje profesionalne karijere nesebično je radila na zdavstvenom prosvećivanju, posebno dijabetičara putem mnogobrojnih predavanja posvećenih ovoj bolesti, potom o pravilnoj ishrani i lečenju, a posebno prevenciji šećerne bolesti. Redovno je pratila savremena dostignuća iz svoje oblasti putem učešća na stručnim i naučnim skupovima, simpozijumima i kongresima.

Za svoj dugogodišnji predani rad nagrađena je Zahvalnicom, Plaketom i Dipolmom DLV-SLD, kao i Godišnjom nagradom za zaštitu narodnog zdravlja DLV-SLD. Dom zdravlja u Bačkoj Palanci dodelio joj je l983. godine Plaketu *Doktor Mladen Stojanović*, a 1989. godine Opština Bačka Palanka nagrađuje je Zlatnom značkom Oktobarske nagrade.

Živela je u skladnoj porodici, a suprug i ćerka su joj pružali pomoć i razumevanje, a ona njima bezgraničnu ljubav i pažnju.

Pored svoje izuzetne stručnosti i velikog iskustva stečenog u radu u različitim sredinama, prim. dr Jožefa Jatić je bila vrlo drag, stpljiv i savestan lekar. Imala je vremena da sasluša svakog bolesnika, da ih obiđe i van radnog vremena ili da im dâ savet u telefonskom razgovoru. Pacijenti su je izuzetno voleli i cenili, a pred vratima njene ambulante je uvek bio najveći broj bolesnika. Kao koleginica bila je omiljena zbog svoje blage naravi i spremnosti da nesebično pomogne svakome ko joj se obrati za pomoć ili savet.

Hvala joj za sve što je pružila bolesnicima, kao i za bezgranično i istinsko prijateljstvo.

Prof. dr Tatjana Ivković Lazar

Dr sc. LJILJANA LEPŠANOVIĆ, naučni savetnik (1937–2020)

Naučni savetnik dr Ljiljana Lepšanović rođena je 1937. godine na Sušaku u Kraljevini Jugoslaviji od oca Stevana Dikovića i majke Ankice rođ. Lučanin. Osnovnu školu i gimnaziju završila je u Zemunu, a na Prirodno-matematičkom fakultetu u Beogradu diplomirala je biologiju 1962. godine. Prvo se zaposlila kao asistent na Institutu za medicinska istraživanja u Novom Sadu, a potom u Zavodu za patološku fiziologiju i laboratorijsku dijagnostiku Medicinskog fakulteta u Novom Sadu. Doktorirala je 1974. godine na Univerzitetu u Beogradu. Na Medicinskom fakultetu je prvo izabrana za naučnog saradnika, potom višeg naučnog saradnika i pred kraj svoje naučne karijere za naučnog savetnika.

Autor je ili koautor pet knjiga, pojedinih poglavlja u 12 monografija i priručnika, publikovala je 330 naučnih i stručnih radova u domaćim i inostranim časopisima. Vodila je tri naučnoistrazivačka projekta, a učestvovala u jednom potprojektu i u 17 naučnoistraživačkih tema. Osnovno područje njenog stručnog i naučnog rada bili su poremećaji metabolizma lipida. Posebno vredi istaći da je bila autor *Dijetetskih tablica* (Sastav osnovnih životnih namirnica i njihov aterogeni indeks, kao i *Tablica referentnih vrednosti osnovnih lipidskih parametara* za decu različitog uzrasta naše populacije). Osnovala je prvu specijalizovanu laboratoriju za izučavanje lipidskih poremećaja u nekadašnjoj Jugoslaviji i njome rukovodila punih 20 godina. Bila je član *Evropskog društva za ateroslekrozu* i *Nemačkog društva za proučavanje gojaznosti*. Dobitnik je Oktobarske nagrade grada Novog Sada zajedno sa svojim suprugom prof. dr Lazarom Lepšanovićem, kao i Povelje za doprinos i zasluge u razvoju i radu Kliničkog centra u Novom Sadu.

Ljiljana Lepšanović je svoj život posvetila usavršavanju laboratorijske dijagnostike poremećaja metabolizma lipida stvorivši solidnu osnovu za dalji razvoj ove metode.

Nalazila je vremena da se posveti i slikarstvu. Slikarstvom i karikaturama se počela baviti još kao učenica gimnazije. Objavljivala je svoje radove u *Ježu* i *Studentu*, a kasnije je radila ilustracije za svoje radove i knjige, posebno one koji su bili namenjeni edukaciji bolesnika i opštoj populaciji. Pohađala je slikarsku školu kod akademskog slikara Boška Petrovića. Bila je aktivna u Sekciji za umetnost DLV-SLD izlažući svoje radove na svim kolektivnim izložbama. Takođe je izlagala u okviru obeležavanja dana *Dr Laza Lazarević* u Šapcu i u galeriji *Hemofarm* u Vršcu. Bila je član Udruženja likovnih stvaralaca Novog Sada.

Prof. dr Tatjana Ivković Lazar

UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

Od 1. januara 2013. godine *Medicinski pregled* je počeo da koristi usluge *e-Ur* − Elektronskog uređivanja časopisa. Svi korisnici sistema − autori, recenzenti i urednici, moraju biti registrovani korisnici sa jednom elektronskom adresom.

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U postupku prijave neophodno je da se pošalje saglasnost i izjava autora i svih koautora da rad nije delimično ili u celini objavljen ili prihvaćen za štampu u drugom časopisu.

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Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings*, *MeSH*.

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

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.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

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

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

∗ 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.

∗ Sveska sa suplementom

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

∗ Monografija u elektronskom formatu

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.

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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.

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– 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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