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THERAPEUTIC DRUG MONITORING OF NEW-GENERATION ANTIEPILEPTICS IN PEDIATRIC PATIENTS: A FOCUS ON FACTORS INFLUENCING THE PLASMA CONCENTRATION

Ivana Damnjanović[1], Nikola Stefanović[1], Tatjana Tošić[2], Aleksandra Catić-Djordjević[1], Ana Kundalić[1], Slavoljub Živanović[3], Radmila Veličković-Radovanović[1,4]

Monitoring the concentrations of antiepileptic drugs (AEDs) in the pediatric population represents an important step in the vast variety of decisions related to the optimization of new-generation epilepsy therapy. The primary objective of this research was to determine the concentrations of lamotrigine (LTG) and levitiracetam (LEV) in the plasma of children and adolescents receiving combined antiepileptic therapy. Secondly, we examined the influence of demographic factors and co-therapy on the measured concentrations of AEDs. The prospective study included 71 subjects diagnosed with epilepsy, aged 2−18 years, receiving combined antiepileptic therapy, which included the following therapeutic regimens/modalities: valproic acid (VA)/LTG, VA/LEV and LTG/LEV. The results indicated that 86.27% of LTG concentrations and 68.97% of LEV concentrations were within the reference range. No statistically significant influence of co-medication on the concentrations of the tested AEDs was recorded. Additionally, the obtained results confirmed that LTG dose was the most significant predictor for LTG concentrations. The results of the conducted research indicated that only LEV dose corrected by body weight could potentially affect LEV concentrations. Although the therapeutic monitoring of new-generation AEDs is not commonly imposed in daily clinical practice, the results of the conducted research indicate that monitoring the concentrations of LTG and LEV can be of great benefit in the pediatric population receiving combined antiepileptic therapy due to the very nature of the disease and the potential pharmacokinetic variability of the investigated antiepileptics.

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Key words: *pediatric population, therapeutic drug monitoring, lamotrigine, levetiracetam*

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Introduction

Epilepsy treatment often requires lifelong use of antiepileptic drugs (AEDs). Effectiveness and safety have been recognized as key issues in the successful treatment of epilepsy, and still represent a difficult goal to achieve in each daily clinical practice (1). Although most patients may be successfully managed with monotherapy, polytherapy remains the reality for more than 30% of patients with epilepsy (2, 3). In the pediatric population, new challenges in AED therapy management include the wide range of combinations of AEDs available, the lack of information regarding optimal dose regimen, unpredictable drug efficacy and changes in pharmacokinetics due to physiological changes during maturation and development (4).

Due to unfavourable pharmacokinetic properties, a high risk of drug–drug interactions and a narrow range of therapeutic options, therapeutic drug monitoring (TDM) of AEDs has traditionally been used to support and optimize epilepsy management (5). Therapeutic drug monitoring of the first-generation AEDs has been commonly performed for decades. Nowadays, the use of old-generation AEDs is decreasing as new-generation AEDs are being increasingly prescribed, mostly due to more predictable kinetics and fewer risks of drug interaction (6). Although new-generation AEDs have lower pharmacokinetic variability, they still show significant changes in

their bioavailability with certain comedications or under specific physiological conditions (7). A routine therapeutic monitoring for most new AEDs is not common in clinical practice. On the other hand, due to the presence of unexpectedly high interindividual variability, TDM is still the focus of investigation, especially in the vulnerable pediatric population (8).

The main aim of the study was to determine the concentrations of lamotrigine (LTG) and levitiracetam (LEV) in children and adolescents receiving combined antiepileptic therapy. The second aim was to examine the influence of demographic factors and co-therapy on the AED concentrations.

Materials and Methods

The research in the form of a prospective study was conducted at the Pediatric Internal Medicine Clinic, Department of Pediatric Neurology, University Clinical Centre of Niš, Serbia and Research Centre for Biomedicine, Faculty of Medicine, University of Niš. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocols were approved by the Ethics Committee of the Faculty of Medicine, University of Niš (Decision No. 12-3782/4). The collection of data was performed over 12 month from May 2020 in the presence of parents or guardians who provided written informed consent.

The study involved 71 patients with diagnosed epilepsy (31 males and 40 females). Inclusion criteria were: diagnosed epilepsy based on criteria of the International Classification of Diseases (G40); patients of both genders aged 2−18 years on combined antiepileptic therapy which included the following therapeutic regimens/modalities: valproic acid (VA)/LTG, VA/LEV and LTG/LEV. The data were collected from medical records and during face-to-face interviews which were performed at the clinic during the control visit, with the patient himself or his parents/guardians. In order to protect patient data, each patient was assigned a code at the beginning of the study, which was used in statistical analysis instead of the patient's name. For the purpose of analysis, the following data were collected: demographic characteristics (gender, age, body weight (BW)), therapy characteristics (drug formulation, administered, dose, dosing interval, plasma drug concentration, and adverse drug effects). Patients included in the study had been on a specific drug dosing regimen for at least 3 weeks to ensure that the steady-state condition had been reached for each of the AEDs included in the therapy. All blood samples were collected in the morning before the next dose of AEDs. Hence, all blood samples corresponded to trough levels.

For the purpose of control and optimization of therapy, blood samples are taken from patients at the request of the doctor. Blood was taken by venipuncture, and sterile disposable vacuum tubes were used for sampling. From the whole blood sample, 200 ml of blood was separated and used to determine the concentration of LTG and LEV. The VA concentrations were routinely determined in the Central Biochemical Laboratory in the University Clinical Centre of Niš and collected from medical records, while the LTG and LEV concentrations were determined using the high-performance liquid chromatography (HPLC) at the Research Centre for Biomedicine in the Medical Faculty, Niš. The blood samples were collected and stored at −80 °C until further analysis. This analysis was performed on an Agilent 1200 HPLC system (Agilent Technologies, Palo Alto, CA., USA) with a diode array detector (DAD). An analytical column C18 Zorbax Eclipse AAA, 150 x 4.6 mm, with a particle size of 3.5 µm manufactured by Agilent was used (Supplementary Information). Lamotrigine and levetiracetam as solid standard compounds were kindly provided by pharmaceutical company Hemofarm AD (Vršac, Serbia).

Lamotrigine and levetiracetam were extracted from 200 µl of plasma by adding 400 µl of a solution of 0.1% trifluoroacetic acid in methanol. After vortexing (1 min) and centrifugation (10 min at 12000 rpm and 4 °C), a volume of 200 µl of the supernatant was transferred to a clean vial with an insert and 10 µl was injected onto a column whose temperature was maintained at 30 °C at a flow rate of 1 ml/min. Compounds were identified and quantified based on UV-Vis signal response compared to standards. Detection of LTG was performed at a wavelength of 240 nm, and LEV at 205 nm. When determining LTG, the mobile phase consisted of a mixture of 0.1% aqueous solution of triethanolamine (TEA) pH 6.5 (A) and acetonitrile (B) with a linear gradient. The proportion of acetonitrile at the beginning of the linear gradient was 23% and was maintained at that level for the next 5 minutes. In 0.5 minutes, the percentage of B rose to 80% and was maintained at that value for the next 3 minutes. After that, in 0.5 minutes, the percentage of component B was returned to the initial 23% and this value remained for 1 minute until the end of the analysis. The total duration of the analysis was 10 minutes. For the determination of LEV, the mobile phase consisted of a 0.1% aqueous solution of TEA (A) and acetonitrile (B). The pH value of the TEA solution was adjusted to 3.9 by adding phosphoric acid. Optimal separation of LEV was achieved by establishing a gradient with the following composition: 0−3.8 min 10−10% B; 3.8−4.3 min 10−80% B; 4.3−7.3 min 80−80% B; 7.3-8.5 min 80−10% B; 8.5−10 min 10% B.

Statistical Analysis

Descriptive data are presented as absolute numbers, percentages, mean values ± standard deviations (SD), centre (median) values and interquartile difference. Data are presented in tables or graphically. In order to estimate the influence of demographic factors, dosage regimens and co-therapy on LTG and LEV concentration, univariate and multivariate regressions were performed. Also, the comparison of antiepileptics dosage regimen and concentration between defined patient groups (sex, age, BW and co-therapy) was done by ANOVA and Student's t-test (normally distributed data) and Kruskal–Wallis and Mann–Whitney U test (not normally distributed data). The significance level was set at 5% in all analyses. All analyses were performed using SPSS statistical analysis software, version 20.0 (SPSS, Chicago, IL, United States).

Results

The study included 71 patients. During the investigation period, we did not record exclusions from the study because there was no expression of serious side effects. The demographic characteristics of the study population are given in Table 1.

The median age was 10.9 years (interquartile range 11 years), with female gender accounting for 56.3% (N = 40) and male contributing for the remaining 43.7% (N = 31). The median BW was 37.1 kilograms (interquartile range: 21 kg).

All respondents were on dual antiepileptic therapy (VA/LTG, VA/LEV and LTG/LEV). A total of 59.1% of respondents received the combination of VA/LTG.

Table 1. Demographic characteristics of respondents

Gender	**Number (%)**	
Male	31 (43.7%)	
Female	40 (56.3%)	
Age (years)	**Number (%)**	Mean: 10.9 Median: 11 Interquartile range: 7
2–12	43 (60.6%)	
> 12	28 (39.4%)	
BW (kg)	**Number (%)**	Mean: 37.1 Median: 35 Interquartile range: 21
< 20	11 (15.5%)	
20–40	38 (53.5%)	
> 40	22 (31%)	

Table 2. Pharmacotherapy characteristics and antiepileptic drug concentrations of the children participating in the study

Therapeutic modalities	**Male (%)**	**Female (%)**	**Total**
VA/LTG	19 (45.24%)	23 (54.76 %)	42 (59.16%)
VA/LEV	8 (40%)	12 (60%)	20 (28.17%)
LTG/LEV	4 (44.44%)	5 (55.56%)	9 (12.67%)
AEL concentration	**Below range (%)**	**In range (%)**	**Above range (%)**
LTG (N = 51)	6 (11.77%)	44 (86.27%)	1 (1.96%)
LEV (N = 29)	8 (27.59%)	20 (68.97%)	1 (3.45)

The therapeutic modalities VA/LEV was administered to 28.2% of respondents. Finally, 12.7% of the respondents participating in the study received the LTG/LEV combination. In the conducted study, it was observed that 86.27% of LTG and 68.97% of LEV measured concentrations during combined antiepileptic therapy were in the reference range. The highest number of concentrations below the reference range was recorded in the group of patients who used LEV as part of combined therapy (27.59%).

The further focus of the research was the factors that influence the pharmacokinetic variability of the selected AEDs, which are considered to contribute to concentrations outside the therapeutic range.

Figure 1 shows the dose and concentration of LTG in relation to gender, age, body weight and co-medication.

In the conducted research, DLTG were higher in the group of female respondents with a statistically significant difference p = 0.049 (1.62 ± 1.14 mg/kg vs. 2.63 ± 1.90 mg/kg) (Figure 1a). The measured CLTG in the group of female respondents were statistically significantly higher compared to the male (5.35 ± 2.70 μg/ml vs. 7.91 ± 4.10 μg/ml; p = 0.018) (Figure 1b). The dose and concentration of LTG in relation to the age of the respondents did not statistically differ within the studied groups. Analyzing the obtained results, it can be seen that higher DLTG were applied (71.34 ± 58.28 mg vs. 108.75 ± 82.23 mg) and higher CLTG were measured (6.33 ± 3.22 μg/ml vs. 7.41 ± 4.40 μg/ml) in the group of respondents with BW > 40kg, but statistical significance was not found between the studied groups.

The dose and concentration of LEV in relation to gender, age, body weight and co-medication are shown in Figure 2.

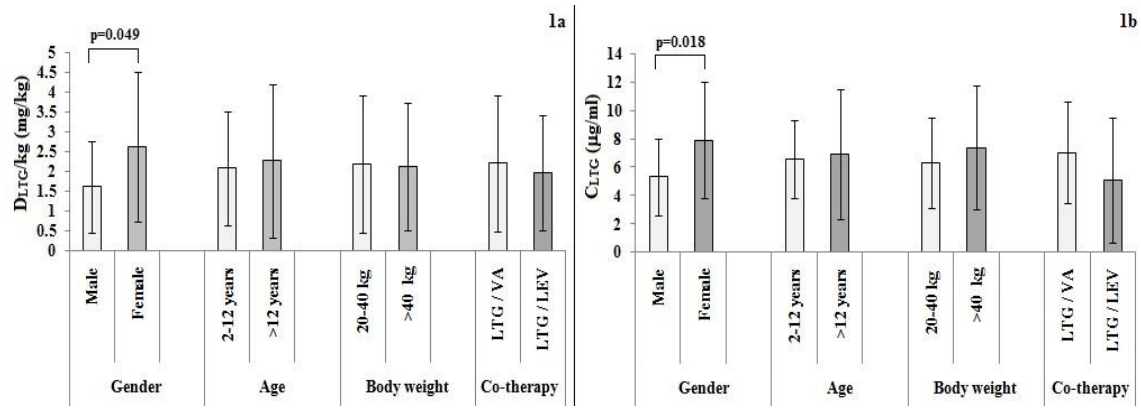

Figure 1. Dose (1a) and concentration (1b) of LTG in relation to gender, age, body weight and co-medication

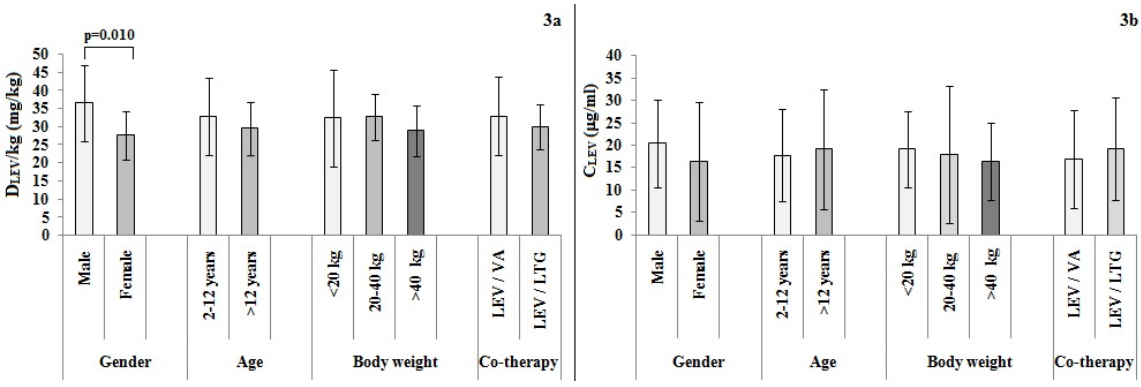

Figure 2. Dose (2a) and concentration (2b) of LEV in relation to gender, age, body weight and co-medication

Table 3. Analysis of the influence of factors on LTG and LEV concentration

Univariate model for LTG				
Parameter	Beta	B, IP-95%	R^2	Significance
Age	0.178	0.182 (0.119−0.483)	3.2%	0.230
Body weight	0.081	0.022 (-0.059−0.104)	0.7%	0.587
Gender	**0.344**	**2.559 (0.465−4.653)**	**11.9%**	**0.018***
D_{LTG}	**0.607**	**0.031 (0.019−0.044)**	**36.8%**	**P < 0,001***
D_{LTG} / kg	**0.453**	**0.992 (0.398−1.586)**	**20.5**	**P = 0,002***
C_{VA}	0.101	0.029 (-0.064−1.21)	1.0%	0.535
C_{LEV}	-0.606	-0.209 (-0.525−0.107)	36.7%	0.150
Multivariate model for LTG				
Parameter	Beta	B, IP-95%	Significance[1]	Significance[2]
Gender	**0.156**	**1.154 (0.712−3.021)**	**0.219**	**39% (< 0.001)**
D_{LTG}	**0.560**	**0.29 (0.16−0.42)**	**P < 0.001***	
Univariate model for LEV				
Parameter	Beta	B, IP-95%	R^2	Significance
Gender	-0.180	-3.960(-12.897−4.977)	3.2%	0.370
Body weight	-0.072	-0.047(-0.311−0.218)	0.5%	0.720
Age	0.098	0.205(-0.653−1.064)	1%	0.627
D_{LEV}	0.032	0.001(-0.007−0.008)	0.1%	0.872
D_{LEV} / kg	0.386	0.353(-0.045−0.816)	12.5%	0.077
C_{LTG}	-0.485	-1.313 (-4.603−1.977)	23.5%	0.330
C_{VA}	0.130	0.067(-0.214−0.347)	1.7%	0.620

B-unstandardized regression coefficient; IP-95 % confidence interval; Beta-standardized regression coefficient; R^2-the proportion of variance around the mean value of C_{LTG} that is explained by the appropriate model; Significance$^{1-1}$ Significance of the predictor within the model, Significance$^{2-2}$ Significance of the model itself

In relation to the gender of the respondents in the conducted study, a statistically significant difference was recorded only for parameter DLEV/kg (36.58 ± 10.58 mg/kg vs. 27.71 ± 6.63 mg/kg, p = 0.010) (Figure 2a). The values of DLEV/kg and CLEV did not differ statistically significantly compared to other analyzed parameters (Figures 2a and 2b).

Univariate regression showed that gender, DLTG, and DLTG/kg were significant predictors of LTG concentration values, while the results of multivariate analysis confirmed that DLTG, but not gender, was a significant predictor of CLTG. Based on the previously obtained results, a univariate linear regression was conducted in order to assess the factors that could potentially affect the CLEV. Subject-related factors (gender, age, BW) and drug-related factors (DLEV, DLEV/kg, CVA, CLTG) were included in the regression model. Univariate regression indicated that the analysed parameters did not represent significant predictors for LEV concentration values, however, the parameter DLEV/kg showed a trend towards statistical significance with a value of p = 0.077.

Discussion

The fundamental objectives of epilepsy treatment are reflected in the optimal control and reduction of the number of seizures, with the minimal risk of side effects (9). From the clinical aspect, it is a real challenge to set up an adequate therapeutic regimen, which would enable a long-term safe and effective therapeutic response. The rational aspect of the application of TDM in epilepsy therapy has been clearly described in recent years (10), and the ultimate goal of its implementation is reflected in the improvement of therapeutic outcomes (11). Therapeutic drug monitoring contributes to and facilitates the work of clinicians in daily practice, due to the fact that reference ranges of AED concentrations can be used as a measure of the effectiveness and safety of antiepileptic therapy (8).

In the conducted research, LTG was present in 71.83% of respondents (Table 2). The dose of LTG (p=0.049) and measured concentrations of LTG (p = 0.018) in the group of female subjects were statistically significantly increased (Figures

1a and 1b). The obtained results can potentially be explained by the influence of hormonal factors; however, further research in this field is still needed. Concerning the subjects' age, the dose and concentration of LTG did not show a statistically significant difference, which is in accordance with the previous research (12, 13). Although BW is often considered a potential factor in the pharmacokinetic variability of LTG, the results of available studies provide inconsistent results (12, 14–16). By analyzing the obtained results, it was observed that BW did not significantly affect DLTG and CLTG. In children, BW does not represent an independent variable, because it is in most cases directly dependent on age. This is why the focus should be primarily aimed at the subject's age as a factor that could potentially affect the pharmacokinetic variability of LTG (17). Lamotrigine has more predictable pharmacokinetics than classic AELs and it attains less potential for interactions (18). It obtains a minor effect on CYP450 isoenzymes and does not displace other drugs from their binding to plasma proteins (19). According to the guidelines, the reference range for monitoring LTG concentrations is 3–15 μg/ml (20). By analyzing the obtained data, it was observed that 86.27% of the measured LTG concentrations were within the reference range, while 13.73% of the concentrations were out of the range (11.77% below and 1.96% above) (Table 2). A statistically significant effect of co-therapy on LTG concentration was not recorded. The increased concentration of LTG in the LTG/VAL group of subjects (Figure 1b) is potentially the result of the inhibition of the UGT 2B7 isoform. The obtained results are in accordance with the research results of Reimers et al. (21). On the other hand, the simultaneous administration of LTG and LEV is considered much simpler, due to the absence of recorded interactions between these two drugs (22). However, more than 40% of the measured LTG concentrations in the co-medication with LEV were in the subtherapeutic range, which might be associated with inadequate seizure control. Univariate regression showed that gender, DLTG, and DLTG/kg are significant predictors for LTG concentration values (Table 3). A multivariate analysis confirmed that DLTG emerged as the most significant predictor for LTG concentration. The obtained results of the multivariate analysis are in accordance with the research conducted by Weintraub et al. demonstrating that DLTG is an important factor for predicting the concentration of LTG (18).

Levetiracetam belongs to the group of new-generation AELs that have been approved for use in the pediatric population since 2004 (23). Its mechanism of action is specific and differs from other AELs. It is characterized by a very favourable pharmacokinetic profile, so the routine administration of TDM of this antiepileptic drug is not recommended. However, there is a growing body of evidence indicating that changes in pharmacokinetics may occur in special populations, specifying the need for monitoring LEV concentrations (24, 25). In the conducted research, LEV was represented in therapy by 40.85% of respondents (Table 2). In relation to the gender of the respondents, a statistically significant difference was recorded in the parameter DLEV/kg ($p = 0.010$, Figure 2a). The results of existing studies indicate that gender does not have a significant effect on the concentration of LEV, which is in accordance with the results of the conducted research (Figure 2b) (24, 26, 27). Literature data suggest that the clearance of LEV is significantly higher in children under the age of 10 compared to the older population (28). One of the explanations is based on the fact that normal values of glomerular filtration as in adults are reached only after the age of 6 (29). Available literature data show that children under 10 years of age have 30–40% higher clearance and therefore require higher doses to achieve optimal concentrations (30). In the conducted research, a statistically significant difference was observed for the DLEV/kg parameter, which was higher in the group of examinees under the age of 12 ($p = 0.003$, Figure 2a). This result is in accordance with the previously mentioned studies. The analysis of the influence of age on CLEV indicated no significant difference and similar results were obtained in the research conducted by Dahlin and associates (31). The subject's BW is an important factor that can affect LEV concentration (25, 30). The results of the conducted research indicate that the values of DLEV/kg and CLEV parameters were not statistically significantly different in relation to the respondents' BW. Currently, only few studies with a relatively small number of subjects are available, which significantly prevents the identification of the influence of important demographic and physiological determinants on the pharmacokinetics of LEV. Further research focused on the concentration-to-dose ratio (C/D ratio) may be useful to evaluate LEV pharmacokinetic variability. Due to its favourable pharmacokinetic profile, LEV is often combined with other AELs (32). The optimal serum/plasma concentration of LEV should be in the interval of 12–46 μg/ml (33). Analyzing the obtained data, it was observed that 68.97% of the total concentrations of LEV were in the reference range, while 27.59% of the measured concentrations were below the defined reference range (Table 2). A statistically significant difference in the distribution of measured LEV concentrations depending on the applied cotherapy (VA/LTG) was not found. The obtained results are in accordance with the results of other available studies which indicate that the simultaneous administration of VPA or LTG does not significantly affect the concentration of LEV (28). The subtherapeutic concentrations of LEV that were recorded in the research, provide the possibility of correction of the dose of LEV within the combined therapy in order to obtain an optimum seizure control. Based on the previously obtained results, a univariate linear regression was conducted in order to assess the factors that might affect the concentration of LEV. Univariate

regression indicated that the analyzed parameters do not represent significant predictors for LEV concentration values, noting that the parameter DLEV/kg was the closest to statistical significance with a value of p = 0.077.

Conclusion

Antiepileptics represent a specific group of drugs characterized by a narrow-range therapeutic index and great variability in pharmacokinetics and therapeutic response, which is especially pronounced in the pediatric population. In the conducted study, it was observed that 86.27% of LTG and 68.97% of LEV measured concentrations during combined antiepileptic therapy were in the reference range. No statistically significant influence of co-medication on the concentrations of the tested AEDs was recorded. The results of multivariate analysis confirm that DLTG is the most significant predictor for LTG concentration. Concerning the LEV concentration, the obtained results indicate that DLEV/kg is an important factor. Although routine monitoring of new-generation antiepileptic drugs is not commonly imposed in daily clinical practice, the results of the conducted research indicate that monitoring the concentrations of LTG and LEV can be of great benefit in children and adolescents who receive combined antiepileptic therapy due to the nature of the disease itself and the possible pharmacokinetic variability of the tested antiepileptics.

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TERAPIJSKI MONITORING ANTIEPILEPTIKA NOVIJE GENERACIJE KOD PEDIJATRIJSKIH BOLESNIKA: FOKUS NA FAKTORE KOJI UTIČU NA KONCENTRACIJU U PLAZMI

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Monitoring koncentracije antiepileptičnih lekova (AEL) u pedijatrijskoj populaciji predstavlja važan korak u donošenju odluka vezanih za optimizaciju savremene terapije epilepsije. Primarni cilj ovog istraživanja bilo je određivanje koncentracija lamotrigina (LTG) i levetiracetama (LEV) u plazmi dece i adolescenata na kombinovanoj antiepileptičnoj terapiji. Sekundarni cilj bio je ispitati uticaj demografskih faktora i koterapije na izmerene koncentracije AEL-a. Prospektivna studija obuhvatila je sedamdeset jednog ispitanika sa dijagnozom epilepsije, starosti od dve godine do osamnaest godina, na kombinovanoj antiepileptičnoj terapiji koja je uključivala sledeće terapijske modalitete: valproinsku kiselinu (engl. *valporic acid* – VA) / LTG, VA/LEV i LTG/LEV. Rezultati sprovedenog istraživanja pokazali su da je 86,27% LTG koncentracija i 68,97% LEV koncentracija bilo u referentnom opsegu. Nije zabeležen statistički značajan uticaj komedikacije na koncentracije ispitivanih antiepileptika. Takođe, dobijeni rezultati potvrdili su da je doza LTG-a bila najznačajniji prediktor za koncentracije LTG-a. Rezultati ovog istraživanja ukazali su na to da jedino doza LEV-a prilagođena telesnoj masi može uticati na LEV koncentracije. Iako se terapijski monitoring antiepileptika novije generacije ne sprovodi rutinski u svakodnevnoj kliničkoj praksi, rezultati našeg istraživanja predočili su da monitoring koncentracija LTG-a i LEV-a može biti od velike koristi u pedijatrijskoj populaciji tokom primene kombinovane antiepileptične terapije, kako zbog same prirode bolesti, tako i zbog potencijalne farmakokinetičke varijabilnosti ispitivanih antiepileptika.

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***Ključne reči**: pedijatrijska populacija, terapijski monitoring leka, lamotrigin, levetiracetam*

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LONGITUDINAL EVALUATION OF THE HEALTH-RELATED QUALITY OF LIFE IN COVID-19 PATIENTS: A COMPARISON BETWEEN PRE-INFECTION AND THREE MONTHS POST-DISCHARGE

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The infectious disease COVID-19, caused by the SARS-CoV-2 virus, continues to be a significant global public health emergency. Alongside the undeniable effects on physical health, there is evidence of a serious impact on mental health as well.

Our study aimed to assess changes in health-related quality of life in COVID-19 patients before hospitalization for SARS-CoV-2 infection and three months after discharge.

Data were collected from 70 participants hospitalized for COVID-19. Participants were examined twice, after admission to the hospital and three months after discharge. Quality of life was measured with the 36-item Short Form Survey (SF-36), Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ9), and Generalized Anxiety Disorder 7-item (GAD-7). The statistical significance of two variables in the same sample at two distinct points in time was compared using a paired-sample T-test.

There was a significant difference in PHQ9 scores before and after hospitalization ($t = 4.738$, $p < 0.01$). We found no significant change in PSQI score before hospitalisation or three months after discharge ($t = -.622$, $p = 536$). Our results showed a significant increase in GAD7 and a significant decrease in physical functioning (PF) ($t = 5.929$, $p < 0.01$) and role limitations due to physical health problems (RP) ($t = 4.385$, $p < 0.01$) scores. The findings indicate that there was no statistically significant difference between pre-infection and three months after discharge in the SF-36 questionnaire's role limitations due to emotional problems (RE) and social functioning (SF) components.

In summary, the results of our study suggest that COVID-19 patients have physical and mental health problems that may persist even after recovery and negatively affect their quality of life.

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Key words: *Health-Related Guality of Life, Coronavirus Disease, 36-Item Short Form Survey, Pittsburgh Sleep Guality Index, Patient Health Guestionnaire-9, Generalized Anxiety Disorder 7-Item*

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Introduction

The infectious disease COVID-19, caused by the SARS-CoV-2 virus, continues to represent a significant global public health danger. The majority of patients who were released passed through various phases of recovery, while consequences on long-term health are presently being evaluated (1). Alongside the clear impacts on physical health, there is evidence of a substantial influence on mental health as well (2). Besides the symptoms of illness themselves, experiences during hospitalisation, physical and social isolation, and death of family members or other patients are factors that could worsen mental health status (3). Additionally, coronavirus can induce immunological reactions that have serious effects on an infected person's mental health and brain function (4). The specific process by which coronavirus affects the brain is unclear. However, it can enter the brain via the olfactory bulb, pass the blood-brain barrier, and interact with ACE2 receptors (5). Furthermore, physiologic abnormalities in the brain, like microglia stimulation and cytokine activation may be connected to mental disorders (6). Experienced stress and compensating mechanisms are two well-known and plainly observable elements that

effect one's actions and symptom presentations (7). A previous investigation on COVID-19 infection suggested that coronavirus infection was associated with long-term mental issues and neuropsychiatric effects (8). COVID-19 patients, in particular, exhibited symptoms of psychological distress symptoms that can result in persistent dysfunction and a reduction in their quality of life; recent data also show an increased chance of having post-traumatic stress disorder during hospitalization (9, 10). Here we provide research in which health-related quality of life parameters were investigated in COVID-19 patients before and three months post-hospital release.

Aim

Our study aimed to assess changes in health-related quality of life in COVID-19 patients before hospitalization for SARS-CoV-2 infection and three months after discharge.

Methods

Research Methodology and Participant Profile

This observational, longitudinal study was carried out in the Infectious Diseases Clinic, University Clinical Centre of Niš, Serbia, from January 2022 to May 2022. Participants were examined twice, during admission to the hospital and three months after discharge. Inclusion criteria were SARS-CoV-2 infection and a minimum age of 18. A positive PCR test done at the time of admission to our hospital proved the patient's infection with SARS-CoV-2. Participants were removed if they had poor questionnaire completion, exhibited evidence of prior mental illness or dementia, had spent more than 12 hours in the Intensive Care Unit, or experienced a fatal outcome. The participants' ages varied from 23 to 79. Demographic data and prior illnesses were gathered from hospital records and self-reported upon admission. Written informed permission was gained by each subject. The study followed the principles specified in the Helsinki Declaration. The Niš University Clinical Centre Ethics Committee accorded their consent to the study proposal.

Instruments

Quality of life was examined with the 36-item Short Form Survey (SF-36), Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ9), and Generalized Anxiety Disorder 7-item (GAD-7). A widely adopted measure for assessing health-related quality of life is the SF-36. Eight scales are measured by SF-36 (11-13): Physical functioning (PF) measures the ability to carry out physical tasks, including walking, using stairs, and house maintenance.

Role limitations due to physical health problems (RP) measure the influence of physical health issues on everyday obligations, such as employment or other regular activities. Bodily pain (BP) measures the degree and effect of pain on everyday activities. The questionnaire covers items for general health (GH), vitality, role limitations due to emotional problems (RE), social functioning (SF), and mental health (MH). GH examines self-reported overall health status, including perceived changes in health throughout time. Vitality examines the levels of energy and fatigue. RE analyzes the impact of emotional health problems on everyday activities, including employment or other regular activities. MH assesses psychological discomfort and well-being, whereas SF measures the effect of physical or emotional challenges on relationships. Scores vary from 0 to 100; lower scores imply greater dysfunction, while higher scores represent reduced dysfunction (13). The SF-36 analyzes two distinct dimensions: a physical dimension and a mental dimension (11-13). The assessment of the physical and mental factors is influenced by each scale in a different way (12). Instead of using an SF-36 overall score, for this study, we used the scores separately for PF, RP, SF, and RE in statistical processing. The Pittsburgh Sleep Quality Index, or PSQI, is a questionnaire developed to quantify a person's sleep quality over one month. Nineteen separate items make up the test, which examines seven major aspects of sleep quality: subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, disturbance in sleep, usage of medications for sleep, and disruption of daily routines. One overall score is derived by adding the outcomes of these seven component scores (14). The Patient Health Questionnaire-9, known as PHQ-9, is a self-administered depression screening instrument. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) provides nine diagnostic criteria for major depressive disorder, which are reflected in the PHQ-9. With a total score that can vary from 0 to 27, each item is rated on a scale of 0 to 3. Higher scores suggest greater depression severity (15). The Generalized Anxiety Disorder-7-item Scale is referred to as the GAD-7. The existence and severity of generalized anxiety disorder (GAD) symptoms are assessed using this seven-item screening questionnaire (16).

Statistical Analysis

Demographic data were presented as mean ± SD. Descriptive statistical analysis was applied for the demographic information, and a paired-sample T-test was applied to evaluate the statistical significance of two variables in the same sample at two different points in time. IBM SPSS Statistics 26 was used for data processing, and $p < 0.05$ was regarded as significant.

Results

Data were gathered from 70 individuals hospitalized for COVID-19. Most of them were male (60%) and had a secondary level of education (45.71%). The mean age of the subjects was 52.03 ± 15.76 years, and the median period since the positive PCR test was 4 days. Specific demographic information is presented in Table 1. The PHQ9 mean score calculated for the duration of hospitalization was 6.600 ± 4.284, and 3 months later it was 4.314 ±

3.0. In contrast, the PSQI and GAD-7 mean scores were higher three months following discharge. In addition, the mean values of RE and SF were similarly greater, although PF and RP were decreased three months after infection (Table 2). To compare the scores of these questionnaires, we performed a paired-sample test for statistical significance between the scores obtained one month before COVID-19 infection and three months after hospital discharge (Table 3). PHQ9 scores before and after hospitalization differed significantly, according to our statistical findings (t = 4.738, $p < 0.01$). We found no significant change in PSQI score before hospitalisation and three months after discharge (t = -.622, $p = 536$). According to our findings, the GAD7 score significantly increased 3 months after hospital discharge (t = -3.978, p < 0.01), and there was a significant decline in physical functioning (PF) (t = 5.929, $p < 0.01$) and RP (t = 4.385, $p < 0.01$) scores from pre-COVID-19 infection to 3 months post-hospital discharge. The results demonstrate that there was no difference in statistical significance in RE and SF components of the SF-36 questionnaire between pre-infection and 3 months after discharge. Paired samples t-test indicated a RE mean difference of -.043 (SD = .428), with a t-value of -.840 and a *p*-value of .404 and an SF mean difference of -.053 (SD = .231), with a t-value of -1.903 and a *p*-value of .051.

Table 1. Demographic data of participants

Variables	**Total N (%), N□70**
Age in years (mean + SD)	52.03 ± 15.76
Gender	
Male	42 (60)
Female	28 (40)
Education level	
Primary school	6 (8.57)
Secondary school	32 (45.71)
Faculty	24 (34.29)
Master degree	7 (10)
Doctoral degree	1 (1.43)
Marital status	
Single	9 (12.86)
Married	50 (71.43)
Divorced	6 (8.57)
Widowed	5 (7.14)
Employment status	
Student	3 (4.29)
Employed	40 (57.14)
Unemployed	27 (38.57)
Chronic illness	
Yes	41 (58.57)
No	29 (41.43)

Table 2. Descriptive statistics

Paired Samples Statistics					
		Mean	**N**	**Std. Deviation**	**Std. Error Mean**
Pair 1	PHQ9	6.6000	70	4.28479	.51213
	PHQ9_3	4.3143	70	2.99537	.35802
Pair 2	PSQI	4.6000	70	3.16869	.37873
	PSQI_3	4.8000	70	2.59095	.30968
Pair 3	GAD7	5.3000	70	2.80966	.33582
	GAD7_3	7.1571	70	3.60610	.43101
Pair 4	PF	.8343	70	.15430	.01844
	PF_3	.6686	70	.28363	.03390
Pair 5	RP	.6500	70	.32804	.03921
	RP_3	.4464	70	.32385	.03871
Pair 6	RE	.7190	70	.31929	.03816
	RE_3	.7620	70	.28454	.03401
Pair 7	SF	.6632	70	.24923	.02979
	SF_3	.7157	70	.18945	.02264

Table 3. Paired Samples Correlations

Paired Samples Test									
		Paired Differences					**t**	**df**	**Sig. (2tailed)**
		Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
					Lower	**Upper**			
Pair 1	PHQ9 - PHQ9_3	2.28571	4.03658	.48246	1.32323	3.24820	4.738	69	**.000**
Pair 2	PSQI - PSQI_3	-.20000	2.68976	.32149	-.84135	.44135	-.622	69	.536
Pair 3	GAD7 - GAD7_3	-1.8571	3.90572	.46682	-2.7884	-.92586	-3.978	69	**.000**
Pair 4	PF - PF_3	.16571	.23383	.02795	.10996	.22147	5.929	69	**.000**
Pair 5	RP - RP_3	.20357	.38845	.04643	.11095	.29619	4.385	69	**.000**
Pair 6	RE - RE_3	-.04300	.42820	.05118	-.14510	.05910	-.840	69	.404
Pair 7	SF - SF_3	-.05250	.23087	.02759	-.10755	.00255	-1.903	69	**.051**

$P < 0.01$

Discussion

As we are in the fourth year since the whole world was confronted with COVID-19, one of the most crucial problems facing global health systems today is to identify and comprehend the unavoidable effects of the SARS-CoV-2 viral infection.

Based on one of the first cross-sectional studies of individuals recovering from COVID-19 in Wuhan, SARS-CoV-2 virus infection is typically associated with several psychiatric disorders, including depression, anxiety, and even suicide. According to this study, 10% of COVID-19 survivors report anxiety or depression, and 29.5% of survivors experience sleep disturbances one month and six months after discharge, respectively (17). Our study's findings suggest that after hospital discharge, the features and standard of sleep in the COVID-19 recovered patients do not dramatically alter. It is essential to keep in mind that the study's sample size was quite small, which could have reduced its ability to identify significant changes. Only a few factors have been linked to improved sleep quality. Poor sleep quality has been connected to female sex, younger age, and persons with a history of mental issues (18). Lack of sleep severely influences cognitive function and quality of life (19, 20). In addition, sleep interruptions could increase depression and anxiety while reducing pain thresholds (21).

A recently published meta-analysis analysed the cumulative prevalence of mental diseases among COVID-19 survivors (22). Despite significant variance across the 27 studies, it was clear that mental and psychological health outcomes are essential for COVID-19 survivors. Prevalence rates for posttraumatic stress disorder (PTSD), anxiety, psychological distress, depression, and sleep disorders were as follows: 22% for anxiety, 36% for psychological distress, 21% for depression, and 35% for sleep disorders. The following risk variables have been connected to an enhanced risk of anxiety, depression, or other unfavourable mental health outcomes: indicators of inflammation, especially IL-6 (23), severity of illness, duration of symptoms, severity of illness at 6-month follow-up, and female sex (24, 25). Based on our results, there seems to be a statistically significant difference in the incidence of generalized anxiety disorder before and after COVID-19 infection, as shown by the GAD7 questionnaire. It is noteworthy to underline that the elevation in GAD7 scores identified in our study could be connected to a range of factors, such as the physical and emotional stress associated with hospitalisation and treatment for COVID-19, as well as the social and economic disruption generated by the pandemic (26, 27). One Chinese study applied the SF-36 questionnaire to investigate the health-related quality of life of COVID-19 patients (28). This showed a worse score at one-month follow-up, with psychological impairment described mainly in women, suggesting that the female gender may be a risk factor for psychological quality of life in these patients (28). In our study, the physical functioning (PF) component of the SF-36 was compared 3 months after discharge to the period before infection. The results showed a significant decrease in the ability to perform physical activities after the patients had recovered from COVID-19. These findings support other studies that have shown COVID-19 to have long-term health impacts, including reduced physical functioning (1). Our findings also indicate a significant decline in RP—as a measure of the impact of physical health problems on daily activities among those who had COVID-19 and recovered. The reduction in physical role functioning may have several effects on the overall well-being of COVID-19 survivors. For instance, it would make it more difficult for them to carry out routine tasks like work or household, which would increase stress and reduce life pleasure (28). Another Chinese study that evaluated health-related quality of life using the SF-36 found that COVID-19 hospitalization had a detrimental impact on patients' quality of life for up to three months following release (12). In this research, poor quality of life appeared to be related to age, gender, and physical symptoms after discharge, suggesting that older adults, particularly women and those with recurrent physical symptoms, are most at risk for poor quality of life.

Conclusion

In summary, the results of our study demonstrate that COVID-19 patients have physical and mental health issues that may persist even after recovery and negatively affect their quality of life. The fact that our study was done at one site and the sample size was quite limited should be emphasized, as this may hamper the generalizability of our findings. However, our study underlines the importance of continuing surveillance and care for COVID-19 survivors to make sure they receive the necessary treatment to address any long-term health concerns. The long-term health implications of COVID-19 may be better understood in the future through research utilizing broader samples and more diverse populations.

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PROCENA KVALITETA ŽIVOTA POVEZANOG SA ZDRAVLJEM KOD PACIJENATA ZARAŽENIH VIRUSOM COVID-19 PRE INFEKCIJE I TRI MESECA NAKON OTPUSTA SA BOLNIČKOG LEČENJA

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Infektivno oboljenje COVID-19, izazvano SARS-CoV-2 virusom, i dalje predstavlja značajnu globalnu pretnju po zdravlje ljudi. Pored toga što ovo oboljenje nesumnjivo utiče na fizičko zdravlje, postoje i dokazi o njegovom ozbiljnom uticaju na mentalno zdravlje.

Naše istraživanje imalo je za cilj da proceni promene u kvalitetu života kod obolelih od COVID-19 pre hospitalizacije i tri meseca nakon otpusta iz bolnice.

Podaci su dobijeni od 70 ispitanika sa postavljenom dijagnozom COVID-19 koji su bili hospitalizovani na Klinici za infektivne bolesti Univerzitetskog kliničkog centra u Nišu. Bili su ispitani dva puta: nakon prijema na bolničko lečenje i tri meseca nakon otpusta. Kvalitet života meren je na osnovu sledećih upitnika: 36-*Item Short Form Survey* (SF-36), *Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ9) i Generalized Anxiety Disorder 7-Item* (GAD-7). Statistička značajnost dveju promenljivih merena u istom uzorku u dva različita trenutka poređena je uz pomoć uparenog T-testa.

Postojala je statistički značajna razlika u PHQ9 skorovima pre hospitalizacije i posle nje ($t = 4,738$; $p < 0,01$). Nije bilo značajne promene PSQI skora pre hospitalizacije i tri meseca nakon otpusta ($t = -0,622$; $p = 536$). Naši rezultati pokazali su statistički značajan porast GAD7 i značajan pad skora komponente fizičkog funkcionisanja (engl. *phisical functioning* – PF) ($t = 5,929$; $p < 0,01$), kao i skora komponente ograničenja zbog fizičkih zdravstvenih problema (engl. *emotional regulation* – RP) ($t = 4,385$; $p < 0,01$). Prema dobijenim rezultatima, nije bilo statistički značajne razlike između perioda pre infekcije i perioda nakon otpusta iz bolnice u komponentama SF-36 upitnika koje se odnose na ograničenja usled emocionalnih problema i na domen socijalnog funkcionisanja (engl. *social functioning – SF).*

Na osnovu rezultata našeg istraživanja može se zaključiti da oboleli od COVID-19 imaju fizičke i mentalne zdravstvene probleme koji mogu trajati i nakon oporavka od infekcije i negativno uticati na kvalitet života.

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***Ključne reči**: kvalitet života, oboljenja izazvana koronavirusom, 36-Item Short Form Survey, Pittsburgh Sleep Quality Index, Patient Health Questionnaire-9, Generalized Anxiety Disorder 7-item*

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CORONAVIRUS DISEASE AND IMMUNOTHERAPY IN JUVENILE IDIOPATHIC ARTHRITIS

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The COVID-19 pandemic was a huge challenge to paediatricians around the world. The treatment of patients with juvenile idiopathic arthritis (JIA) and COVID-19 infection could present a potential ethical and medical dilemma. Here we discuss the results of a medical survey made on the parents of children with JIA. Our primary aim was to determine if there was a significant difference in the number of flares of JIA after COVID-19 infection between the group of children who were receiving biological drugs and children not receiving biologicals. Other goals were to investigate the parents' motivation to vaccinate children against SARS-CoV-2 and to determine the most frequent symptoms of COVID-19 infection in these children. A retrospective study was based on the data of a telephone survey conducted between March 10, 2022, and May 12, 2022, including 65 paediatric patients with JIA. The data were provided from the Heliant Health information system database. In children who tested positive for SARS-CoV-2, the most frequent symptom was fever, followed by upper respiratory symptoms. Four flares of JIA were observed in the group of children on biological therapy, while in the group without biologicals two flares followed the COVID-19 infection. The parents' motivation for vaccination against SARS-CoV-2 was extremely low. Our survey-based research did not find a significant difference regarding the COVID-19 infection between children with JIA on biologicals and children with JIA not receiving biologicals, but it did emphasise the parents' hesitancy about vaccination. We propose building a unique database for patients with the diagnosis of JIA which could improve the quality of life of these patients.

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Key words: *coronavirus disease, juvenile idiopathic arthritis, severe acute respiratory syndrome coronavirus 2, flare, biologicals*

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Introduction

The start of the coronavirus disease (COVID-19) pandemic was announced on March 11, 2020 by the World Health Organization (WHO). From that moment, until writing the introductory part of this article, it was estimated that the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) took approximately 20 million lives (1), thus leaving deep and unfathomable consequences on society, medicine, economy, however, it also contributed to the development of various sociological and cultural phenomena. SARS-CoV-2 is an infective agent constituted of nucleocapsid, membrane, envelope, and spike (S) protein. It is characterized by a high transmission efficacy and genetic similarity to SARS and MERS viruses. The spike protein engages with ACE-2 receptors of human cells, which allows the entry of a virus particle in the cell (2–5). Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. Its aetiology is still unknown, although it is thought to be provoked by a complex interaction between genetic and environmental factors such as infections, human leukocyte antigen (HLA), gut microbiota, etc. It is classified by the International League of Associations for Rheumatology (ILAR) into several subtypes (6–9). Due to its pathophysiology, it is considered a polygenic autoinflammatory disease. Disease-modifying antirheumatic drugs (DMARDs) represent a group of drugs used in the treatment of rheumatic diseases in the paediatric and adult populations. A specific mechanism of monoclonal antibodies provides targeted neutralization of certain cytokines involved in the pathogenesis of JIA. These medications can silence the disease course and provide remission periods for patients

with JIA (10, 11). Although interleukin-6, interleukin-1 and tumour necrosis factor inhibitors safety profiles are regarded highly acceptable, their use in patients with JIA, and especially in patients with comorbidities, could provoke an increased risk of infections (12–14). Another aspect of COVID-19 pandemic is dealing with COVID-19 paediatric patients who have comorbidities. Patients with JIA constitute such population. Pfizer-BioNTech COVID-19 vaccine is an mRNA-based vaccine and the only vaccine registered for use in the paediatric population in Serbia. Vaccine hesitancy, mostly caused by misinformation, was a major problem in fighting with COVID-19 pandemic, especially in paediatric patients (15). Potential flares that can be provoked by other infections could possibly occur after COVID-19 infection. Fever that can occur in both COVID-19 and JIA must be carefully evaluated. Other important aspects are when to vaccinate taking into consideration immunosuppressive therapy in JIA patients. Therefore, patients with JIA and COVID-19 infection could present a potential ethical and medical dilemma, and every single case must be closely monitored. Here we discuss the results of a medical survey conducted during pandemics, involving parents whose children were diagnosed with JIA.

Aim

Our primary aim was to determine if there was a significant difference in the number of juvenile idiopathic arthritis flares that could be related to SARS-CoV-2 infection between the group of children with JIA who were receiving biological drugs and children with JIA not receiving biological drugs. Other goals were to investigate the parents' motivation to vaccinate children against SARS-CoV-2 and to determine the most frequent symptoms of COVID-19 infection in this population.

Materials and Methods

A retrospective study based on the data of a telephone survey was conducted between March 10, 2022 and May 12, 2022, and it included 65 paediatric patients diagnosed with juvenile idiopathic arthritis. Parents were beforehand informed to anticipate a call from a physician. The survey referred to the period from the beginning of the pandemic. Children were divided into two groups—one that was receiving monoclonal antibodies as a part of the treatment for JIA (n = 9), and the control group that consisted of children with the diagnosis of JIA, who were not receiving biological drugs. The control group (n = 26) included children who were receiving methotrexate and other DMARDs, but also children in disease remission. Some of the research data considering the total duration of JIA, parent's phone numbers and treatment were provided through the Heliant database. Other data were provided from the survey. The survey contained a series of closed and open-ended questions about COVID-19, to which parents gave answers, and it could be roughly divided into four clusters: 1) Positivity or prolonged contact with household members; 2) Symptoms that predominated infection; 3) Potential flares of JIA that followed the infection; 4) Vaccinal status or parents motivation to vaccinate children against SARS-CoV-2. A Chi-squared test was used for group comparison.

Results

Gender, age, and duration of the disease (JIA) are shown in Table 1. The number of positive tested children or children with JIA in prolonged contact with household members tested positive for COVID-19, a number of flares that followed COVID-19 infection and number of parents who vaccinated or were motivated to vaccinate their children are shown in Table 2, along with the most frequently noted symptoms. Therapy of children on biological drugs was adalimumab (n = 18, 48.6%), etanercept (n = 11, 29.7%) and tocilizumab (n = 8, 21.6%) together with methotrexate. For two cases, the data for the type of biological treatment in the Heliant healthcare information system database were not available.

Table 1. Characteristics of JIA patients

	Biological therapy		Control group		Total
Gender	Male	Female	Male	Female	Male and female
	10(25.64%)	29(74.35%)	11(40.74%)	15(59.25%)	65(100%)
Age	11.75 ± 4.70		9.71 ± 4.61		10.87 ± 4.75
Disease duration*	7.11 ± 10.90†		3.93 ± 2.32†		5.84 ± 8.67

*Total time with the diagnosis of JIA. †Disease duration was unknown for one case on biological therapy and two cases in the control group. The biological therapy group showed a greater variation of data for disease duration.

Table 2. Survey results

	Biological therapy	Control group	Total	Symptoms
Positive / contact*	31 (79.48%)	20 (76.93%)	51 (78.46%)	- Fever - Nasal congestion, rhinorrhoea - Cough, sore throat - Myalgias, fatigue
Flares of JIA†	4 (10.25%)	2 (7.70%)	7 (10.78%)‡	
Motivated / vaccinated	3 (7.69%)	1 (3.84%)	4 (6.15%)	

*Tested positive or in prolonged contact with family or household members who tested positive for COVID-19. †Flares of JIA that followed COVID-19 infection. ‡In one case, exacerbation of JIA did not occur after COVID-19 infection. No significant statistical difference b/w the groups was noted $p > 0.05$.

In the group without biologicals, treatment was methotrexate (n = 14, 53.8%), hydroxychloroquine (n = 2, 7.7%), naproxen with methotrexate (n = 2, 7.7%), naproxen (n = 2, 7.7%), prednisone with methotrexate (n = 1, 3.8%) and physical therapy (n = 5, 19.2%). In one case (n = 1, 3.84%), the disease exacerbation occurred after parents did not show up for regular check-ups during lockdown for about two months. In children that tested positive for SARS-CoV-2 on PCR or antigen test (n = 22), the most frequent symptom was fever (n = 14, 63.6%). Fever was < 39 °C in all cases, except in one where it measured above 39 °C (on one occasion 39.8 °C). Other symptoms noted were upper respiratory symptoms (cough, nasal congestion, sore throat, etc.), fatigue, myalgias and conjunctivitis. Parents of three children noted an asymptomatic infection (n = 3, 14%) that was proven with antibody testing. In most cases, symptoms were mild and mostly lasted less than a week. In one case, parents noted that their child had a loss of smell and taste problems that persisted for almost six months. No significant statistical difference was found in the number of flares that followed COVID-19 infection between children with JIA who were receiving biological drugs and children with the diagnosis of JIA not receiving biological drugs (χ^2 with Yates correction was 0.0077, p = .930299. Not significant at $p < .05$). As a reason for not vaccinating their children or lack of motivation for vaccination, most parents reported a misconception that vaccines were not tested enough and were experimental. Relative risk for flares was R = 1.33 (R > 1) in the group of children receiving biologicals compared to the group of children without biologicals in their treatment.

Discussion

In our survey-based research, we tried to examine whether there was a significant difference in the number of flares that could be related to SARS-CoV-2 infection, between paediatric patients with the diagnosis of JIA who were on biological therapy and paediatric patients with the diagnosis of JIA not receiving these drugs.

Key points:

-Patients with the diagnosis of juvenile idiopathic arthritis (JIA) usually had a mild form of COVID-19 disease.

-There were cases where flares of JIA occurred after the infection with SARS-CoV-2.

-We failed to prove that a greater risk of flares after SARS-CoV-2 infection existed in the group of paediatric patients with JIA who were receiving biological drugs.

-It was evident that parents' motivation to vaccinate their children against SARS-CoV-29 was extremely low.

The course of COVID-19 infection in children is usually milder and more asymptomatic compared to the adult population. The most frequent symptoms noted by authors are fever, cough, and rhinorrhoea, which is consistent with our results (Table 2). Most paediatric patients who required ICU admission had comorbidities such as cancer (16–17). The course of COVID-19 infection in paediatric patients with JIA is generally not much different than the course of infection in the rest of the paediatric population, although the risk of exacerbations of JIA triggered by infection was observed (18). This was also evident in our study. It was noted that COVID-19 infection could provoke flares of JIA in paediatric patients in remission or with inactive disease (19, 20). Increased relapse rate during lockdown was found in one Italian study (18), which could be caused by organization problems and general healthcare management. Nevertheless, the full impact of COVID-19 is still to be investigated for this group of patients. The total number of disease exacerbations observed in our study could also be caused by factors other than COVID-19, not evaluated by the survey (prolonged period off drugs, worsening of disease activity, stress, etc.). We could speculate about a protective effect of

TNF-α blockers against cytokine storm syndrome (CSS) in paediatric patients with JIA who are on TNF-α inhibitors, as this potential effect was described in adult patients with rheumatic disease (21, 22). A small discrepancy between our two groups in the number of flares after COVID-19 (biologicals vs. without biologicals, 4 : 2, with RR = 1.33) could be a consequence of disease severity, however, a larger study is needed to evaluate the true meaning of these data. Patients who require monoclonal antibodies in treatment are more likely to have more serious illnesses and likely more prone to disease exacerbations. Smell and taste dysfunction that lasted for almost six months was noted in one child in our study. Prolonged loss of taste and smell is a symptom described as part of Long COVID (23, 24). Parents of children who were receiving biological drugs talked more freely about COVID-19 vaccination, and there is a slight discrepancy in motivation towards vaccination between the two groups (biologicals vs. without biologicals 3 : 1). This could be caused by frequent contact with healthcare workers. Parents' extremely low motivation for vaccinating their children against COVID-19 can be caused by multiple factors. A significant component of vaccination hesitancy may be conflicting and inadequate media coverage (25, 26). Parents who are vaccinated are more likely to vaccinate their children. The important factor for this decision may be parents' level of education (27, 28). Having in mind that most parents noted as a reason for not vaccinating their children that vaccines were not tested enough and were experimental, an adequate strategy and promotion campaign could present a potential solution to this problem (15, 29).

Conclusion

Our survey-based research did not demonstrate a significant difference in terms of COVID-19 infection-provoked flares between children with JIA who were receiving biological drugs and children with JIA who were not on biologicals, but it did emphasize the problems with parents' trust in vaccines, so similar surveys can be helpful in the future, and on the larger scale they could provide more significant and reliable data. Therefore, we propose building a unique database for paediatric patients with the diagnosis of juvenile idiopathic arthritis, so that healthcare workers dealing with this population could have a better concept of how to provide a better quality of life for their patients.

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COVID-19 I IMUNOTERAPIJA U JUVENILNOM IDIOPATSKOM ARTRITISU

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Pandemija COVID-19 predstavlja ogroman izazov za pedijatre širom sveta. Dece obolele od juvenilnog idiopatskog artritisa (JIA) koja imaju COVID-19 i koja su po indikacijama na biološkoj terapiji može lekare dovesti do medicinske i etičke dileme. Nastojali smo da u ovom radu odgovorimo na pitanje da li je sklonost ka egzacerbacijama JIA nakon preležane infekcije COVID-19 veća kod dece sa JIA na biološkoj terapiji nego kod dece sa JIA koja nisu na biološkoj terapiji. Osim toga, ispitali smo motivaciju roditelja za vakcinaciju dece i simptome bolesti COVID-19 u ovoj populaciji. Retrospektivna studija sprovedena je na osnovu rezultata ankete rađene između 10. 3. 2022. i 12. 5. 2022. godine koja je obuhvatila 65 pedijatrijskih bolesnika. Anketa je sadržala niz zatvorenih i otvorenih pitanja na koja su odgovarali roditelji. Deo podataka koji se ticao trajanja JIA, brojeva telefona i terapije preuzet je iz *Heliant* informacionog sistema. Za poređenje grupa korišćen je Hi-kvadrat test. Pokazalo se da je najčešći simptom bila povišena telesna temperatura, a pratili su je simptomi vezani za gornji respiratorni trakt. Egzacerbacija osnovne bolesti koja je usledila nakon COVID-19 infekcije u grupi dece na biološkoj terapiji sa JIA potvrđena je u četiri slučaja, dok je u grupi dece sa JIA koja nisu bila na biološkoj terapiji pogoršanje zabeleženo dva puta. Prilikom poređenja dveju pomenutih grupa nije nađeno statistički značajno odstupanje. Motivacija roditelja za vakcinaciju protiv SARS-CoV-2 bila je izuzetno niska. Studija koja bi obuhvatila veći broj obolelih od JIA dala bi pouzdanije podatke o uticaju COVID-19 na ovu grupu bolesnika. Predlaže se formiranje jedinstvene baze podataka dece sa JIA, budući da bi ona u budućnosti mogla pomoći kliničarima da poboljšaju kvalitet života ovih bolesnika.

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***Ključne reči**: bolest izazvana koronavirusom, juvenilni idiopatski artritis, severe acute respiratory syndrome coronavirus 2, biološka terapija, egzacerbacija*

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POLYACRYLATE POLYALCOHOL COPOLYMER (VANTRIS®) AS AN OPTION FOR MINIMALLY INVASIVE MANAGEMENT OF VESICOURETERAL REFLUX: OUR EXPERIENCE

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Minimally invasive treatment of vesicoureteral reflux (VUR) has gained popularity in recent decades for numerous advantages of the procedure itself: easy to perform, short inpatient care time compared to open techniques, a rare occurrence of serious complications, and short duration of stay in hospital. There are two groups of injectable tissue augmentation agents: biodegradable and non-biodegradable. Vantris® is a combination of two groups.

The aim of the study was to determine the effectiveness of Vantris® as an option in the minimally invasive treatment of VUR.

We conducted a prospective study for a period of five years (2015–2019). A total of 24 patients, or 39 renal reflux units (RRJ) were treated with Vantris®.

Reflux was unilateral in 9 patients (37.5%), and bilateral in 15 patients (62.5%). Reflux grade was V in two ureters (5.12%), IV in 6 ureters (15.38%), III in 22 (56.42%), II in three (7.69%) and I in 6 (15.38%). Median follow-up was 12 months and included urinalysis, urinary tract ultrasound, and voiding cystoureterography at one year. Reflux was eliminated in 36 ureters (92.31%). Two patients developed ureterovesical junction obstruction, while one patient required another injection treatment.

Vantris® can be used to treat VUR successfully and with a low percentage of complications. The application is simple, the rate of complications is reduced to a minimum, and therefore it could become the treatment of choice for the treatment of VUR.

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Key words: *vesicoureteral reflux, children, Vantris®*

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Introduction

Vesicoureteral reflux (VUR) is a condition described even in the early beginnings of pediatric urology. It was reported back in 1893 by Pozzi. It is the retrograde flow of urine from the urinary bladder to the upper urinary tract, caused by abnormalities of the vesicoureteral junction, in the case of primary VUR. There is also secondary VUR, occurring as a consequence of an increased intravesical pressure which can result from numerous causes. It is more common in white children, predominantly boys up to the age of one year, but after the age of 1, it is more frequent in girls. Available literature data show the incidence of 0.4–1.8% in patients without urinary tract infection and 10–40% in patients with urinary tract infection (1).

Although the spontaneous resolution rate is almost 100% for grades I and II, and 20–60% for grades III–V, surgical and endoscopic management of VUR remains the treatment option in clearly defined cases: breakthrough while on antibiotic prophylaxis and recurrent urinary infection, the presence or *de novo* development of renal scarring, and persistent reflux (2).

The concept of endoscopic treatment of VUR has many advantages such as easy to perform, short duration, minimally invasive procedure, rare occurrence of serious complications, no visible scarring, low treatment cost, and short hospitalization (3). Rare complications include vesicoureteral junction obstruction and the development of contralateral reflux. The success rate of endoscopic management of VUR is defined as reflux grade reduction or complete reflux resolution.

Polyacrylate polyalcohol copolymer (PPC) (Vantris®, Promedon, Argentina) is a novel tissue-augmenting agent that is applied endoscopically.

The most significant indication of its use is the resolution of VUR.

Aim of the paper

This prospective study aimed to evaluate the Vantris efficacy in treating children with VUR.

Material and Methods

We conducted this prospective study for five years (2015–2019). The study included 24 patients with a total of 39 refluxing renal units (RRU). Apart from standard laboratory analyses (blood count, urinalysis, biochemical analyses), according to the European Society of Pediatric Urology (ESPU) Guidelines for the diagnosis of VUR, all the patients underwent ultrasound imaging and voiding cystourethrography (VCUG) to precisely determine the reflux grade. According to the American Urological Association (AUA), scintigraphy with 99m-dimercaptosuccinic acid (DMSA) is reserved for children with high reflux grade (III–V), those with high values of creatinine, and those with recurrent urinary tract infections. The study included only cases with primary VUR. All refluxing renal units (RRU) were treated with Vantris®. The study encompassed results following only one injection treatment and one-year follow-up period.

Results

Unilateral reflux was present in 9 patients (37.5%), and bilateral in 15 patients (62.5%) (Figure 1). In 19 RRU reflux was on the right side, in 20 RRU it was left-sided (Figure 2). Reflux was grade V in two RRU (5.12%), grade IV in 6 RRU (15.38%), grade III in 22 RRU (56.42%), grade II in three (7.69%), and grade I in 6 (15.39%) (Figure 3). Mean follow-up time was 12 months; the follow-up included urinalysis, and ultrasound of the kidneys and bladder. VCUG was performed only in cases of recurrent urinary infections.

Reflux was eliminated in 36 RRU (92.31%). Two patients developed vesicoureteral junction obstruction, and one patient required an additional injection treatment due to persistent VUR, nonetheless reflux grade decreased after administering one injection (Figure 4).

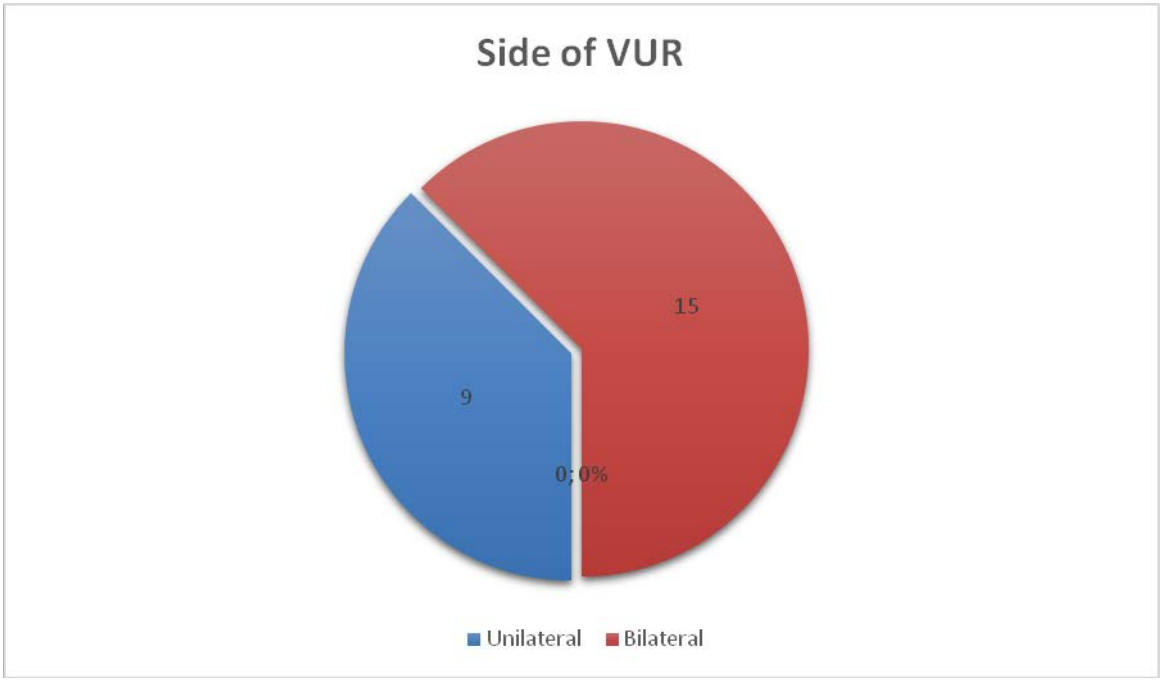
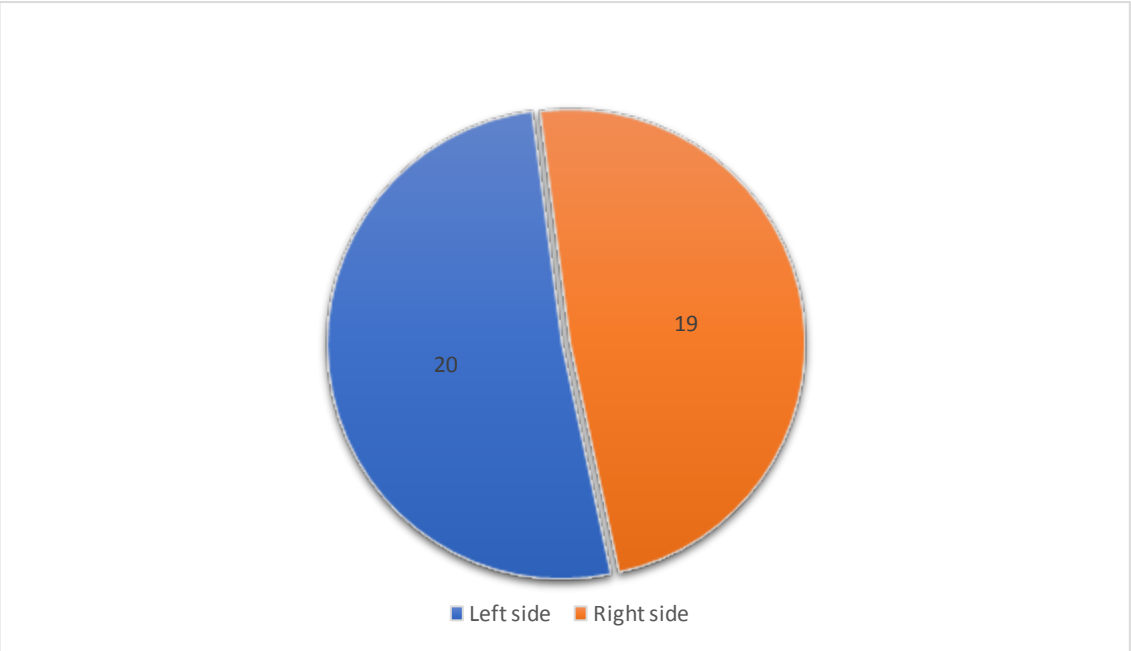


Figure 1. Distribution of VUR according to the side



Figures 2. Distribution of VUR according to the side

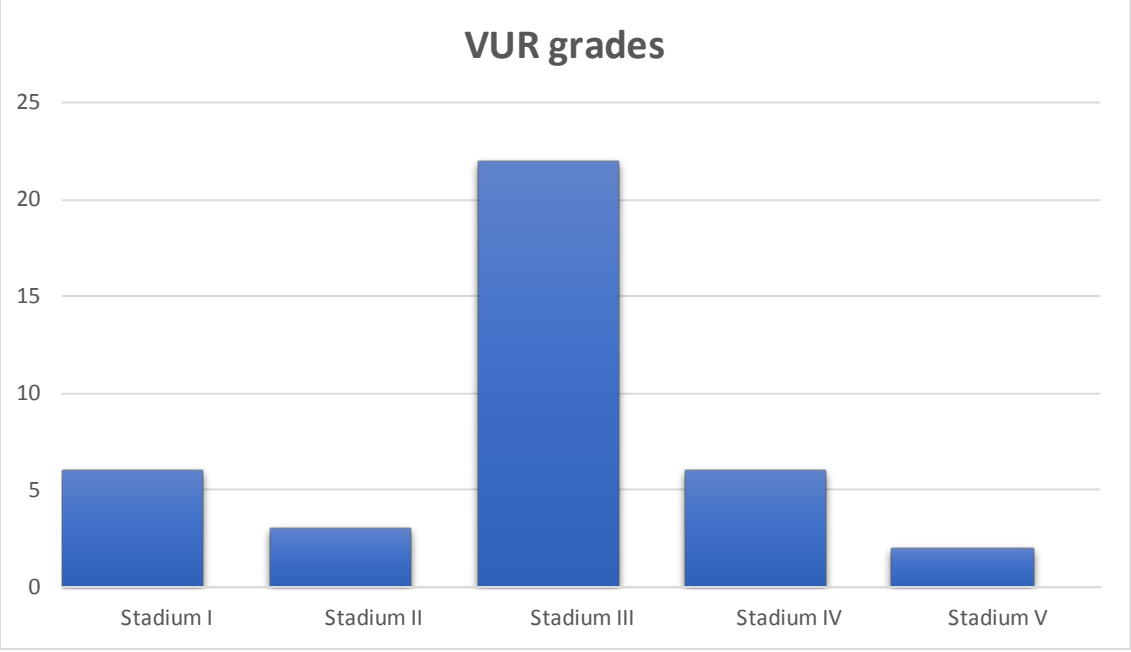


Figure 3. Distribution of patients according to the grade of reflux

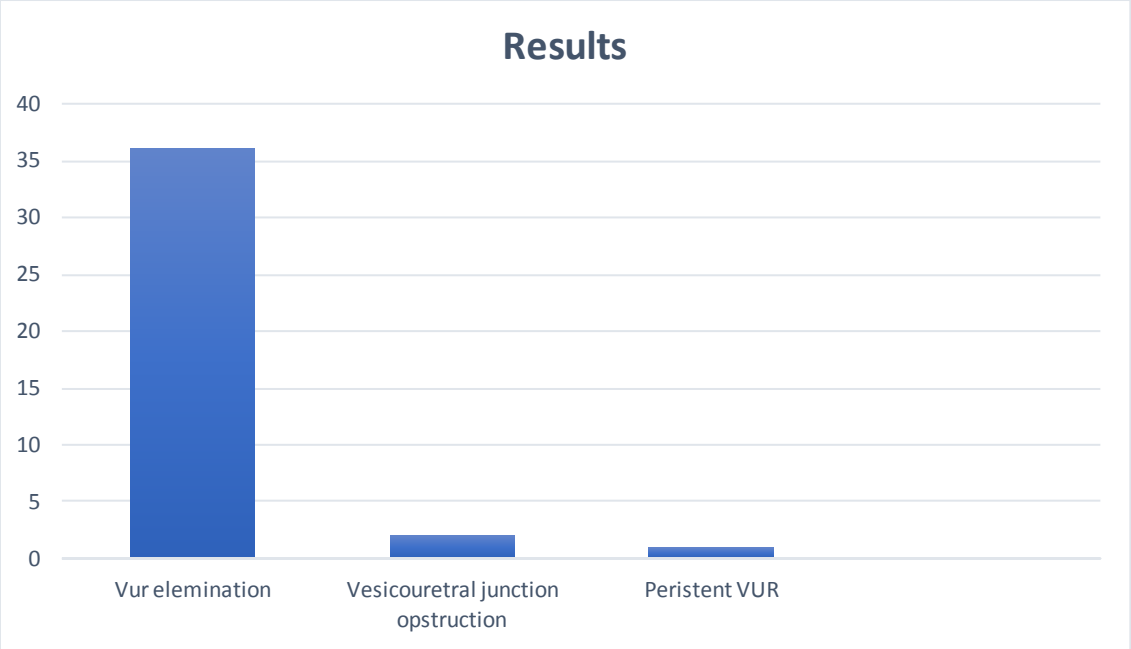


Figure 4. Results of Vantris® application in the treatment of VUR, our experiences

Discussion

According to International classification, there are V grades of VUR: grade I, reflux in lower third of the ureter only; grade II, reflux in the ureter and pyelon, without dilatation; grade III is characterised by mild dilatation/tortuous ureters and mild dilatation of pyelon; grade IV, moderate dilatation of the ureter, pyelon and calyces, but maintenance of papillary impressions in most calycles; and grade V, dilatation of the ureter, pyelon and calyces, gross tortuosity of the ureter, with loss of papillary impression (4).

The principal aim of VUR management is to preserve the renal parenchyma by preventing pyelonephritis and subsequent renal scarring. There are several options for treating VUR, watchful waiting, antibiotic prophylaxis, surgical treatment, and endoscopic procedures that, with advancements in minimally invasive procedures, pose the first line of treatment (5).

There are three surgical modalities in treating VUR: open or laparoscopic extravesical techniques, intravesical techniques, and endoscopic treatment. The introduction of the STING procedure in 1984 by O'Donnell and Puri was a huge advancement in minimally invasive treatment of vesicoureteral reflux, so that in recent years endoscopic management of VUR has become a treatment of choice for all reflux grades worldwide (6). A modified STING procedure, called the HIT (hydrodistension implantation technique) means hydrodistention of the ureter and submucosal injection into in distal ureter at the "6 o'clock position". A modified HIT procedure (double HIT) has also been introduced recently by using two injections, sub-ureteral and sub-mucosal, to coapt the ureteral orifice (7).

All the agents for endoscopic tissue augmentation are classified into two big groups: biodegradable and non-biodegradable (8). Biodegradable injectable agents have a high rate of reabsorption after a year, while non-biodegradable agents stimulate the formation of the fibrotic capsule, providing stability and long-term effects. Vantris® belongs to the latter group (a combination of both groups of injectable agents); it is composed of particles of polyacrylate polyalcohol copolymer immersed in a glycerol and physiological solution. When injected in tissues, the material remains stable throughout time (3). Injections are administered in ureteral submucosa; tissue augmentation occurs, that is, an elongation of the intramural parts of the ureters, thus providing an effective anti-reflux mechanism. The carriers of the active substance (glycerol and physiological solution) are eliminated by the reticular system through the kidneys, while the active substance remains *in situ*. We believe that the very non-biodegradable component of Vantris® and its stability through time has a favourable effect, having in mind the percentage of recurrences after endoscopic treatment with biodegradable agents such as dextranomer/hyaluronic acid copolymer (Deflux). Lee et al. reported in their retrospective study a

high recurrence rate of VUR after initial treatment with Deflux. The initial success of the treatment was similar to already reported results, with the postoperative success of 73%, while the recurrence rate in the first year was 26% (9).

Successful surgical treatment of VUR is defined as the complete elimination of reflux; however, a decrease in reflux grade is also considered as successful surgical treatment of VUR. In a meta-analysis of 5,527 patients, Elder et al. reported the success rate of first endoscopic treatment of 78.5% for VUR grades I and II, 72% in grade III, 63% in grade IV and 51% in grade V. The second treatment success rate after the first treatment failure was 68%, and the third treatment success rate was 34%. Considering all the cases, the success rate of endoscopic treatment of VUR was 85% (10). By comparing endoscopic and open surgical methods, literature data show that endoscopic treatment of reflux, which can prevent further urinary infections and renal scarring, may have equally good results as open surgical techniques (11, 12).

However, the question arises of the success rate in endoscopic treatment of high-grade reflux. In a retrospective study by Chung et al., out of a total 323 ureters, 234 were treated endoscopically, while 92 were treated by ureteral reimplantation. They reported that both methods were safe and effective in treating VUR, but with significantly higher success rate in surgical treatment of VUR grades IV and V, while, on the other hand, endoscopic treatment was characterized by shorter hospital stay and shorter recovery, so they believe that endoscopic treatment should be the first-line treatment for lower grade VUR, while surgical treatment should be reserved for more severe cases and after the failure of previous endoscopic treatment (13). Apart from being associated with treatment success rate, reflux grade is also associated with the onset of complications, and they more commonly occur in higher grade VUR—one of the complications that can occur after endoscopic treatment is vesicoureteral junction obstruction. In a large multicenter study enrolling a total of 611 patients and 6 centres worldwide, Kocherov et al. reported vesicoureteral junction obstruction of 1.2%, which is in accordance with our results. They believed that the cause of this complication occurrence is already present ureteral pathology, meaning that a certain number of their patients initially presented with already obstructed vesicoureteral reflux, and Vantris® application resolved reflux on one hand but exacerbated obstruction on the other hand. Ureter obstruction was resolved surgically. They reported a success rate for reflux after initial treatment with Vantris® of 94%, which is consistent with the results of our study, while 3.8% of patients required additional Vantris® application, which is also in agreement with our study. Patients indicated for additional Vantris® application had a more severe reflux grade (14).

The results of our study are also in accordance with the results of Dothan et al., with the overall success rate in correcting reflux utilizing Vantris® of 94.9%. Additional injections were required in 2.1% of patients, while 2.7% of patients developed ureterovesical junction obstruction (15). Also, a total of 83 patients underwent this treatment during a multicentre study in South America in the period 2006–2006. Reflux was eliminated in 88.6% of patients, and decreased to a lower degree in 6.8% of patients (1).

Our results with injection therapy of VUR using Vantris® are promising and are similar to results already published in the literature. Reflux was eliminated in 92.31% of units, but it should be pointed out that there were patients with associated anomalies of the urinary tract in the group of unsuccessfully treated patients.

This study has several limitations. All the cases were a single-centre experience, with a small sample size. Also, the SARS-CoV2 virus pandemic affected daily activities at our Institution, so the follow-up period was limited to one year, thus data on long-term results of reflux resolution by using Vantris® are lacking.

Conclusion

Utilization of polyacrylate polyalcohol copolymer (Vantris®), a tissue augmenting agent, is a simple method with a high success rate even after a single injection. The success rate depends on the severity of reflux, so the failure is mostly associated with high-grade reflux. The rate of complications after application is low, mostly in patients with already present ureteral pathology. For all aforementioned, Vantris® is one of the agents of choice for permanent resolution of VUR.

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POLIAKRILAT-POLIALKOHOL KOPOLIMER (VANTRIS®) KAO OPCIJA U MINIMALNO INVAZIVNOM ZBRINJAVANJU VEZIKOURETERALNOG REFLUKSA: NAŠE ISKUSTVO

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Minimalno invazivno zbrinjavanje vezikoureteralnog refluksa u poslednjim decenijama postalo je popularno, i to zbog brojnih prednosti same procedure, koju odlikuju jednostavno izvođenje, kraće vreme izvođenja nego kod otvorenih tehnika, retka pojava ozbiljnijih komplikacija, kao i skraćivanje boravka u bolnici. Postoje dve grupe injekcionih agenasa za augmentaciju tkiva: biorazgradivi i nebiorazgradivi. Vantris® (poliakrilat-polialkohol kopolimer) predstavlja kombinaciju ovih dveju grupa.

Cilj studije bilo je utvrđivanje efikasnosti kopolimera Vantris® kao opcije u minimalno invazivnom zbrinjavanju vezikoureteralnog refluksa (VUR).

Sproveli smo prospektivnu studiju koja je obuhvatila period od pet godina (2015–2019). Ukupno je 24 bolesnika, tj. 39 renalnih refluksivnih jedinica bilo tretirano koplimerom Vantris®

Refluks je bio jednostran kod devet bolesnika (37,5%), a obostran kod 15 bolesnika (62,5%). Stepen refluksa bio je V kod dva uretera (5,12%), IV kod šest uretera (15,38%), III kod 22 uretera (56,42%), II kod tri uretera (7,69%) i I kod šest uretera (15,38%). Srednje vreme praćenja iznosilo je 12 meseci i uključivalo je pregled urina, ultrazvučni pregled urinarnog trakta i mikcionu cistouretrografiju nakon godinu dana. Refluks je eliminisan u 36 uretera (92,31%). Kod dvoje bolesnika razvila se opstrukcija vezikoureteralnog spoja. Kod jednog bolesnika bio je potreban dodatni injekcioni tretman.

Vantris® se za tretiranje VUR-a može koristiti uspešno i sa malim procentom komplikacija. Budući da je primena jednostavna, a stopa komplikacija svedena na minimum, mogao bi postati tretman izbora za lečenje VUR-a.

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***Ključne reči**: vezikoureteralni refluks, deca, Vantris®*

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HUMAN PAPILLOMAVIRUS: A CROSS-SECTIONAL SURVEY ON KNOWLEDGE AND ATTITUDES AMONG STUDENTS OF UNDERGRADUATE HEALTH STUDIES

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The study aimed to assess the knowledge and attitudes of future healthcare professionals in Bosnia and Herzegovina (BIH) regarding the nature of human papillomavirus (HPV), HPV testing, and vaccination.

This descriptive-analytical, prospective, cross-sectional survey was conducted using a standardized questionnaire among students in the first and third year of undergraduate studies considering different study programs at the Faculty of Health Studies, University of Sarajevo.

The research resulted in 110 fully completed questionnaires. The percentage of students who had heard about HPV was 88.9% in the first year and 92.3% in the third year of health studies. Third-year students had better general knowledge of HPV ($p = 0.007$) and attitudes toward HPV testing ($p = 0.009$). Significant differences were in general knowledge of HPV among students of all study programs ($p < 0.001$) and in the knowledge of HPV testing ($p = 0.001$) and vaccination ($p = 0.001$). Health Care and Physiotherapy students had more knowledge and better attitudes when compared with other study programs.

The level of knowledge about HPV infection among students in BIH is low regardless of study year and program. Targeted interventions in health education could have a positive impact on spreading knowledge about HPV and adopting preventive methods in the future.

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Key words: *human papillomavirus, papillomavirus infection, students, vaccination, surveys, questionnaires*

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Introduction

Papillomaviruses belong to the *Papillomaviridae* family and represent a group of small non-enveloped viruses with a double-stranded circular DNA genome (1). According to the Global Health Strategy for Sexually Transmitted Infections (2016–2021) of the World Health Organization (WHO), human papillomavirus (HPV) infection requires control due to its high association with cervical cancer. HPV also plays a significant role in different cancers in both genders (2–5).

The virus is present in sexually active populations infecting more than 80% of women of reproductive age. However, 80% of infections are transient and eliminated by the immune system without consequences. The remaining 20% of them can lead to the formation of genital cancer precursors (6). Increased risk for HPV infection can be associated with a range of sexual partners and sexual intercourse at an early age. The higher the number of partners, the higher the risk of exposure to HPV, and the greater the exposure to the virus, the higher the chance of infection, which can lead to cervical cancer (7, 8).

High-risk types of HPV are the most common causes of cervical cancer. Cervical cancer is the third most common type of cancer in women and a common cause of death in women between the age of 15 and 44 (9). In 2018, 570 000 new cases of cervical cancer were registered worldwide, and 311 000 women died. Almost 85% of cancer cases are being reported in less

developed countries (9). The most common high-risk types are HPV16 and 18 (10). In addition to other sexually transmitted agents, HPV infection is also prevalent among men who have sex with men (MSM population). HPV infection is associated with several cancers in men, including anal, penile, and oral cancers (11).

The natural flow of HPV infection and the long-term development of precancerous changes in the cervix make cervical cancer preventable at the primary, secondary and tertiary levels. Primary prevention includes health education and vaccination against HPV. Secondary prevention involves screening (early detection of asymptomatic forms of the disease). Lastly, tertiary prevention implies the treatment of precancerous lesions, thereby preventing their progression to invasive cervical cancer (12). Vaccination and mass screening of women using validated diagnostic HPV tests and/or Pap smear test (Papanicolaou cytological test) are the main preventive measures against cervical cancer worldwide (13, 14). Local studies based on vaccine-targeted HPV types are of great importance for the secondary prevention of cervical cancer (15, 16).

Currently, three HPV vaccines are available, namely Cervarix bivalent (GlaxoSmithKline Biologicals, Rixensart, Belgium), Gardasil tetravalent (Merck & Co., New Jersey, USA), and Gardasil9 - nanovalent (Merck & Co., New Jersey, USA) (17). Vaccination is recommended for individuals who have not been in contact with the HPV types covered by the vaccines. For this reason, vaccination during adolescence before sexual intercourse and potential exposure to the virus is desirable (18). In 2015, the WHO recommended a 2-dose vaccination program for girls aged 9 to 15 and a 3-dose program for girls over 15 years (17).

In Bosnia and Herzegovina (BIH) an organized cervical cancer screening program has not been established yet. Annually, about 30% of women of reproductive age in BIH become infected with high-risk HPV (15). Previous studies on the high school population and undergraduate medical student's knowledge and behavioural risks have suggested that insufficient sexual education and inadequate knowledge about the prevention of sexually transmitted diseases, casual sex partners, and unprotected sex may affect the prevalence of HPV and other sexually transmitted infections (STIs) (19, 20). Moreover, belief in adverse effects of vaccines without medical knowledge and social and cultural attitudes are the main reason for the low interest in vaccination against HPV (21).

All aspects of HPV infection and its linkage to cancer development might be adopted at a younger age to prevent the potential consequences later. Therefore, it is necessary to continuously raise awareness of this problem for preventive measures to be fully implemented primarily by health professionals.

This survey aimed to assess the knowledge and attitudes of future health professionals in BIH about the nature of HPV, HPV testing, and vaccination.

Material and Methods

Participants

This descriptive-analytical, prospective, cross-sectional survey enrolled undergraduate first and third-year students of different study programs of the Faculty of Health Studies (Health Care, Physiotherapy, Laboratory Technology, Sanitary Engineering, and Radiological Technology) of the University of Sarajevo (FHS UNSA), during the academic year 2019-2020. The research lasted from May to June 2020, and 110 respondents participated.

Material

The research was conducted using a standardized questionnaire entitled “What do you know about HPV?”, developed by Waller et al. (2013) (22). The questionnaire examined knowledge and attitudes about the nature of HPV, HPV testing, and HPV vaccination. The questionnaire consisted of questions that respondents could answer correctly, incorrectly, or “Don't know”. The answer “Don't know” was evaluated as an incorrect answer. The respondents received 1 point for each correct and 0 points for an incorrect answer. The total result of the knowledge and attitudes of the survey was the sum of all responses, and the higher the number, the more it was an indicator of the respondent's better knowledge about HPV.

Statistics

The data were reviewed for accuracy and summation of scores and then analyzed by Microsoft Excel and IBM SPSS software. Results were processed using descriptive statistics expressed by the mean and standard deviation for continuous variables and frequency and percentage for categorical variables. The normality of the data distribution was determined using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The statistics of reliability and consistency of questions were estimated using Cronbach’s Alpha indicator > 0.7. Comparisons of categorical responses used Pearson's Chi-square test of exact probability. A value of < 0.05 was considered statistically significant.

Results

Considering the entire questionnaire, respondents of the first year of study had 649 (41.2%) correct and 926 (58.8%) incorrect answers, while the respondents of the third year of study answered correctly on 1080 (47.5%)

questions and 1195 (52.5%) incorrectly. Respondents of the third study year had significantly more correct answers, $p < 0.001$ (Table 1). However, the knowledge of the first and the third year of study respondents was poor (Figure 1/A and B).

The number of correct answers significantly differed according to the study program, $p < 0.001$. The highest number of correct answers was provided by the students of Health Care (50.3%), followed by the students of Physiotherapy (50.2%), Laboratory Technology (46.5%), Sanitary Engineering (43.6%), and students of Radiological Technology (35.7%) (Table 1, Figure 1/C–G). The knowledge was unsatisfactory regardless of the study program.

Assessment of general knowledge about HPV

Out of the total population (N = 110), 40/45 (88.9%) of respondents attending the first year of study and 60/65 (92.3%) of respondents attending the third year of study knew about HPV. According to the year of study, no significant difference in the number of respondents who know about HPV was observed, $p = 0.540$.

However, a significant difference in the percentage of correct answers to the 11th and 13th questions from the first section of the questionnaire, "General knowledge about HPV", between the respondents of different years of study was recorded. Significantly more respondents of the third year of study (53.8%, $p = 0.034$) answered correctly to the 11th question compared to those of the first year of study (33.3%). Similarly, on the 13th question, significantly more respondents from the third year of study (72.3%, $p = 0.041$) answered correctly compared to the first year of study (53.3%). The number of correct answers to other questions from this section was not significantly different between first- and third-year students at the Faculty of Health Studies, University of Sarajevo (Table 2).

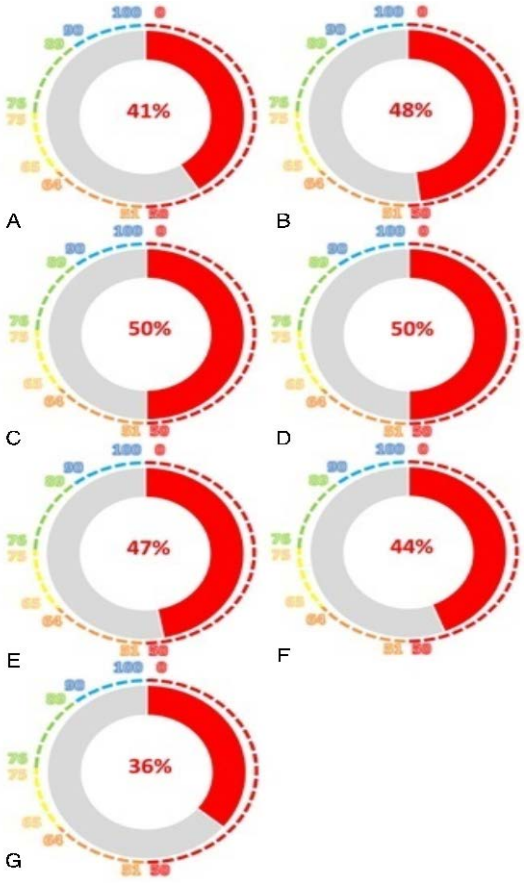

Figure 1. The level of knowledge and attitudes of the students according to the year of study and study program

The level of knowledge (percentage of correct answers) was assessed according to the scale: ≤ 50% - unsatisfactory knowledge; 51–64% - satisfactory knowledge; 65–75% - good knowledge; 76–89% - very good knowledge; and ≥ 90% - excellent knowledge. The level of knowledge of A) the first year of study, and B) the third year of study; C) Health Care, D) Physiotherapy, E) Laboratory Technologies, F) Sanitary Engineering, and G) Radiological Technologies study program

Table 1. Differences in the total number of correct answers according to the year of study and study program

			General knowledge and attitudes toward			
			HPV	*HPV testing*	*Vaccination against HPV*	Entire questionnaire
Year of sty	1st	Correct answers	415 (57.6%)	94 (34.8%)	140 (23.9%)	649 (41.2%)
		Incorrect answers	305 (42.4%)	176 (65.2%)	445 (76.1%)	926 (58.8%)
		Total	720 (100%)	270 (100%)	585 (100%)	1575 (100%)
		Chi-Square	7.353	6.683	3.362	14.770
			p = 0.007	**p = 0.009**	**p = 0.067**	**p < 0.001**
	3rd	Correct answers	666 (64.0%)	175 (44.9%)	239 (28.3%)	1080 (47.5%)
		Incorrect answers	374 (36.0%)	215 (55.1%)	606 (71.7%)	1195 (52.5%)
		Total	1040 (100%)	390 (100%)	845 (100%)	2275 (100%)
Study prgrm	Laboratory Technologies	Correct answers	295 (63.6%)	74 (42.5%)	103 (27.3%)	472 (46.5%)
		Incorrect answers	169 (36.4%)	100 (57.5%)	274 (72.7%)	543 (53.5%)
		Total	464 (100%)	174 (100%)	377 (100%)	1015 (100%)
	Radiological Technologies	Correct answers	214 (51.4%)	46 (29.5%)	65 (19.2%)	325 (35.7%)
		Incorrect answers	202 (48.6%)	110 (70.5%)	273 (80.8%)	585 (64.3%)
		Total	416 (100%)	156 (100%)	338 (100%)	910 (100%)
	Sanitary Engineering	Correct answers	150 (62.5%)	35 (38.9%)	44 (22.6%)	229 (43.6%)
		Incorrect answers	90 (37.5%)	55 (61.1%)	151 (77.4%)	296 (56.4%)
		Total	240 (100%)	90 (100%)	195 (100%)	525 (100%)
	Physiotherapy	Correct answers	192 (66.7%)	51 (47.2%)	73 (31.2%)	316 (50.2%)
		Incorrect answers	96 (33.3%)	57 (52.8%)	161 (68.8%)	314 (49.8%)
		Total	288 (100%)	108 (100%)	234 (100%)	630 (100%)
	Health Care	Correct answers	230 (65.3%)	63 (47.7%)	94 (32.9%)	387 (50.3%)
		Incorrect answers	122 (34.7%)	69 (52.3%)	192 (67.1%)	383 (49.7%)
		Total	352 (100%)	132 (100%)	286 (100%)	770 (100%)
		Chi-Square	241.368 **p < 0.001**	130.876 **p = 0.011**	194.523 **p =0.001**	48.419 **p < 0.001**

A p-value of < 0.05 was considered statistically significant (bolded numbers in the Table).

The best knowledge about HPV was shown by the respondents of the study program of Health Care (21/22, 95.5%). They were followed by students of the study programs of Physiotherapy (17/18, 94.4%), Sanitary Engineering (14/15, 93.3%), and Laboratory Technology (27/29, 93.1%), while the lowest knowledge was shown by the respondents of the Radiological Technology study program (21/26, 80.8%).

No significant difference in the number of participants who responded correctly about HPV according to the study program (p = 0.363) was observed.

A significant difference among the respondents of different study programs in the percentage of correct answers to questions number 10 and 13 of the first section, "General knowledge about HPV", (p = 0.008 and p = 0.014) was seen. The highest number of correct answers to question 10 showed students of Laboratory Technologies (89.7%) and Sanitary Engineering (80.0%), then students of Health Care (63.6%), and Radiological Technologies and Physiotherapy (with 50%), p = 0.008. The highest number of correct answers to question 13 was provided by students of Health Care (81.8%), followed by students of Physiotherapy

(77.8%) and Sanitary Engineering (73.33%). Students of the study program Laboratory Technology provided 62.1% of correct answers, while the lowest number of correct answers to the 13th question were provided by the students of Radiological Technologies (38.5%), p = 0.014. The number of correct answers to other questions from the first section of the questionnaire was not significantly different within observed study programs (Table 2).

Assessment of general knowledge about HPV testing

Considering the general knowledge about HPV testing, 35/45 (77.8%) of respondents in the first year and 55/65 (84.6%) in the third year of study knew about HPV testing. According to the year of study, the difference in the number of respondents who knew about HPV testing was not significant (p = 0.361).

The best knowledge about HPV testing was shown by the respondents of the Physiotherapy study program (16/18, 88.9%). They were followed by the students of the study programs of Sanitary Engineering (13/15, 86.7%), Laboratory Technologies (25/29, 86.2%), and Health Care (17/22, 77.3%), while the lowest knowledge was shown by the respondents of the Radiological Technology study program (19/26, 73.1%). No significant difference in the number of respondents who knew about HPV testing (p = 0.582) of different study programs was seen.

No significant difference was observed in the percentage of correct answers from the second section of the questionnaire, "Knowledge about HPV Testing", between respondents of the first and third year of study and of different study programs (Table 3).

Table 2. Assessment of general knowledge about HPV by year of study and study program

Question	Answer	First Year	Third Year	Total	Pearson Chi-Square	p	Laboratory Technologies	Radiological Technologies	Sanitary Engineering	Physiotherapy	Health Care	Total	Pearson Chi-Square	p
1. HPV can cause cervical cancer	True	77.8%	89.2%	84.5%	2.669	0.102	89.7%	76.9%	80.0%	83.3%	90.9%	84.5%	2.675	0.614
	False	22.2%	10.8%	15.5%			10.3%	23.1%	20.0%	16.7%	9.1%	15.5%		
2. A person could have HPV for many years without knowing it	True	80.0%	81.5%	80.9%	0.041	0.840	79.3%	76.9%	73.3%	88.9%	86.4%	80.9%	2.039	0.729
	False	20.0%	18.5%	19.1%			20.7%	23.1%	26.7%	11.1%	13.6%	19.1%		
3. Having many sexual partners increases the risk of getting HPV	True	82.2%	92.3%	88.2%	2.595	0.107	86.2%	76.9%	100.0%	94.4%	90.9%	88.2%	6.116	0.191
	False	17.8%	7.7%	11.8%			13.8%	23.1%	0%	5.6%	9.1%	11.8%		
4. HPV is very rare	True	73.3%	73.8%	73.6%	0.325	0.569	75.9%	65.4%	93.3%	61.1%	77.3%	73.6%	5.588	0.232
	False	26.7%	26.2%	26.4%			24.1%	34.6%	6.7%	38.9%	22.7%	26.4%		
5. HPV can be passed on during sexual intercourse	True	82.2%	84.6%	83.6%	0.111	0.739	89.7%	73.1%	80.0%	94.4%	81.8%	83.6%	4.620	0.329
	False	17.8%	15.4%	16.4%			10.3%	26.9%	20.0%	5.6%	18.2%	16.4%		
6. HPV always has visible signs or symptoms	True	71.1%	64.6%	67.3%	0.510	0.475	72.4%	50.0%	60.0%	72.2%	81.8%	67.3%	6.546	0.162
	False	28.9%	35.4%	32.7%			27.6%	50.0%	40.0%	27.8%	18.2%	32.7%		
7. Using condoms reduces the risk of getting HPV	True	77.8%	83.1%	80.9%	0.483	0.487	86.2%	65.4%	80.0%	94.4%	81.8%	80.9%	6.738	0.150
	False	22.2%	16.9%	19.1%			13.8%	34.6%	20.0%	5.6%	18.2%	19.1%		
8. HPV can cause HIV/Aids	True	35.6%	38.5%	37.3%	0.096	0.757	44.8%	26.9%	20.0%	38.9%	50.0%	37.3%	5.358	0.253
	False	64.4%	61.5%	62.7%			55.2%	73.1%	80.0%	61.1%	50.0%	62.7%		
9. HPV can be passed on by genital skin-to-skin contact	True	51.1%	60.0%	56.4%	0.854	0.355	65.5%	34.6%	60.0%	66.7%	59.1%	56.4%	6.912	0.141
	False	48.9%	40.0%	43.6%			34.5%	65.4%	40.0%	33.3%	40.9%	43.6%		
10. Men cannot get HPV	True	64.4%	69.2%	67.3%	0.277	0.599	89.7%	50.0%	80.0%	50.0%	63.6%	67.3%	13.797	**0.008***
	False	35.6%	30.8%	32.7%			10.3%	50.0%	20.0%	50.0%	36.4%	32.7%		
11. Having sex at an early age increases the risk of getting HPV	True	33.3%	53.8%	45.5%	4.513	**0.034***	51.7%	46.2%	33.3%	55.6%	36.4%	45.5%	2.828	0.744
	False	66.7%	46.2%	54.5%			48.3%	53.8%	66.7%	44.4%	63.6%	54.5%		
12. There are many types of HPV	True	57.8%	70.8%	65.5%	1.985	0.159	51.7%	69.2%	73.3%	77.8%	63.6%	65.5%	4.235	0.375
	False	42.2%	29.2%	34.5%			48.3%	30.8%	26.7%	22.2%	36.4%	34.5%		

13. HPV can cause genital warts	True	53.3%	72.3%	64.5%	4.183	**0.041***	62.1%	38.5%	73.3%	77.8%	81.8%	64.5%	12.559	**0.014***
	False	46.7%	27.7%	35.5%			37.9%	61.5%	26.7%	22.2%	18.2%	35.5%		
14. HPV can be cured with antibiotics	True	53.3%	47.7%	50.0%	0.338	0.561	44.8%	38.5%	53.3%	61.1%	59.1%	50.0%	3.378	0.497
	False	46.7%	52.3%	50.0%			55.2%	61.5%	46.7%	38.9%	40.9%	50.0%		
15. Most sexually active people will get HPV at some point in their lives	True	24.4%	32.3%	29.1%	0.797	0.372	24.1%	30.8%	40.0%	33.3%	22.7%	29.1%	1.835	0.766
	False	75.6%	67.7%	70.9%			75.9%	69.2%	60.0%	66.7%	77.3%	70.9%		
16. HPV usually does not need any treatment	True	4.4%	10.8%	8.2%	1.416	0.234	3.4%	3.8%	0%	16.7%	18.2%	8.2%	7.506	0.111
	False	95.6%	89.2%	91.8%			96.6%	96.2%	100.0%	83.3%	81.8%	91.8%		

*A p-value of < 0.05 was considered statistically significant (bolded numbers in the table)

Table 3. Assessment of knowledge about HPV testing by year of study and study program

Question	Answer	First Year	Third Year	Total	Pearson Chi-Square	p	Laboratory Technologies	Radiological Technologies	Sanitary Engineering	Physiotherapy	Health Care	Total	Pearson Chi-Square	p
1. If a woman tests positive for HPV she will definitely get cervical cancer	True	64.4%	70.8%	68.2%	0.490	0.484	62.1%	53.8%	66.7%	83.3%	81.8%	68.2%	6.769	0.149
	False	35.6%	29.2%	31.8%			37.9%	46.2%	33.3%	16.7%	18.2%	31.8%		
2. An HPV test can be done at the same time as a Pap smear test	True	51.1%	63.1%	58.2%	1.565	0.211	58.6%	53.8%	66.7%	61.1%	54.5%	58.2%	0.830	0.934
	False	48.9%	36.9%	41.8%			41.4%	46.2%	33.3%	38.9%	45.5%	41.8%		
3. An HPV test can tell you how long you have had an HPV infection	True	15.6%	29.2%	23.6%	3.755	0.097	24.1%	7.7%	26.7%	22.2%	40.9%	23.6%	7.399	0.116
	False	84.4%	70.8%	76.4%			75.9%	92.3%	73.3%	77.8%	59.1%	76.4%		
4. HPV testing is used to indicate if the HPV vaccine is needed	True	26.7%	35.4%	31.8%	0.932	0.334	37.9%	23.1%	20.0%	22.2%	50.0%	31.8%	6.497	0.165
	False	73.3%	64.6%	68.2%			62.1%	76.9%	80.0%	77.8%	50.0%	68.2%		
5. When you have an HPV test, you get the results the same day	True	24.4%	33.8%	30.0%	1.119	0.290	41.4%	15.4%	26.7%	44.4%	22.7%	30.0%	6.855	0.144
	False	75.6%	66.2%	70.0%			58.6%	84.6%	73.3%	55.6%	77.3%	70.0%		
6. If an HPV test shows that a woman does not have HPV, her risk of cervical cancer is low	True	26.7%	36.9%	32.7%	1.271	0.260	31.0%	23.1%	26.7%	50.0%	36.4%	32.7%	3.959	0.412
	False	73.3%	63.1%	67.3%			69.0%	76.9%	73.3%	50.0%	63.6%	67.3%		

A p-value of < 0.05 was considered statistically significant

Assessment of knowledge about HPV vaccination

By assessing knowledge about HPV vaccination, 22/45 (48.9%) of respondents in the first year and 35/65 (53.8%) in the third year of the study knew about HPV vaccination. According to the year of study, the difference in the number of respondents who knew about HPV vaccination was not significant (p = 0.609).

Significantly more respondents of the third year of study (33.8%) answered correctly to question number 7 of the third section of the questionnaire, "Knowledge about HPV vaccination", compared to respondents of the first year of study (8.9%), p = 0.002. The number of correct answers to other questions from this section was not significantly different between first- and third-year students (Table 4).

The best knowledge about HPV vaccination was shown by the respondents of the study program Physiotherapy (13/18, 72.2%), Radiological Technologies (14/26, 53.8%), Laboratory Technologies (15/29, 51.7%), and Health Care (10/22, 45.5%), while the lowest knowledge was shown by the respondents of the study program Sanitary Engineering (5/15, 33.3%).

No significant difference in the number of respondents from different study programs who knew about HPV vaccination (p = 0.244) was observed.

A significant difference was recorded in the percentage of correct answers to questions 2 and 3 in the third section of the questionnaire, "Knowledge about HPV vaccination", (p = 0.016 and p = 0.018, respectively) among the respondents of different study programs. The

highest number of correct answers to question 2 was provided by the students of the Physiotherapy program (33.3%), followed by the students of Sanitary Engineering (13.3%), Laboratory Technologies (6.9%), and Health Care (4.5%). The students of Radiological Technologies had the lowest percentage of correct answers (3.8%), p = 0.016. The highest number of correct answers to question 3 was provided by students of Physiotherapy (77.8%), followed by students of Health Care (59.1%), Laboratory Technologies (55.2%), Radiological Technologies (46.2%), and Sanitary Engineering (20.0%), p = 0.018. The number of correct answers to other questions from the third section of the questionnaire was not significantly different within study programs (Table 4).

Table 4. Assessment of knowledge about HPV vaccination by year of study and study program

Question	Answer	First Year	Third Year	Total	Pearson Chi-Square	p	Laboratory Technologies	Radiological Technologies	Sanitary Engineering	Physiotherapy	Health Care	Total	Pearson Chi-Square	p
1. Girls who have had an HPV vaccine do not need a Pap smear test when they are older	True	62.2%	56.9%	59.1%	0.309	0.578	65.5%	42.3%	40.0%	72.2%	72.7%	59.1%	8.763	0.067
	False	37.8%	43.1%	40.9%			34.5%	57.7%	60.0%	27.8%	27.3%	40.9%		
2. Two of the vaccines offer protection against genital warts	True	4.4%	15.4%	10.9%	3.275	0.070	6.9%	3.8%	13.3%	33.3%	4.5%	10.9%	12.135	**0.016***
	False	95.6%	84.6%	89.1%			93.1%	96.2%	86.7%	66.7%	95.5%	89.1%		
3. The HPV vaccines offer protection against all sexually transmitted infections	True	53.3%	52.3%	52.7%	0.011	0.916	55.2%	46.2%	20.0%	77.8%	59.1%	52.7%	11.855	**0.018***
	False	46.7%	47.7%	47.3%			44.8%	53.8%	80.0%	22.2%	40.9%	47.3%		
4. Someone who has an HPV vaccine cannot develop cervical cancer	True	51.1%	56.9%	54.5%	0.362	0.547	58.6%	42.3%	33.3%	66.7%	68.2%	54.5%	7.204	0.126
	False	48.9%	43.1%	45.5%			41.4%	57.7%	66.7%	33.3%	31.8%	45.5%		
5. HPV vaccines offer protection against most cervical cancers	True	24.4%	30.8%	28.2%	0.526	0.468	27.6%	11.5%	33.3%	38.9%	36.4%	28.2%	5.507	0.239
	False	75.6%	69.2%	71.8%			72.4%	88.5%	66.7%	61.1%	63.6%	71.8%		
6. The HPV vaccine requires three doses	True	11.1%	15.4%	13.6%	0.412	0.521	17.2%	7.7%	13.3%	22.2%	9.1%	13.6%	2.614	0.624
	False	88.9%	84.6%	86.4%			82.8%	92.3%	86.7%	77.8%	90.9%	86.4%		
7. The HPV vaccines are the most effective if given to people who have never had sex	True	8.9%	33.8%	23.6%	9.176	**0.002***	24.1%	11.5%	46.7%	11.1%	31.8%	23.6%	8.901	0.064
	False	91.1%	66.2%	76.4%			75.9%	88.5%	53.3%	88.9%	68.2%	76.4%		
8. The HPV vaccine is offered to girls aged 12−13 years	True	22.2%	24.6%	23.6%	0.084	0.771	27.6%	15.4%	26.7%	22.2%	27.3%	23.6%	1.489	0.829
	False	77.8%	75.4%	76.4%			72.4%	84.6%	73.3%	77.8%	72.7%	76.4%		
9. The HPV vaccine is offered to women aged 30−45 years	True	22.2%	24.6%	23.6%	0.084	0.771	20.7%	23.1%	20.0%	11.1%	40.9%	23.6%	5.455	0.244
	False	77.8%	75.4%	76.4%			79.3%	76.9%	80.0%	88.9%	59.1%	76.4%		
10. The HPV vaccine that is offered is free	True	4.4%	9.2%	7.3%	0.903	0.342	6.9%	7.7%	13.3%	0%	9.1%	7.3%	2.349	0.672
	False	95.6%	90.8%	92.7%			93.1%	92.3%	86.7%	100.0%	90.9%	92.7%		
11. The HPV vaccine that is offered protects against genital warts	True	17.8%	15.4%	16.4%	0.111	0.739	17.2%	11.5%	6.7%	22.2%	22.7%	16.4%	2.592	0.628
	False	82.2%	84.6%	83.6%			82.8%	88.5%	93.3%	77.8%	77.3%	83.6%		
12. The HPV vaccine is offered to boys aged 12−13 years	True	24.4%	23.1%	23.6%	0.028	0.868	20.7%	23.1%	13.3%	22.2%	36.4%	23.6%	3.020	0.554
	False	75.6%	76.9%	76.4%			79.3%	76.9%	86.7%	77.8%	63.6%	76.4%		
13. The HPV vaccine is usually offered in schools	True	4.4%	9.2%	7.3%	0/903	0.342	6.9%	3.8%	13.3%	5.6%	9.1%	7.3%	1.462	0.833
	False	95.6%	90.8%	92.7%			93.1%	96.2%	86.7%	94.4%	90.9%	92.7%		

A p-value of < 0.05 was considered statistically significant

Discussion

All aspects of HPV infection and its linkage to cancer development might be adopted at a younger age to prevent the potential consequences later. In countries that still do not have an established organized cervical screening program, such as BIH, it is substantial to continuously raise awareness about the nature of HPV infection, diagnosis, and vaccination. A considerable responsibility rests on future healthcare workers who, based on their knowledge, will point out this problem, impose the need to establish preventive measures and participate in their systematic and organized implementation.

The students' knowledge presented in this study was unsatisfactory regardless of the year and study program. Similarly, awareness of HPV and its link to cervical cancer was low in the general population of women in China and even lower among government and medical staff (23).

According to a study by Badgujar et al. (24), students showed a better understanding of cancer development and the formation of genital warts associated with HPV when compared to already employed respondents. In the present study, significantly more respondents in the third year of study ($p = 0.041$) and the Health Care study program ($p = 0.014$) correctly answered to the question of whether HPV can cause genital warts.

In a study at the University of Great Britain conducted through a conversation with many students in different fields (25), neither male nor female respondents were aware of how HPV is transmitted or what genital warts are, despite being familiar with the HPV vaccines and the regimen of their taking at the age before being sexually active. On the other hand, the male respondents considered HPV among the top health issues in men.

A study by Keser et al. (26) involved students in the third, fourth, and fifth year of Dentistry. Many more students in the fourth and fifth study years participated, and they showed better knowledge when it comes to human papillomavirus-related oral cancer (some types of HPV cause oral cancer, $p = 0.000$; $p < 0.05$). Undergraduate students attending health sciences and other schools at the Universities of Genoa and Bari (27) showed poor knowledge but good attitudes about HPV. Therefore, they concluded that future healthcare workers need training on HPV. Although the knowledge from respondents of our study was also poor, third-year undergraduate health students gave more correct answers to questions about general knowledge of HPV and HPV testing ($p = 0.007$ and $p = 0.009$, respectively) than first-year students. It is crucial to continuously educate health workers and increase awareness among the general population about the issue of cervical cancer. This will not only aid in preventing the disease but also help manage individuals infected with HPV more effectively.

According to a survey among 500 students in Pakistan (28), most of whom attended some health or biological disciplines, poor knowledge about HPV was shown. Namely, one group of students stated that HPV causes AIDS, while another group stated that HPV infection could be prevented/treated using antibiotics. Significant differences were recorded in the number of correct answers about general knowledge about HPV, HPV testing ($p = 0.011$), and vaccination against HPV ($p = 0.001$) among students of different study programs. The best knowledge about HPV, HPV testing, and vaccination showed the students of Health Care, then students of Physiotherapy, Laboratory Technologies, and Sanitary Engineering, while the students of Radiological Technologies had the lowest knowledge level.

The level of knowledge about HPV infection among students attending the first year at the Faculty of Medicine of Tîrgu Mureş University in Romania was poor compared with the students attending the sixth study year, where even 75% of them answered they would vaccinate their child against HPV (29).

Also, first-year students entering University in Western Turkey showed significantly poor general knowledge about HPV, with 59.6% of respondents having zero as their questionnaire score, but very few of them, regardless of gender, intended to be vaccinated (30).

Among 957 medical and paramedical students (31), only 44.9% showed good knowledge about HPV vaccination, with only 17.9% of respondents considering that the vaccine was more than 95% effective. General knowledge about the vaccine dosing and its role in preventing HPV-causing conditions was poor.

Comparing the results from our study a statistically significant difference in knowledge about HPV vaccination between the respondents of the first and third year of study was not observed, and knowledge was unsatisfactory. Only when it comes to the effectiveness of HPV vaccines when given to people who have never had sexual intercourse, we noticed a statistically better knowledge of students in the third year of study.

School-age is a very receptive time for cancer prevention and the HPV vaccine strategy because most people are infected with HPV in that period of life (32).

Conclusion

Future health professionals are expected to show better knowledge and attitudes than our study has proven. Therefore, we believe that investing more efforts in education of all health worker profiles will help promote awareness about preventive measures to preserve the reproductive health of the at-risk population. Achieving a high level of knowledge about the nature of HPV infection could improve the implementation of organized cervical screening programs in our country and enable a more responsible approach towards addressing this issue.

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HUMANI PAPILOMA VIRUS: ISTRAŽIVANJE ZNANJA I STAVOVA STUDENATA DODIPLOMSKIH ZDRAVSTVENIH STUDIJA

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Cilj ove studije bio je proceniti znanje budućih zdravstvenih radnika u Bosni i Hercegovini (BiH) o prirodi humanog papiloma virusa (HPV), HPV testiranju i vakcinaciji i njihove stavove prema tome.

Ovo deskriptivno-analitičko prospektivno istraživanje preseka sprovedeno je korišćenjem standardizovanog upitnika koji su popunjavali studenti prve i treće godine dodiplomskih studija različitih studijskih programa Fakulteta zdravstvenih studija Univerziteta u Sarajevu.

Istraživanje je rezultiralo sa 110 potpuno popunjenih upitnika. Procenat studenata zdravstvenih studija koji su čuli za HPV iznosio je 88,9% na prvoj godini, a 92,3% na trećoj godini. Studenti treće godine imali su bolje opšte znanje o HPV-u ($p = 0,007$) i HPV testiranju ($p = 0,009$). Značajne razlike uočene su u opštem poznavanju HPV-a kod studenata svih studijskih programa ($p < 0,001$), u znanju o HPV testiranju ($p = 0,001$), te vakcinaciji ($p = 0,001$). Studenti programa Zdravstvena nega i Fizioterapija imali su više znanja i primerenije stavove od studenata na drugim studijskim programima.

Bez obzira na studijsku godinu i program, može se reći da je nizak nivo znanja koje o HPV infekciji imaju studenti u BiH. Ciljane intervencije u zdravstvenom obrazovanju mogle bi u budućnosti pozitivno uticati na širenje znanja o HPV-u i na usvajanje preventivnih metoda.

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***Ključne reči**: humani papiloma virus, infekcija papiloma virusom, studenti, vakcinacija, ankete, upitnici*

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MAGNETIC RESONANCE IMAGING BASED MORPHOMETRIC ASSESSMENT OF GLENOID

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This study aimed to evaluate the morphological variations of the glenoid in an Asian population and compare them with those in the Western population. A retrospective study of 100 patients who presented with shoulder pain between Jan. 2018 and Jan. 2019 was done. The glenoid height, width and version were measured on coronal and axial images. The overall mean version was found to be an anteversion of 0.40 ± 3.6. The average glenoid widths in males and females were 29 mm and 25.2 mm respectively, whereas the overall average glenoid width was 27 ± 3.2 mm. The average glenoid heights in males and females were 35.7 mm and 32.4 mm respectively, whereas the overall average glenoid height was 34 ± 2.5 mm. The glenoid dimensions in the Asian population were found to be slightly less than the ones in the Western population. This difference has to be considered when choosing a prosthesis for shoulder arthroplasty.

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Key words: *glenoid, magnetic resonance imaging, arthroplasty, central India*

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Introduction

Reverse Total Shoulder Arthroplasty (RTSA) was reserved for patients with a failed total shoulder replacement or a massive or irreparable cuff tear. With the initial success of the RTSA and the bony increased offset-reverse shoulder arthroplasty (BIO-RSA), the indications of the RTSA have been extended.

A wide variety of RTSA prostheses is available in the market, most of which are designed based on data from the Western population. Even a subtle change in the dimensions of prosthesis can lead to its improper placement. For the same reason, implanting the glenoid component of RTSA prosthesis is a challenge. Therefore, glenoid dimensions such as glenoid length and width play a crucial role in choosing an ideal prosthesis. As mentioned above, due to the wide variations in the demographic anatomy of the shoulder joint, a prosthesis designed based on western demographic data may not be suitable for use in different populations. This discrepancy has been identified by several groups and has led to studies to identify the demographic differences in glenoid morphology. Magnetic resonance imaging (MRI) has the added advantage of evaluation of the glenoid cartilage as well. The glenoid diameter changes significantly with the thickness of the glenoid cartilage thereby affecting the prosthesis design.

A number of studies have been done to identify glenoid morphology in various populations based on cadaveric specimens as well as 3-dimentional Computed Tomography (3D CT) of living subjects. This study aims to evaluate the glenoid width, height and version of a small Indian population on MRI and to compare these with that of the Western population.

Materials and Methodology

A retrospective study of 100 patients, who presented with shoulder pain between Jan. 2018 and Jan. 2019, was done in a single institution in India. Patients between the ages of 20 and 80 years were included in the study. Patients with a history of surgery or significant trauma were excluded from the study. IEC approval and consent from patients were obtained from all cases.

Multiplanar T2 weighted and proton density (PD) weighted fat-suppressed images were obtained in a GE 1.5 Tesla Seimens MRI machine. Proton density weighted images were obtained with TR 2400 ms and TE 30 ms. T2 weighted images were obtained with TR 3500 ms and TE 60 ms. Axial and oblique coronal sections of 3 mm thickness were obtained with an FOV of 140 mm. Oblique coronal images were obtained parallel to the Supraspinatus tendon. Images were taken with the patient in the supine position, arm adducted and forearm in the supine position. All the scans were done by the same technician using a standard protocol which included the above-mentioned sequences as well.

Glenoid dimensions such as height, width and version were measured on coronal and axial images. The angle between a line drawn along the glenoid surface and a mid-glenoid line was measured on an axial PD FatSat section with maximum glenoid width to determine the glenoid version (Figure 1)(1). The mid-glenoid line, A was drawn from the medial edge of the scapula to the mid-point of the glenoid. A second line, B was drawn along the surface of the glenoid. The angle between line A and line B was taken as the angle of the version. The angle of the version was calculated by subtracting the measured angle from 90 degrees. A negative angle was considered retroversion and a positive angle was considered anteversion. The glenoid width was measured on axial T2/PD FatSat as the maximum anteroposterior distance (Figure 2). The glenoid height was measured on coronal T2/PD FatSat as the maximum superior-inferior distance (Figure 3).

Statistical analysis was done using SPSS (Version 17.0) software. Both t-test and ANOVA tests were used for data analysis.

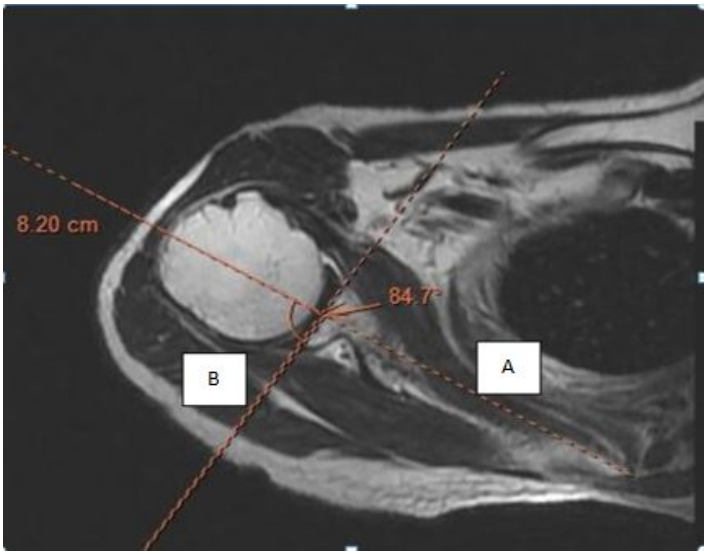

Figure 1. Measurement of glenoid version on an axial T2 weighted image

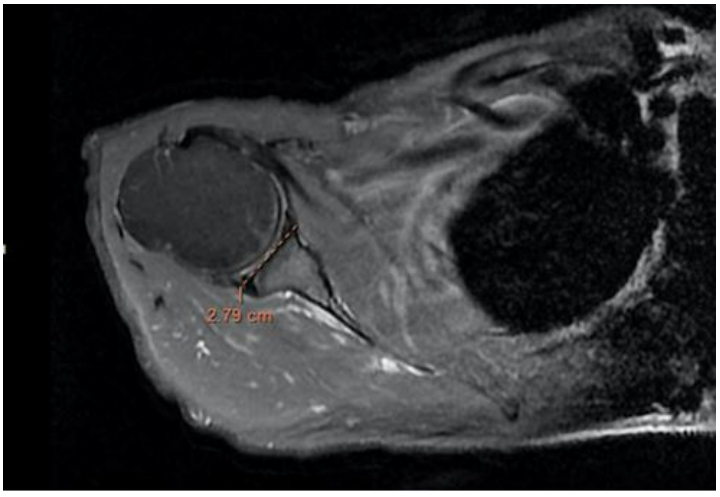

Figure 2. Measurement of glenoid width on an axial PD image

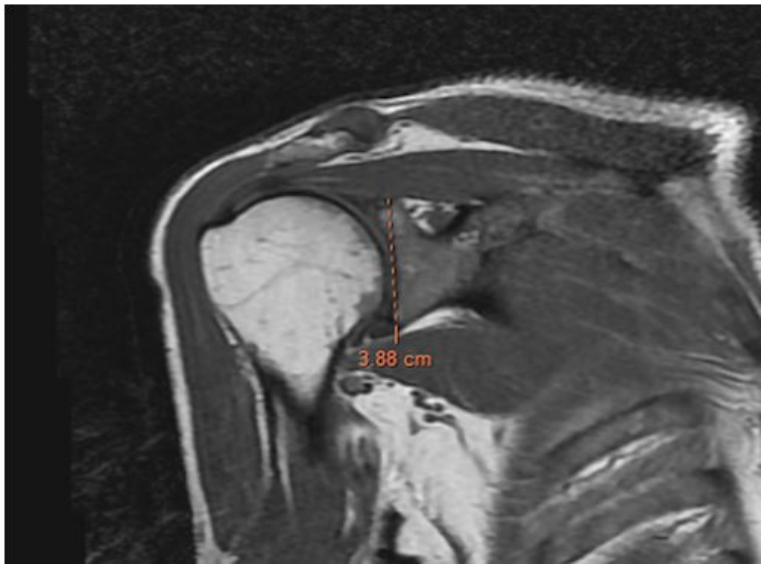

Figure 3. Measurement of glenoid height on a coronal PD image

Results

A total of 100 patients were selected for the study, out of which 49 were males and 51 were females. The mean age in this study was found to be 43.2 ± 13.8 years. The mean glenoid retroversion was found to be 3.45 ± 2.23 and anteversion was found to be 2.66 ± 1.95. The overall mean version was found to be an anteversion of 0.40 ± 3.6. The average glenoid widths in males and females were 29 mm and 25.2 mm respectively, whereas the overall average glenoid width was 27.0 ± 3.2 mm. The average glenoid heights in males and females were 35.7 mm and 32.4 mm respectively, whereas the overall average glenoid height was 34.0 ± 2.5 mm (Table 1 and Table 2).

Table 1. Comparison of glenoid width and height in males and females

	MALE (mm)	FEMALE (mm)
GLENOID WIDTH	29	25.2
GLENOID HEIGHT	35.7	32.4

Table 2. Average glenoid dimensions in the study population

	MEAN (mm)	STANDARD DEVIATION (mm)
GLENOID VERSION • RETROVERSION • ANTEVERSION	 3.45 2.66	 2.23 1.95
GLENOID WIDTH	27.0	3.2
GLENOID HEIGHT	34.0	2.5

Discussion

Most of the studies on the glenoid normal morphometry of the Indian population are based on CT of living subjects or cadaveric specimens. Relatively fewer studies have been done based on MRI, which is the modality of choice to evaluate patients with shoulder joint pathologies. Unlike other studies, the strength of our study is the consideration of the regional articular cartilage thickness which can further affect the congruity of the implants and can make small but important changes in the morphometric dimension of the glenoid base plate and design.

Reverse total shoulder replacement has been gaining popularity all over the world since its approval by the US FDA in 2003 for the management of arthritis associated with rotator cuff diseases (2). It is now being widely used for other conditions such as inflammatory arthropathy with an associated rotator cuff tear, proximal humeral fractures, post-traumatic arthritis, and fixed glenohumeral dislocation as well as revision arthroplasty (3) . The long-term success of RTSA makes it a preferred procedure over total shoulder replacement. But compared to total shoulder arthroplasty, the incidence of peri-operative complications is higher in RTSA, comprising about 15% (4). The most common of these complications are instability, loosening of prosthesis, scapular notching and infections. Out of these, instability of the joint and mechanical failure have been partly attributed to a faulty implant. An improper size or placement of the glenoid baseplate can result in the same. Only a limited number of glenoid baseplate sizes are available for RTSA and there is a great demographic variation in glenoid morphology, hence, the higher incidence of peri-operative complications. The smallest available baseplate for RTSA measures about 25 mm (5).

Glenoid variations between sexes should be considered when choosing an appropriate prosthesis. However, there have been very few studies that have taken this into account. A study done by Sandra et al. in Switzerland has shown significant differences in glenoid height and width of males and females. The average glenoid height in males was found to be 39.5 ± 3.5 mm whereas in females it was 34.8 ± 2.2 mm. The average glenoid width in males was 30.3 ± 3.3 mm and in females was 26.2 ± 1.6 mm (6).

A 3D C-based study done by Meshram et al. on an Indian population, found the mean glenoid height to be 33.9 ± 3.1 mm, glenoid width to be 24.2 ± 2.1 mm and glenoid retroversion to be 3.4 ± 4.7 (7). These values were found to be slightly less than the values in our study, which could probably be due to the higher sensitivity of CT for the evaluation of bone. A study done by Singh et al. on 100 dry scapula specimens of a similar population found the mean glenoid height to be 34.24 ± 3.27 mm and the mean glenoid width to be 23.93 ± 2.67 mm (8).

A dry specimen study done by El-din et al. in an Egyptian population found the mean glenoid height to be 38.95 ± 2.73 mm and the mean glenoid width to be 28.15 ± 2.69 mm. This study found a racial difference in glenoid morphology and pointed to a possibility of the same affecting the stability of the glenohumeral joint (9). A study done by Churchill et al. on 344 dry scapular specimens in the USA found the mean glenoid height, width and version to be 35.1 mm, 25.7 mm and 1.2 degrees, respectively (10).

In our study, the mean glenoid retroversion and anteversion were found to be 3.45 ± 2.23 and 2.66 ± 1.95, which were comparable to previous studies done on a similar population (7). There was no correlation between sex and age with the glenoid version.

The main drawback of this study was the presence of intra- and inter-observer variations. However, this was issue was addressed to a great extent by obtaining an average of three readings. Another limitation of this study was the relatively small sample size, which may not accurately represent the diverse Indian population.

Conclusion

The glenoid dimensions of our population are comparable with other Indian populations considered in this study. However the same is found to be slightly higher in the Western population. These differences in glenoid dimensions have to be considered in planning Reverse Total Shoulder Arthroplasty (RTSA) as they can significantly alter the outcome of the procedure. There is a clinical necessity to develop appropriate glenoid base plates for a better prosthesis fit in the Indian population.

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MORFOMETRIJSKA PROCENA GLENOIDA UPOTREBOM MAGNENTNOREZONANTNOG IMIDŽINGA

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Rad je imao za cilj da proceni morfometrijske varijacije glenoida u azijskoj populaciji i uporedi ih sa onima u zapadnoj populaciji. Retrospektivna studija obuhvatila je 100 bolesnika lečenih zbog bolova u ramenu u periodu od januara 2018. do januara 2019. godine. Dimenzije glenoida, visina, širina i verzija bile su merene na koronalnim i aksijalnim snimcima. Utvrđeno je da je ukupna srednja verzija bila anteverzija od 0,40 ± 3,6. Prosečna širina glenoida kod muškaraca iznosila je 29 mm, a kod žena 25,2 mm, dok je ukupna prosečna širina bila 27 mm ± 3,2 mm. Prosečna visina glenoida kod muškaraca bila je 35,7 mm, a kod žena 32,4 mm; ukupna prosečna visina bila je 34 mm ± 2,5 mm. Došlo se do zaključka da su dimenzije glenoida u azijskoj populaciji nešto manje od onih u zapadnoj populaciji. Ovu razliku treba uzeti u obzir prilikom izbora proteze za artroplastiku ramena.

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***Ključne reči**: glenoid, magnetnorezonantni imidžing, artroplastika, centralna Indija*

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DIGITAL TECHNOLOGIES AS SUPPORT TO HEALTHCARE SYSTEMS IN PROMOTION OF HEALTH AND PREVENTION OF DISEASE: RAISING AWARENESS AS AN AIM OF COMMUNICATIONS

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The paper analyzes the approach to one very important phenomenon in the modern environment, which is defined as digital transformation in the healthcare system. The increasing influx of digital technologies into business processes leads to the point where the provision of healthcare services can no longer be viewed only in traditional frameworks, but it is necessary to look at the unlimited options of digital technologies, digital content and digital communications in the provision of healthcare services.

The needs of the healthcare system and certain changes resulting from the development of communication and information technologies such as the Internet, social networks, mobile applications, etc. require organized work on the implementation of a strategy for new ways of doing business in healthcare. Health information and early screening awareness of oncological diseases increase the motivation for active participation of people in the implementation of preventive measures, treatments and rehabilitation.

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Key words: *digital communication, social networks, e-health, m-health, oncological diseases*

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Introduction

With the development of new communication technologies, satellites for communication and Internet connectivity, spatial distance and time are no longer obstacles, the boundaries of national states are being overcome and the world is becoming a ″global village″ (1). Information flow, connectivity and networking are significant features of the new, reshaped world (2). The process of globalization itself is often viewed only through the basic aspect: economy–profit–capital (3). A significant determinant of a nation's ability to be successful on the path of global progress is the preservation of people's health (4). The healthcare systems of developed countries, on the basis of their development strategy, highlight the essence of prevention in preserving human health by identifying factors of risk and promoting activities to eliminate them. Medicine, as a humanistic science, has always based its development on the exchange of research experiences and the finding of new diagnostic and therapeutic procedures so that they would be available to humanity in a very short time. This requires the constant development of digital technologies, ensuring their availability as well as strengthening the connections between doctors in order to respond to the global market and ensure healthcare knows no borders.

At this point, it is necessary to point out the importance of digital medicine (5–8). Namely, this new digital age of medicine indicates the use of digital tools in medical practice, at the core of which is the development of technological solutions for monitoring, processing and integrating huge amounts of data at the individual and population level to help solve health problems and challenges faced by patients, clinicians and health systems.

The essence of its operation is focused on caring and empowering patients to take charge of their health, thereby emphasizing true prevention, while at the same time helping clinicians manage the increasing volume and complexity of patient data in a cost-effective and time-saving manner (6).

The subject of research in this paper is the review and analysis of the role of digital communications in health promotion, with a special focus on information about oncological diseases. It should be emphasized that digital communication is a phenomenon of modern society (9), and the basis is the rapid exchange of information and the interaction of people in real-time (10). It represents any exchange of data in digital form, which allows people to connect and communicate with each other (11). The paper defines the options for improving health activities in order to better inform people and raise awareness about the prevention and early screening of oncological diseases.

Methodological Concept: Instrument and Research Results

This research used the questionnaire named *Questionnaire on Digital Communications in the Prevention of Oncological Diseases* which contains 25 questions and comprises many sections (12-13). The questionnaire is distributed on the social network Facebook to the respondents. In addition to descriptive statistics, statistical analyzes of testing, primary and secondary materials were also used.

The research was conducted on a sample of 150 respondents of both sexes chosen by the random selection method. The analysis was carried out in the period from September to December 2019 in the form of a cross-sectional study. The sample was stratified by:

- gender (male-female)
- age (≤ 29; 30 to 39; 40 to 59; ≥ 60)
- education (without education, primary school, secondary school, faculty)
- marital status (married, divorced, widower/widow, single).

Respondents of both genders participated in the research, 81 respondents (54%) were female and 69 respondents (46%) were male. There was no significant difference in gender distribution between respondents. According to age, 52 respondents (35%) were younger than 29 years old, 9 respondents (26%) were between 30 and 39 years old, 26 respondents (17%) were 40 to 49 years old, 15 respondents (10%) were 50 to 59 years old, while 18 respondents (12%) were over 60 years old. If we take into account that the questionnaire was distributed on the Facebook page and that this network is mostly followed by younger people, it can be noted that 61% of respondents were under 40. According to the *Pew Research Center's report*, 62% of all online men and 72% of all online women use Facebook (14). The greater presence of the female population can be explained by the existence of a large number of contents that are in the sphere of activity and interest of women, as well as the presence of numerous ongoing obligations related to work, home, children—which require quick execution. In such an environment, women looking for quick and useful advice and information use the Internet and various other types of social networks significantly more. The largest number of respondents, 63 of them (43%) were married, 53 respondents (37%) were single, 23 respondents (14%) were divorced, and 9 respondents (6%) were widowed. According to previous reports, marital status is not a parameter for monitoring presence on social networks. However, in today's busy life with little free time and increasing alienation of people, it is a realistic assumption that those who live alone use social networks more often. According to the level of education, 88 respondents (59%) had secondary education, 38 respondents (25%) graduated from faculty, 19 respondents (13%) completed primary school, and 5 respondents (3%) had no education. Referring again to the *Pew Research Center's report*, 60% of adults with secondary degree or less use Facebook, 71% of users hold a college degree, and 77% of users hold a university degree (9). Life in the modern world is a fast-paced, full of obligations, with the need for quick contacts and information, and access to the Internet from a mobile phone offers unlimited possibilities. Easy handling, which does not require special knowledge, is one of the reasons why more and more elderly people are becoming users of social networks.

In the following paragraphs, we will look at an analysis related to the assessment of general health, performed screening and received information about malignant diseases.

Information about malignant diseases was received by 76 respondents (50.7%), 12 respondents (8%) were never informed, while 62 respondents (41.3%) were not sure if they had ever received information. This can be explained by possible unreliable sources of information when respondents were not sure of the accuracy of information about malignant diseases and whether they could be considered information at all.

It was revealed that 114 respondents (76%) had never undergone screening for any oncological condition, while 31 respondents (21%) were not sure whether the tests they had undergone previously were part of cancer screening. Only 5 respondents (3%) had undergone some kind of screening for the detection of oncological conditions in the past. Screening represents the recognition of a previously undetected disease, using a screening test in a seemingly healthy, i.e., asymptomatic target population. The goal of breast cancer screening is to reduce mortality, while with organized cervical and colon cancer screening, both incidence and mortality are reduced.

Screening methods should be highly sensitive, specific and easy to apply. Early detection of cervical cancer can be done through a cytological smear of the cervix (Pap test), for early detection of colon cancer, it is recommended to undergo an immunochemical test for occult bleeding in the stool and colonoscopy, and for early detection of breast cancer, mammography is the recommended procedure. Screening is a complex process that requires the use of several factors: the functioning of the call system, media companies aimed at the target population, the development of recommendations for doctors and other medical personnel, patient consent, sufficient financial resources and the selection of an appropriate test. According to the recommendations of the European Commission, the acceptable level of population participation in screening is 45%, and the desirable level is 65%. The screening will have the maximum effect if it is carried out as part of an organized program for the target group, which gives social networks an exceptional advantage in the promotion of planned actions (8).

The subjective assessment of the respondents' health on an ordinal Likert scale from 1 to 10, indicated that the largest number of respondents, 62 of them (41%) evaluated their health as excellent (10), 25 respondents (17%) with a score of 9, 11 respondents (7%) with a score of 8, 23 respondents (15%) with a score of 7, 19 respondents (13%) with a score of 6 and 10 respondents (7%) with a score of 5 (neither good nor bad). There were no respondents with a subjective assessment of health from 1 to 4. Taking into account that most of the respondents in the survey were under 40 years of age, we can assume that the most common assessment of general health was excellent/good in accordance with their age (Figure 1).

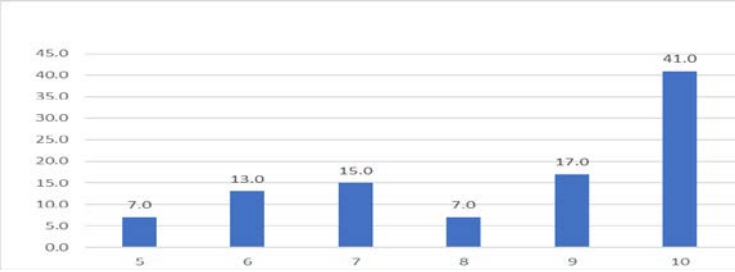

Figure 1. Subjective assessment of health

(Figure taken from Sinanovic (12))

About 44% of respondents believed that they were at no risk of contracting cancer, while only 15% of them (22 respondents) were absolutely certain that they had no predisposing factors for contracting cancer (Likert scale scores 1, 2, 3, 4, 5). Forty respondents (26%) had a low risk or suspected that there was a possibility of contracting malignant diseases (ratings on the Likert scale 6 and 7), while 24 respondents (16%) believed that there was a more pronounced risk of the disease (ratings on the Likert scale 8 and 9). In assessing the risk of the occurrence of malignant diseases in the future, there was a great risk and anxiety in 11 respondents (7%), probably because of already existing problems or family burden.

A larger number of them, 76 respondents (51%) were informed about malignant diseases from written sources, 62 respondents (41%) were not sure that they received information in written form. A small number of them, 12 respondents (8%) had never received information about malignant diseases in written form. The most common source of information about malignant diseases was the Internet for 58 respondents (38%), television for 36 respondents (24%), while only 24 (16%) respondents received information from a doctor. Professional magazines and educational courses were mentioned by 25 respondents (17%) as a source of information about oncological diseases, which we can assume are professionally or educationally related to medicine. Only 8 respondents (5.3%) were not informed about malignant diseases. The Internet is increasingly used as a key source of information about malignancies among the general public, patients, and caregivers. Approximately 90% of the population regularly accesses the Internet in Europe, North America and Japan (13). Websites are one of the main sources of cancer information in Japan.

Providing information about cancer on social networks has several advantages, e.g. the internet provides quick and easy access to cancer information and information seekers can seek advice anonymously. These benefits of information can enable them to increase their knowledge and ability to actively participate in making personal healthcare decisions (14).

Electronic communication between patients and doctors is currently developed in many rich and better organized healthcare systems. This is

why the Internet is a valuable platform for oncology education, although its usage implies the existence of potential threats. Electronic sources for the mass dissemination of useful oncology content often face the potential dissemination of unwanted, uncontrolled and sometimes harmful information. Currently, blogs and social networks are used significantly more for sharing experiences about treatment, disease courses, diagnostic procedures and emotional support, and less for the dissemination of scientific oncology information (15).

Serbia is the first country in Europe in terms of the death rate from cancer, and the rate increases annually by an average of 2.5%, which indicates that the problem of malignant tumours is very serious in our country. Every year, some form of malignancy is discovered in about 33,000 people and about 21,000 people die from this disease. Breast, colon and cervical cancer are the most common among women, and that is the reason why we are "among the leading European countries". As for men, they most often suffer and die from lung, prostate and colon cancer. Considering the obvious increase in cancer patients, it is necessary to educate people about early recognition of cancer symptoms, as well as risk factors (12).

Respondents seem to have insufficient understanding of the seriousness of malignant diseases so that 75 respondents (50%) believed that they needed more information about malignant diseases, 32 respondents (21%) did not want more information, while 49 respondents (29%) were not sure whether they had the necessary information about oncological conditions. So far the research has shown that only five to ten percent of cancers are hereditary. This means that non-inherited causes of cancer—lifestyle choices, food and fitness levels have a direct impact on overall cancer risk. Organized education programs should encourage people of all age groups to take care of their health by changing their lifestyle and diet, conducting check-ups, preventive examinations and monitoring their health status in order to detect any changes that should be consulted with medical experts. In these health promotion activities, digital technologies take precedence: the Internet and numerous social networks because they connect millions of users. According to the data obtained from this research on social media usage, all respondents used the Internet. Among the respondents who used social networks, 70 of them (46%) used Facebook, 46 respondents (31%) used WhatsApp, and 34 respondents (23%) used Twitter. Most of the respondents, 119 of them (79%) accessed social networks several times during the day, 12 respondents (8%) accessed them once a day, while 6 respondents (4%) accessed them once a week. Only 13 respondents (9%) did not use social networks at all. Such data on the number of the Internet accesses do not deviate from some research in more developed European countries and the explanation is direct (without the need to log in), easy and fast access via mobile phones and its applications.

The rich content and many innovations of the Internet have particularly attracted the young population, and as a result of this situation, the frequency of using the Internet and social networks has increased significantly, while it should be emphasized that an increasing number of older users are appearing (12). Dissatisfaction with the state of healthcare in our country leads people to increasingly Google the symptoms they have in the hope of getting an explanation for their ailments. They often "consult" the Internet even before they decide to go to the doctor. On various forums you can meet people who compare the symptoms they have, they often tend to self-diagnose, which in some cases can be disastrous for the prognosis and outcome of the disease. Real and meaningful information about health should motivate people to visit a doctor and consult about their ailments. According to the research, only 52 respondents (35%) received information about health on WhatsApp, 52 respondents (35%) sometimes received health information on this platform, and 46 respondents (30%) did not use this network for health topics. Sixty-three respondents (42%) received information about health on Facebook, 54 respondents (36%) sometimes received health information on this platform, while 33 respondents (22%) did not use this network to review health topics. Twitter, in contrast to other social networks for receiving and exchanging information about health and diseases, was used by 23 respondents (15%), 41 respondents (27%) sometimes received health information on Twitter, while 58% of respondents did not use this network for health-related information or communication. Most often, this network is used to communicate about current political and social topics and significantly less about health and diseases. It should be emphasized, however, that Twitter is a very popular social network in European countries, the leading source of content related to health, so that people can get real-time answers to numerous health-related questions and concerns or symptoms that they experience and want to address about. Many Twitter accounts specialize in certain diseases: diabetes, kidney diseases, depression, heart diseases and many others where one can often get expert health advice.

Our research went a step further, so it emphasized the examination of the influence of messages from social networks on treatment decisions. Thus, the influence of information on social media about health and diseases on decision-making about the method of treatment was present in 45 respondents (30%) while a large number of respondents, 80 of them (53%) sometimes made decisions about health or disease treatment based on information received from social networks. On the other hand, the

information did not influence the attitude of 25 respondents (17%) towards treatment.

Frequent and long-term use of social networks can lead to isolation and exclusion from social activities. Life in the virtual world becomes the only real one, and hundreds of information that are received, without even thinking about them, become the only truth (9). As a result of unreserved trust in information and advice, lack of verification and validity of information and some errors in people's actions can often occur with serious health consequences. Postponement of going to the doctor, incorrect interpretation of symptoms and a mix of multiple therapies from the Internet are often the reason for emergency hospitalizations. It is important for people to be informed about health or diseases in order to take an active role in protecting or maintaining their health as well as treatment, but it is necessary to consult with their doctor about the information from social networks that has left an impression on them.

Information on whether and to what extent health information from social media is checked, suggests that only 37 respondents (25%) checked their accuracy in a conversation with a healthcare professional, 32 respondents (21%) checked their accuracy sometimes, while 81 respondents (54%) did not check the accuracy of the posted information. Frequently, the reason for this lies in the large number of paramedical articles or comments, which, on the other hand, can lead to a bad attitude towards health. It is also noted that based on publications about health, methods of treatment or preparations recommended for treatment, 42 respondents (30%) started self-medication without consulting a doctor, 83 respondents (53%) did it sometimes, while 25 respondents (17%) did not undertake independently treatment or did not accept information without expert consultation. Additional information according to the respondents was that 47 of them (32%) received the best information about health on Facebook, 39 respondents (25%) received the best health-related information on YouTube, 29 respondents (20%) received it on Google, while only 14 respondents (9%) presented WhatsApp as a social network with good health information. Published scientific papers and works of signed authors can be read after retrieving through Google search, which justifies the veracity of the information and instils confidence. By the way, YouTube is known for its video displays that provide real-time information from experts in various fields and the existence of the possibility of contact makes this social network acceptable and the information obtained reliable.

Visiting the health forums can provide additional information on a particular topic. Our research showed that 65 respondents (43%) regularly visited health forums, while 48 respondents (32%) visited them occasionally. These forums are great for sharing similar experiences, providing support, and publishing actions, experiences and opinions of people on a given topic. In contrast, only 37 respondents (25%) did not visit health forums at all. It should be emphasized that the forums also provide professional advice because a large number of people comment based on experiences or previously acquired verified information and knowledge. In fact, forums have a professional character, with reliable information because they are organized by health workers from a certain speciality. Internet users often look for disease-specific information that will enable them to recognize a particular health problem or confirm that diagnostic and treatment measures are correct. Certainly, one way to improve the health of Internet users is to encourage them to turn to known and trusted websites when looking for health information. Forums provide insight into the experiences of others, but information from forums can be combined with information on health websites developed and controlled by experts, which can help make informed medical decisions for personal health or the health of loved ones. The importance of sharing experiences about health problems on social networks also has a big impact on health. Visitors who attend forums about some health problems feel the sincerity in the group, support and engagement in order to solve the problem. For that reason, in our research, 70 respondents (47%) stated that the experiences and recommendations of people with similar health problems meant something to them, 26 respondents (17%) stated that occasionally that kind of support meant something to them, while 54 respondents (36%) did not experience the forum in that way and the information they received there did not mean anything to them. Certainly, forums run by health professionals are significantly more visited and provide reliable guidance about health or illness, but the experiences of people who survive health problems and undergo therapeutic procedures can be significant emotional support for patients or family members. It was also observed that in the context of needs and desires related to healthcare, the largest number of respondents, 68 of them (46%) wished to consult with a medical expert online from home, in peace. Similarly, 71 respondents (47%) wished to establish online contact with a doctor in case of any medical need, indicating their trust in doctors as providers of professional information. However, 11 respondents (7%) did not think that online contact with a doctor would satisfy their healthcare needs. A larger number of respondents, 86 of them (57%) were interested in contacting a doctor by phone in case of any health issues. Additionally, 45 respondents (30%) occasionally needed to contact a doctor in case of real needs or uncertainty regarding the treatment of health problems, while 13% believed that they did not need a contact in this way because they probably support personal contact with a doctor. Further, 74 respondents (49%) had health applications

installed on their mobile phones, while 76 respondents (51%) did not have any such application, which indicates insufficient knowledge of the content and possibilities of health applications. Of course, the choice of social networks and applications mainly depends on the mobile device that is being used at that moment. Applications created exclusively for mobile phones are on the rise and social connections use all the advantages of smartphones, such as GPS, cameras, speed and constant internet connection. Although at the moment the impact of these applications is not great, thanks to innovative configurations and mass acceptance, applications are becoming an integral part of people's daily lives. A mobile application that aims to maintain and encourage a healthy lifestyle and isnot related to the diagnosis, prevention or treatment of disease cannot be considered a medical device (12). Therefore, mobile applications help people to improve their health behavior, motivate them with positive changes and above all risk factors (obesity, excessive caloric intake, physical inactivity...) gain an important place in providing important health information and raising awareness about a healthy lifestyle.

Although they placed the greatest trust in the doctor as a reliable source of professional information, 87 respondents (58%) believed that their health centre was not capable of providing them with the necessary health information, 39 respondents (26%) believed that they occasionally received the required information, while only 24 respondents (16%) believed that they could obtain the necessary health information there. Patient autonomy, as one of the basic postulates of medical ethics, enables patients to make their own decisions regarding medical treatment based on their knowledge. To make that decision, patients must have access to all relevant information about their condition and all options for treatment. For that reason, doctors help the patient in making a decision with timely and truthful information about risk factors, the nature of the disease, possible consequences, available treatment, as well as possible positive and/or negative outcomes or risks of treatment. Informing patients is one of the standards of ethical behaviour (16), which is expected from doctors and other medical personnel in their daily work with patients. In this way, the medical profession proves that it respects the rights of the patient and his autonomy, which enables each user of health services to freely choose a doctor based on the information received, accept or reject the advice or proposed treatment, and make their own decisions about medical treatment and procedures.

Discussion

The increasing influx of digital technologies into business processes leads to the point where the provision of health services can no longer be viewed only in traditional frameworks, but it is necessary to look at the unlimited possibilities of digital technologies, digital content and digital communications in the provision of healthcare services. The traditional way of providing health services with the implementation of digital technologies provides great opportunities in the exchange of knowledge and information between health workers, health associates and patients, increases the accessibility of expert consultations, actively involves patients in the process of diagnosis and treatment, and above all, provides enormous opportunities for preventive action in the preservation of health.

Digital technologies are changing the way of connecting users of healthcare services in terms of realizing the possibility of establishing two-way communication with healthcare professionals in real-time and any place. A number of healthcare systems dealing with the analysis of patients' needs and demands have identified information technologies as key elements to improve the quality of healthcare. There is evidence that digital communication with healthcare providers improves the quality of health (17,18) and that healthcare consumers would benefit from increased partnerships between health information technology and healthcare providers.

The concept of digital strategy in the healthcare system focuses on the collection of necessary epidemiological information, information on the incidence, prevalence and mortality of certain diseases, risk factors, and availability of medical experts with the formation of a sub-strategy of digital business, primarily Web and mobile strategies, to organize e-health and m-health, with emphasis to social networks and their capacity to connect people and quickly spread information (19).

Based on the results of the research, we can draw some significant conclusions. The obtained results clearly indicate that digital technologies in the healthcare system are necessary in order to raise awareness about oncological diseases, increase the information of the population and prevent malignant diseases. Another advantage is that the Internet allows us to access health information and healthcare services in any geographical area, which leads to the internationalization of healthcare (20). The Internet in a very fast and cheap way ensures communication with the whole world allowing for quick identification of the target e-health services. At the same time, it enables effective communication at the patient's request. What social media provides us is real-time information (21) from various health experts and the exchange of patients' experiences. In such conditions, it was noticed that users recognize e-health and m-health as a new type of promotion on prevention, early diagnosis and treatment of oncological diseases. Research has shown that the information provided to cancer patients means a lot in the treatment process, but their information needs are still not met (22). In addition, the research showed that social networks with numerous contents about health represented a

very effective way of healthcare promotion and disease prevention. Mobile applications help the promotion and control of a healthy lifestyle while forums represent an important form of communication for groups of users, providing professional, experiential and emotional support for a specific medical problem. In the context of the obtained research, there are also numerous studies, which show that about 60% of doctors have increased their interaction with patients via the Internet using social media (Twitter and Facebook) in order to educate patients, monitor their health, and encourage them to change their lifestyle with the hope that those efforts lead to better health education, greater compliance and better outcomes (23). Information and the dissemination of the latest knowledge have become an important element of business functioning as well as the satisfaction of many life needs of modern man.

All the findings suggest that social media indeed enable healthcare institutions to get closer to their users, share information on health policy and practice issues, promote health behaviors, interact with the public, educate and motivate patients to take an active role in their treatment and provide meaningful health information to the community (24).

Conclusion

The paper analyzes the approach to one very important phenomenon in the modern environment, which we define as digital transformation in the healthcare system. It is certainly necessary to point out that when it comes to receiving information from a doctor through some form of digital communication, the doctor-patient relationship becomes an extremely complex process that requires the education of health workers, with the goal of proper information exchange.

Healthcare workers are a source of health information that patients trust more than the Internet, but due to the availability and speed of obtaining information, the Internet is the source most often used by the public to quickly find health information in order to be informed. If health services become available to everyone to the same extent, they restore trust in the healthcare system and by providing expert information to people, they open up enormous opportunities to work on the prevention of many diseases. Although it has been observed that users recognize e-health and m-health as a new form of promotion for the prevention, early diagnosis and treatment of oncological diseases, and that the information provided to cancer patients means a lot in the treatment process, their needs for information are still not satisfied. However, based on all the results obtained, it was determined that digital technologies in the health system are necessary in order to raise awareness about oncological diseases, increase the information of the population and prevent malignant diseases. One of the advantages is that the Internet allows us to access health information and health services in any geographical area.

Informing and disseminating the latest knowledge have become an important element of business functioning, but also the satisfaction of many life needs of modern man.

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DIGITALNE TEHNOLOGIJE KAO PODRŠKA ZDRAVSTVENIM SISTEMIMA U PROMOCIJI ZDRAVLJA I PREVENCIJI BOLESTI

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U radu se analizira pristup veoma važnom fenomenu u savremenom okruženju koji se definiše kao digitalna transformacija u zdravstvenom sistemu. Sve veći upliv digitalnih tehnologija u poslovne procese dovodi do toga da se pružanje zdravstvenih usluga više ne može posmatrati samo u tradicionalnim okvirima već je neophodno sagledati i neograničene mogućnosti digitalnih tehnologija, digitalnih sadržaja i digitalnih komunikacija u pružanju zdravstvenih usluga. Potrebe zdravstvenog sistema i promene koje nastaju razvojem komunikacionih i informacionih tehnologija poput interneta, društvenih mreža, mobilnih aplikacija i sl. zahtevaju organizovan rad na sprovođenju strategije za implementiranje novih načina poslovanja u zdravstvu. Informisanost o zdravlju i podizanje svesti o ranom skriningu onkoloških bolesti povećavaju motivisanost za aktivno učešće u sprovođenju preventivnih mera, lečenju i rehabilitaciji.

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***Ključne reči**: digitalna komunikacija, društvene mreže, e-zdravlje, m-zdravlje, onkološke bolesti*

Original article

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THE FREQUENCY OF INFECTIONS WITH *UREAPLASMA UREALYTICUM* AND *MYCOPLASMA HOMINIS* AND THEIR CORRELATION WITH POSITIVE RESULTS FOR *CANDIDA* SPECIES IN PREGNANT AND NON-PREGNANT WOMEN

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Mycoplasma hominis, Ureaplasma urealytium and *Candida species (Candida* spp.) are potentially pathogenic strains of microorganisms that can often be found in the genital tract of healthy women. However, the mentioned strains with additional factors can lead to numerous complications. The research aimed to determine the one-year prevalence of infection with *Mycoplasma* and *Ureaplasma* in pregnant and non-pregnant patients, as well as the correlation of infection with *Candida* spp. The study included 206 outpatients 30.8 ± 7 years of average age treated for symptoms of vaginal infection at the Department of Gynaecology and Obstetrics of the Clinical Hospital Center of Kosovska Mitrovica. All patients were tested for *Mycoplasma* and *Ureaplasma* by taking a standard vaginal and cervical smear. Cultures were seeded according to standard protocols. Out of 206 patients, 71 were pregnant. A positive test for *Mycoplasma* was found in 32 patients, *Ureaplasma* in 96, and 52 patients in the entire sample had vaginal candidiasis. Six pregnant women were positive for *Mycoplasma* and 29 for Ureaplasma. Vaginal candidiasis was significantly more common in pregnant patients compared to non-pregnant patients (n = 40, p = 0.046). *Ureaplasma* infection was associated with candidiasis in 33 patients (p = 0.005). Almost half of the patients (46.6%) tested positive for *Ureaplasma*. In pregnant women, the most common infection was with *Candida* spp. *Ureaplasma* infection was often associated with vaginal candidiasis in the entire sample, and one should be careful in the treatment of these infections and rationally use antibiotics in correlation with the clinical findings with preventive use of vaginal antimycotics.

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Key words: *Ureaplasma urealyticum, Mycoplasma hominis, Candida species*

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Introduction

Vaginal microflora is a specific compartment of the normal flora of the human organism (1). It is mainly composed of lactobacilli (> 70%) that use glycogen as a substrate for the creation of lactic acid, which gives the vagina a specific acidic environment, which is generally around 4.5. All this happens in the presence of estrogen (2). For various reasons, there may be changes in the pH of the vaginal environment and infection may occur. Symptoms of vaginal infections are one of the most common reasons women visit the doctor (3). Vaginal infections can be caused by all microorganisms that can also be inhabitants of normal vaginal flora. One of the most common causes of infection is *Candida* spp. which occurs in 70% of women at least once in their life and can greatly affect the quality of life (4). In addition, genital mycoplasmas are often isolated as causative agents of infection (5). The most frequently isolated are M. *hominis* and U. *urealyticum*, which represent cell-free prokaryotes that are obligate parasites but also conditionally pathogenic. Genital mycoplasma infections can be asymptomatic, but they can also lead to serious complications, which is why their detection is very important, especially during pregnancy and the period before conception. They can cause, in addition to the mentioned vaginitis and cervicitis, vaginosis, spontaneous premature birth,

chorioamnionitis, spontaneous abortion, ectopic pregnancy and infertility (6, 7).

Our research aimed to examine the prevalence of infection with M. *hominis*, U. *urealyticum* as well as their relationship with *Candida albicans* infection in pregnant and non-pregnant patients of the Kosovska Mitrovica Health Centre.

Material and Method

The research included 206 pregnant and non-pregnant outpatient women with symptoms of vaginal infection, average age 31.8 ± 7.3 years (min 19, max 56), treated at the Department of Gynaecology and Obstetrics of the Clinical Health Center Kosovska Mitrovica in the period from June to December 2022.

All patients were informed that their brief anamnestic data, as well as the results of vaginal and cervical smears, would be used for the purpose of a cross-sectional epidemiological study and would not be used for other purposes.

All women were tested for genital mycoplasmas by taking a standard vaginal and cervical smear with monitoring the frequency of *Candida* spp. Cultures were seeded according to standard protocols. The culture of samples for *Candida* was performed on Saburo agar while testing for *Mycoplasma* and *Ureaplasma* was performed with the commercial Mycoview Quantum test. We considered a number > 104 as a positive result, and for Candida, a significant number and more.

Of the statistical methods, absolute and relative numbers were used, and the method for testing statistical hypotheses was the chi-square test.

Results

Of the 206 women, 135 were non-pregnant women and 71 were pregnant women, as we can see in Figure 1.

In Figure 2, we can see the frequency of infections in the entire sample with the highest frequency of *Ureaplasma* infection.

In Figure 3, we can see the frequency of infections in relation to pregnancy shown in absolute numbers.

A positive test for *C. albicans* was statistically significantly more common in pregnant women than in non-pregnant women. (chi-square = 3.995, p = 0.046)

In Table 1, we can see the correlation of a positive test for *Ureaplasma* with vaginal candidiasis

C. albicans was statistically significantly more common in women with *Ureaplasma* infection in the entire sample (chi-square 7.9, p = 0.005).

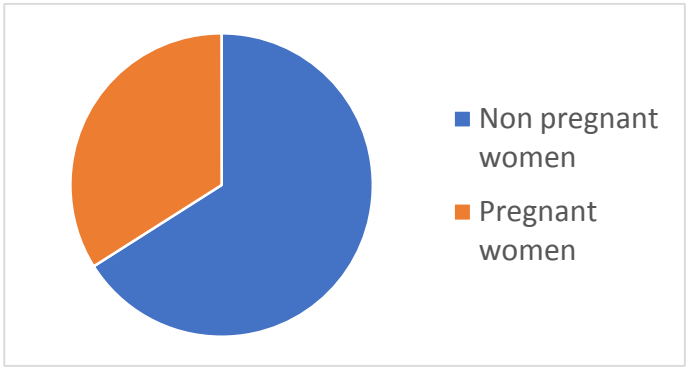

Figure 1. Distribution of female patients in relation to pregnancy

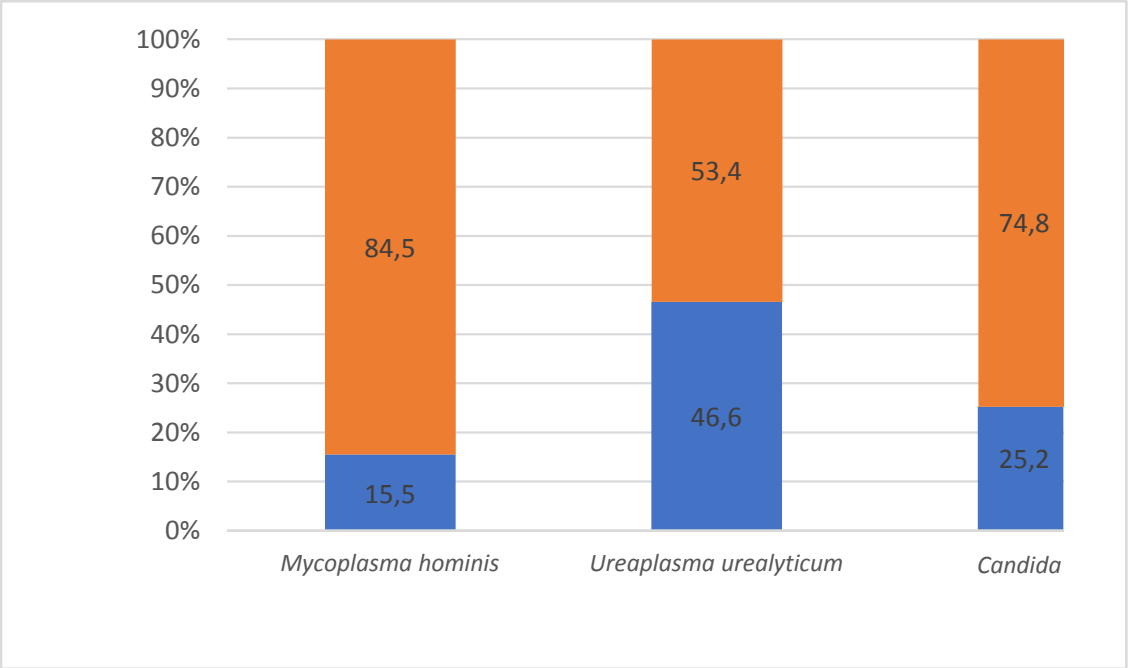

Figure 2. Frequency determination of infections in the entire sample shows the highest frequency of *Ureaplasma* infection

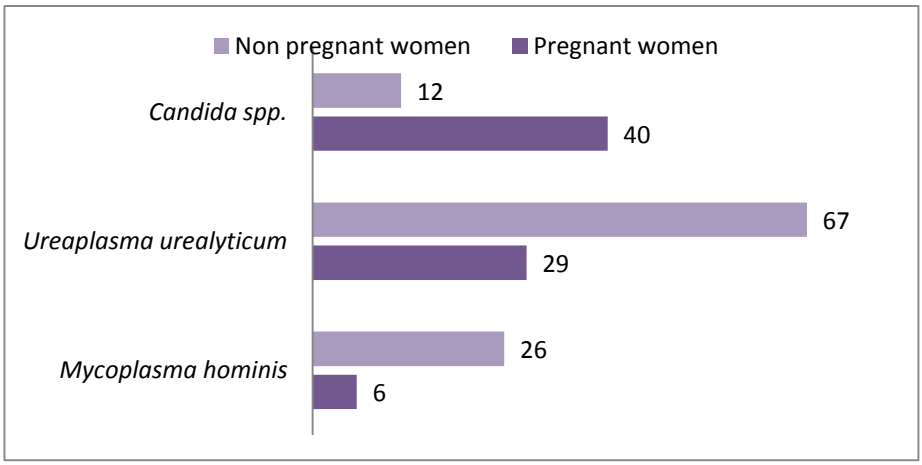

Figure 3. Frequency of infections in relation to pregnancy shown in absolute numbers

Table 1. Correlation of positive findings for ureaplasma with vaginal candidiasis in the entire sample

			Candida spp.		Total
			Negative	Positive	
Ureaplasma urealyticum	Negative		91	19	110
			59.1%	36.5%	53.4%
	Positive		63	**33**	96
			40.9%	**63.5%**	46.6%
Total			154	52	206
			100.0%	100.0%	100.0%

Discussion

Our results show that vaginal infections with proven pathogens are extremely common and their timely diagnosis is essential to avoid persistent infection and subsequent complications previously listed. U. *urealyticum* infection in our sample was present in 46% of the tested women, which is more compared to several multicenter studies from different countries that showed that *Ureaplasma* was present in about 35% of tested subjects and *Mycoplasma* in 10%. This can be explained by the larger number of respondents and the different methodology of the examination (8, 9, 10). Epidemiological data related to *C. albicans* infection show that its frequency does not change much over the years in different parts of the world and that it amounts to somewhere around 40%, which is slightly higher compared to our sample because we tested only women with symptoms of vaginal infection, and *Candida* can often be isolated even in women who do not have symptoms (11, 12). The results of infection with *Ureaplasma* and *Candida* are in accordance with data from the literature where the frequency of Ureaplasma is slightly lower than infection with *Candida*, Payne et al. showed this through research using the real-time PCR method and showed the impact of these infections on pregnancy (13). In 2016, Jovanović et al. conducted a survey of the frequency of vaginal infections in pregnancy and found that one of the most common causes is *C. albicans* and that its prevalence increases during pregnancy by about 30%, which is in line with our results. In our sample, *Candida* was significantly more common in pregnancy than in non-pregnant women, and we can explain this by a change in the immune status as well as changes in the hormonal milieu (14).

The limitations of our research are a short follow-up period, as well as a smaller number of respondents. In future research, it is necessary to extend the duration of the study, and therefore to increase the number of respondents in order to confirm or supplement the findings obtained in this research.

Given that other factors, such as previous conditions and current chronic diseases, were not examined, the findings from this research can serve as a starting point for a future prospective study that would examine the importance of infections as well as their many complications.

Regardless, the high percentage of women who tested positive for genital infections in such a short period in a relatively small area speaks of the importance of this research.

Conclusion

Considering our results, every symptomatic vaginal infection with an adequate clinical picture should be tested for genital *Mycoplasmas* and adequately treated. Considering the frequent association of genital mycoplasma infection with vaginal candidiasis, care should be taken in treatment and vaginal probiotics must be prescribed to prevent further colonization by *C albicans.*

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UČESTALOST INFEKCIJA BAKTERIJAMA *UREAPLASMA UREALYTICUM I MYCOPLASMA HOMINIS* I NJIHOVA KORELACIJA SA POZITIVNIM NALAZOM NA GLJIVICU *CANDIDA SPECIES* KOD TRUDNICA I ŽENA KOJE NISU TRUDNE

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Mycoplasma hominis, Ureaplasma urealytium i *Candida species (Candida* spp.) predstavljaju potencijalno patogene sojeve bakterija koji se često mogu naći u genitalnom traktu zdravih žena. Međutim, pomenuti sojevi uz dodatne faktore mogu dovesti do mnogobrojnih komplikacija. Cilj istraživanja bio je da se utvrdi jednogodišnja prevalencija infekcije mikoplazmom i ureaplazmom kod trudnica i žena koje nisu trudne, kao i korelacija sa infekcijom glijivicom *Candida* spp*.* U istraživanje je bilo uključeno 206 ambulantno lečenih žena sa simptomima vaginalne infekcije, prosečne starosti 30,8 godina ± 7 godina, koje su bile lečene na Odeljenju ginekologije i akušerstva Kliničko-bolničkog centra u Kosovskoj Mitrovici. Sve žene bile su testirane na mikoplazmu i ureaplazmu, uz uzimanje standardnog vaginalnog i cervikalnog brisa. Zasejavanje kultura izvedeno je po standardnim protokolima. Od 206 žena, 71 bila je trudna. Nalaz na mikoplazmu bio je pozitivan kod 32 žene, kod njih 96 nalaz na ureaplazmu bio je pozitivan, dok su vaginalnu kandidijazu imale 52 žene iz celog uzorka. Kod šest trudnica nalaz na mikoplazmu bio je pozitivan, a kod njih 29 nalaz na ureaplazmu bio je pozitivan. Vaginalna kandidijaza bila je značajno češća kod trudnica nego kod žena koje nisu bile trudne (n = 40; p = 0,046). Infekcija ureaplazmom bila je kod 33 bolesnice udružena sa kandidijazom (p = 0,005). Kod velikog broja testiranih žena i iz jedne i iz druge grupe nalaz na ureaplazmu bio je pozitivan. Kod trudnica je najčešća bila infekcija gljivicom *Candida* spp. Činjenica da je infekcija ureaplazmom često bila udružena sa vaginalnom kandidijazom u celom uzorku upućuje na to da treba biti oprezan u lečenju ovih infekcija i racionalno upotrebljavati antibiotike u skladu sa kliničkim nalazom i uz preventivnu upotrebu vaginalnih antimikotika.

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***Ključne reči**: Ureaplasma urealyticum, Mycoplasma hominis, Candida species*

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OSTEOPOROTIC VERTEBRAL FRACTURES: FROM DIAGNOSIS TO REHABILITATION

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Osteoporotic vertebral fractures represent a significant sociomedical problem that impairs the quality of life of the elderly population. Clinical examination, supplementary diagnostic methods (X-ray, Computed Tomography – CT, Dual-Energy X-ray Absorptiometry – DXA, Lateral Vertebral Assessment – LVA) and fracture risk assessment tool (FRAX) are crucial for effective assessment of fracture severity, timely decision on treatment method, and initiation of rehabilitation. Of great practical importance is the effect of antiresorptive therapy on callus formation. In patients who suffer from osteoporosis, and despite treatment have a fracture, it is recommended not to interrupt bisphosphonate therapy, which was started several months before the diagnosed fracture. Bisphosphonates should be introduced into the treatment in a period of 2–4 months from the occurrence of the fracture, depending on the location of the fracture, that is, the time required for callus formation. Recombinant parathyroid hormone is an effective anabolic therapy that accelerates bone regeneration during fractures, increases callus volume and faster bone strength. Osteoporosis therapy should not be started without checking the total and ionized Ca, P, 25(OH)D, and PTH as well as general biochemical analyses, and then introducing antiresorptive or anabolic therapy. Rehabilitation treatment is individually designed and includes balance exercises, strength exercises, range of motion and postural training leading to improvement of spinal mobility, muscle strength and overall functionality. The aim of this review was to highlight the timely diagnosis, evaluation, and treatment of osteoporotic vertebral fractures.

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Key words: *osteoporotic vertebral fractures, dual-energy x-ray absorptiometry, fracture risk assessment tool, therapy, rehabilitation*

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Introduction

Osteoporotic vertebral fractures affect approximately 1 in 3 women and 1 in 5 men over the age of 50 (1, 2) leaving significant physical, psychological, and social consequences for patients, leading to reduced mobility, functional limitations, and decreased quality of life (3, 4). Rehabilitation interventions have been shown to improve pain, functional outcomes, and overall well-being in patients with osteoporotic vertebral fractures (5–7). Pathophysiology and clinical presentation have shown that osteoporotic vertebral fractures result from a combination of reduced bone mineral density and changes in bone microarchitecture (7, 8). Studies have demonstrated that the trabecular bone, particularly in the vertebral bodies, is most susceptible to osteoporotic fractures due to its high metabolic activity and abundant remodelling (9–11). Clinically, patients with osteoporotic vertebral fractures may experience acute or chronic back pain, which can be worsened by movement, prolonged sitting, or activities involving spinal loading (12). Height loss and kyphotic deformity are also common clinical features, contributing to postural changes and functional limitations. Potential hip fractures present great potential risk that cannot be overlooked (13–15).

Radiological Examination

Imaging techniques such as X-rays, CT scans, and MRI are used to diagnose and assess the severity of osteoporotic vertebral fractures (7). DXA is the absolute gold standard (13) for bone mineral density measurements and a widely used

technology for assessing bone health and measuring bone mineral density (BMD) (14–16).

DXA may offer precise and accurate measurements of BMD at various skeletal sites, including the spine, hip, and forearm. It utilizes low-dose X-ray beams that pass through the bone, allowing for the calculation of BMD based on the differential absorption of these beams by bone and surrounding tissues. The BMD results obtained are compared to reference values, typically provided by age-matched and gender-matched populations, to determine if an individual's bone density is within the normal range or if osteoporosis or osteopenia is present. In addition, it provides information about body composition. It can determine the percentage of lean mass, fat mass, and total body fat, allowing for the evaluation of body composition changes over time (14–17). This feature is particularly useful in monitoring the effects of interventions, such as exercise and nutrition, on body composition and overall health. Moreover, DXA can estimate the risk of fractures by utilizing algorithms that combine BMD measurements with clinical risk factors. These algorithms, such as the Fracture Risk Assessment Tool (FRAX), provide a comprehensive assessment of an individual's fracture risk over a specified period, aiding in treatment decisions and preventive strategies (18).

Lateral Vertebral Assessment (LVA) is a radiographic method that provides quantitative measurements of vertebral heights and allows for the identification of vertebral fractures. It offers advantages such as low radiation exposure and quick assessment, making it a valuable tool for screening and monitoring osteoporosis-related fractures. LVA complements DXA by providing additional information about vertebral fractures and aiding in fracture risk assessment (19, 20).

Fracture Risk Assessment and Risk Factors

Factors that increase the risk of developing osteoporosis encompass being 50 years of age or older, being of the female gender, belonging to the Caucasian ethnicity (particularly of northern European or Asian descent), having a genetic predisposition, having a petite and slender physique, experiencing undernourishment, leading a sedentary lifestyle, having a history of amenorrhea, late menarche, or early menopause, suffering from deficiencies in estrogen and androgen hormones, engaging in alcohol consumption or cigarette smoking, maintaining a diet low in calcium, and using certain medications (such as steroids, insulin, anticonvulsants, chemotherapeutics, or heparin) (21–23).

The FRAX index combines DXA measurements and clinical risk factors to estimate the probability of future fractures. FRAX integrates clinical risk factors and bone mineral density (BMD) measurements to estimate the 10-year probability of specifically both major osteoporotic fracture (hip, clinical spine, forearm, or shoulder) and hip fracture. The clinical risk factors taken into account by FRAX include age, sex, previous fracture history, parental history of hip fracture, smoking status, alcohol consumption, glucocorticoid use, rheumatoid arthritis, and secondary causes of osteoporosis. By considering these risk factors along with BMD measurements, FRAX provides a comprehensive assessment of an individual's fracture risk. FRAX calculations are based on large population-based cohorts and validated in numerous studies. It helps identify individuals at high risk of fracture who may benefit from early interventions, such as pharmacological treatments, lifestyle modifications, and fall prevention strategies. FRAX does not consider all possible risk factors, such as vitamin D deficiency or secondary causes of osteoporosis (14–18, 24, 25).

Conservative Management

Conservative management strategies for osteoporotic vertebral fractures aim to alleviate pain, improve function, and promote healing without surgical intervention. Various classes of medications are commonly used for treating osteoporotic fractures. Bisphosphonates, like alendronate and risedronate, inhibit bone resorption (26). Selective estrogen receptor modulators (SERMs), such as raloxifene, mimic estrogen's effects on bone (27). Teriparatide stimulates bone formation and is administered via injections (28). Denosumab, a monoclonal antibody, targets bone resorption (29). Calcitonin helps regulate calcium levels but has modest fracture risk reduction (29). Due to the wide range of pharmacological options today, a complete assessment of the patient's overall condition must be made before choosing the appropriate treatment (26–30).

When we discuss efficient medications, we cannot skip to mention that anabolic agents, like romosozumab, promote bone formation by inhibiting sclerostin and are highly effective, especially in postmenopausal women with severe osteoporosis. The effect of antiresorptive therapy on callus formation is important. Bisphosphonates should be introduced into the treatment within a callus formation period which is 2–4 months from the fracture occurrence. For patients who suffer from osteoporosis and despite treatment have a fracture, it is recommended to continue therapy which has started months before the diagnosed fracture. Recombinant parathyroid hormone is an effective anabolic therapy which accelerates bone regeneration during fractures, increases callus volume and faster bone-strengthening (28, 30).

Biomarkers

Biochemical markers in bone metabolism, including serum cross-linked C-telopeptide of type I collagen (CTX), N-terminal telopeptide (NTx),

tartrate-resistant acid phosphatase 5b (TRACP 5b), and bone-specific alkaline phosphatase (BALP) provide crucial insights into bone health. Elevated CTX and NTX levels indicate increased bone resorption, while higher BALP levels suggest enhanced bone turnover. These markers help assess the effectiveness of treatments like anti-resorptive medications. Additional markers like osteocalcin (OC), serum procollagen type I N-propeptide (PINP), and dihydropyrimidine dehydrogenase (DPD) aid in early bone loss detection and treatment guidance, enhancing patient care when combined with clinical assessments and imaging techniques. Total and ionized calcium Ca, P, 25(OH)D, PTH and general biochemical analyses have to take place before introducing antiresorptive or anabolic therapy (31–33).

Rehabilitation of Patients with Osteoporotic Vertebral Fractures

Mechanical stimulation affects bones in two distinct ways. Firstly, repetitive strain can have a negative impact, resulting in minor damage to bone structure. Conversely, strains surpassing a certain threshold stimulate new bone production and enhance bone resilience under greater loads. The interconnectedness of these effects is commonly referred to as the mechanistic theory, which plays a pivotal role in preventing osteoporotic fractures. It revolves around the concept of minimal effective strain (MES), crucial for safeguarding bone density. To maintain bone structure, strain within the physiological range (800–1,500 μstrain) is essential. Deviations from this range yield varying outcomes, including increased bone resorption at less than 800 μstrain, strengthened bones at 1,500–3,000 μstrain, or even pathological fractures at 15,000 μstrain. Hence, rehabilitation programs aimed at preventing bone loss should incorporate kinesitherapy alongside conventional pharmacological treatments (30, 33, 34).

The management of vertebral fractures can be categorized into three phases: the acute phase, the post-acute phase, and the rehabilitation phase. In the acute and post-acute stages, the primary objectives include effective pain management and ensuring the stability of the fracture (35). Conservative treatment involves the use of an orthosis, designed to provide spinal stabilization. Orthoses are typically employed for a duration of 8 to 12 weeks to aid in the healing of fractures. During the initial 8 weeks following a vertebral fracture, patients are advised to refrain from engaging in resistive strength training. However, relaxation exercises, breathing routines, and range of motion exercises can be introduced to counteract joint rigidity (36–40). Still, it is crucial to minimize prolonged bed rest during these phases and instead encourage mobility in patients. Prolonged bed rest has the potential to lead to undesired consequences such as muscle atrophy, weakness, joint stiffness, pressure sores, deep vein thrombosis, respiratory issues, disorientation, and even depression (38, 39).

Before initiating the rehabilitation phase, radiological assessment of progress in fracture healing is pivotal. In the early stages, it is advisable to introduce neuromuscular stabilization exercises targeting the thoracolumbar region, which help immobilise this area. Within the rehabilitation program, exercises to strengthen the dorsal extensor muscles aimed at reducing kyphosis are recommended. Moreover, postural retraining, balance enhancement, and proprioceptive exercises are crucial for minimizing the risk of falls and secondary fractures (39–43).

The rehabilitation phase has to be individually tailored, still it must be underlined that resistance training, balance exercises and postural training lead to improvements in spinal mobility, muscle strength and overall functionality of the patients.

Physical Modalities

Physical modalities used to improve bone repair include various therapeutic techniques and treatments aimed at enhancing bone healing and bone health. Some of these modalities include low-intensity pulsed ultrasound (LIPUS) (44), electrical stimulation (45), functional electrical stimulation (FES) (46), magnetic field therapy (47), and vibration therapy (48).

LIPUS therapy involves the use of low-intensity ultrasound waves to stimulate bone healing. It is often used to accelerate fracture healing and can promote the formation of new bone (44). Electrical stimulation methods such as direct current, inductive coupling, and capacitive coupling have been employed to promote bone repair. These modalities can enhance the production of bone cells and help in the healing process (45). FES involves the use of electrical currents to stimulate muscle contractions. It is used to counteract muscle atrophy and promote bone health in individuals with limited mobility, such as those with spinal cord injuries (46). Pulsed electromagnetic field (PEMF) therapy uses electromagnetic fields to stimulate bone repair. It is often utilized in the treatment of non-union fractures and other bone-related conditions (47). Whole-body vibration therapy and localized vibration therapy are techniques that involve the application of mechanical vibrations to stimulate bone formation and improve bone density (48).

It is important to note that the choice of physical modality depends on the specific condition, the stage of bone healing, and the recommendations of healthcare professionals. Individualized treatment plans are typically created to address the unique needs of each patient.

Nutrition in Supporting Bone Healing

Nutritional therapy plays a significant role in supporting the healing process and overall bone health following an osteoporotic vertebral fracture. Calcium is essential for maintaining good bone health. It is important to ensure that the patient is consuming an adequate amount of calcium through dietary sources such as dairy products (low-fat or non-fat milk, yoghurt, cheese), fortified plant-based milk alternatives, leafy greens (kale, collard greens), and fortified cereals. Aim should be around 1,000 to 1,200 milligrams of calcium daily, but individual requirements may vary (49). Vitamin D is also crucial for calcium absorption and bone health. Spending time in the sun (with sunscreen) allows the body to produce vitamin D naturally. Additionally, it is recommended to include vitamin D-rich foods in the diet, such as fatty fish (salmon, mackerel), egg yolks, and fortified foods like orange juice and cereals. Magnesium contributes to bone health by helping to convert vitamin D (50, 51) into its active form. Good sources of magnesium include nuts, seeds, whole grains, and green leafy vegetables. Usage of vitamin D supplements if levels are low is a mandatory step.

Furthermore, Vitamin K is necessary for bone mineralization (52). It can be found in foods like leafy greens (kale, spinach, collard greens), broccoli, Brussels sprouts, and certain vegetable oils. Protein intake is essential for the repair and maintenance of bones and muscles (53). Lean protein sources like poultry, fish, lean meats, beans, lentils, and tofu are preferable. High sodium intake can lead to calcium loss in the urine (54). Maintaining a balanced intake of phosphorus is one of the challenges. While it is important for bone health, an excessive intake can interfere with calcium absorption. Phosphorus is naturally present in many foods, including dairy products, meats, and nuts (55).

Conclusion

The comprehensive management of patients with osteoporotic vertebral fractures involves a multidisciplinary approach, combining rehabilitation interventions, radiological examinations, biochemical markers, conservative management strategies, and prevention of complications. By addressing these aspects, healthcare professionals can optimize patient outcomes, alleviate pain, improve functional abilities, and enhance the overall well-being of individuals affected by osteoporotic vertebral fractures.

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VERTEBRALNI PRELOMI U OSTEOPOROZI: OD DIJAGNOSTIKE DO REHABILITACIJE

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Vertebralni prelomi u osteoporozi predstavljaju značajan sociomedicinski problem koji narušava kvalitet života starije populacije. Klinički pregled, dopunske dijagnostičke metode (rendgenski snimak (RTG), kompjuterizovana tomografija (engl. *Computed Tomography* – CT), osteodezintometrija (engl. *Dual-Energy* X-ray *Absorptiometry* – DXA), dezintometrija lumbalnog dela kičme (engl. *Lateral Vertebral Assessment* – LVA) i procena rizika od nastanka preloma (engl. *Fracture Risk Assessment Tool* – FRAX)) ključni su za efikasnu procenu težine preloma, pravovremenu odluku o načinu lečenja, kao i za započinjanje rehabilitacije. Od velikog praktičnog značaja jeste efekat antiresorptivne terapije na formiranje kalusa. Preporučljivo je da se kod osoba koje boluju od osteoporoze, a uprkos lečenju imaju prelom, ne prekida terapija bisfosfonatima, započeta nekoliko meseci pre dijagnostikovanog preloma. Bisfosfonate treba uvoditi u lečenje od dva do četiri meseca po nastanku preloma, u zavisnosti od lokacije preloma, odnosno vremena potrebnog za formiranje kalusa. Rekombinantni paratireoidni hormon predstavlja efikasnu anaboličku terapiju koja ubrzava regeneraciju kostiju tokom preloma, povećava zapreminu kalusa i omogućava brže postizanje čvrstoće kostiju. Terapiju osteoporoze ne treba započeti bez provere ukupnog i jonizovanog Ca, P, 25(OH)D, PTH, kao i opštih biohemijskih analiza; tek nakon toga treba uvesti antiresorptivnu ili anaboličku terapiju. Rehabilitacioni tretman koncipira se individualno i obuhvata vežbe ravnoteže, vežbe snage, vežbe obima pokreta i posturalni trening, koji dovode do poboljšanja pokretljivosti kičme, snage mišića i ukupne funkcionalnosti. Cilj ovog pregleda bio je da se ukaže na pravovremenu dijagnostiku, evaluaciju, kao i na lečenje preloma pršljenova u osteoporozi.

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***Ključne reči**: prelomi pršljenova u osteoporozi, osteodezintomerija, procena rizika od nastanka preloma, terapija, rehabilitacija*

Review article

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GUIDELINES FOR MONITORING WOMEN WITH COAGULATION DISORDERS

Miodrag Savović

Irrespective of the progress in the recognition and treatment of women who suffer from bleeding disorders, modern medical science has yet to adjust the diagnosis, therapy and care to their needs. An increasing number of women are being diagnosed with the mentioned disorders. Some who consult a gynaecologist owing to heavy menstrual bleeding actually have a coagulation disorder. Failure to recognise this disorder is widespread. Heavy menstrual bleeding is a condition that women with such disorders experience from the onset of the reproductive period. It affects their quality of life. What is more, they face the problem of accepting the potential risks of transmitting the disease to their child. Timely recognition and registration of these patients are essential. It is important to talk with and consult healthcare professionals, as well as to prescribe adequate therapy that enables physicians to cope with the various needs of women during the reproductive period.

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Key words: *menarche, coagulopathies, abnormal uterine bleeding*

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Introduction

The maturation of the central nervous system (CNS), the hypothalamus and the pituitary gland lead to the synthesis of a more significant amount of gonadotropin, which becomes sufficient for activating ovarian function. The increased and cyclical production of hormones accelerates the growth and development of secondary sexual characteristics. The most important event at the beginning of puberty is the first menstrual bleeding - menarche, and in our climate, it occurs at the age of 12, on average. Normal menstrual bleeding results from a decrease in the concentration of estrogen and progesterone in the blood two days prior to its occurrence, and the cessation of bleeding occurs when the estrogen level increases once more. Bleeding is a result of vasoconstriction, myometrial contraction and local platelet aggregation (1). Menstrual bleeding lasts from 2 to 7 days, with a blood loss of 40 ml per cycle, and happens at 21 to 45 days (2). International Federation of Gynaecology and Obstetrics (FIGO) introduces a new classification system for abdominal bleeding: Abnormal Uterine Bleeding (AUB) (3). The diagnosis of AUB depends on the volume and length of the bleeding, the existence of pain with respect to the first day of the cycle, data on the present infections, physical and emotional stress, weight change, data on the use of drugs (warfarin, heparin, hormones) or herbal preparations (ginkgo, ginseng), history of coagulation diseases with a positive family history, evaluation of being overweight, symptoms of the Polycystic Ovary Syndrome (PCOS) syndrome, insulin resistance, thyroid disease, presence of changes on the vulva, vagina, cervix, presence of possible pregnancy, fibroids, adnexal tumours, adenomyosis and infection. A pregnancy test, blood count, vaginal and urinary analysis, especially for *Chlamydiae trachomatis*, cervical cytology, and thyroid hormone level should be considered. A coagulation status test should be performed in the event of profuse and prolonged bleeding. Furthermore, an ultrasound examination needs to be employed in order to determine the thickness of the endometrium and to observe the possible presence of pregnancy, as well as the changes in the small pelvis. Cervical biopsy and curettage, hysteroscopy and laparoscopy can be additionally used in diagnosis. The treatment of patients depends on the aetiology, physical examination, laboratory and other analyses. In patients with submucosal myomas, infections, thrombophilia and early abortions or pelvic tumours, it is essential to administer therapy for the underlying condition (4). A large number of

patients have ovarian dysfunction (AUB-O), which is treated in the following manner:

- Hormonal therapy: Progestins (medroxyprogesterone acetate – 10 mg per day, or norethindrone acetate – 5 mg per day) for ten days, with the monitoring of bleeding;
- Oral hormonal contraceptives (OHC) may be prescribed to reduce bleeding. At first, these should be administered four times a day for 1–2 days, then two pills a day until the 5th day, and then one a day until the 20th day. The therapy is to be conducted in three successive cycles with one tablet a day;
- Gonadotropin-releasing hormone agonists (GnRH agonists) can be included in treating severe bleeding, in the form of one injection per month during six cycles;
- Conjugated estrogens can be intravenously administered in hospitalized women experiencing heavy bleeding for 4 hours, in 3 to 4 doses, followed by oral therapy with conjugated estrogens, 2.5 mg daily, or ethinyl estradiol, 20 mcg daily, for three weeks, with the addition of progestagen for the last ten days of therapy.

In case of abnormal bleeding after unsuccessful hormone treatment, hysteroscopy should be performed, and organic lesions (polyp, submucosal myoma) or neoplasm (endometrial cancer) should be ruled out.

In the absence of a specific pathology, the therapy for bleeding can be one of the following: endometrial ablation, placement of an intrauterine system with levonorgestrel or hysterectomy (5, 6).

The most common symptom is menorrhagia (bleeding that lasts more than seven days, or more than 80 ml) (7). Other symptoms may include haemorrhagic ovarian cysts and endometriosis. ACOG (American College of Obstetricians and Gynaecologists) recommends that all female patients under 18 who experience abnormal bleeding should be tested for coagulation disorders, especially von Willebrand disease. It has a prevalence of 1.3% and is the most common disorder which causes menorrhagia during menarche (8). Screening involves determining partial thromboplastin time (aPTT), prothrombin time (PT), the evaluation of platelet function, and the determination of the von Willebrand factor antigen in the plasma and VWF activity in the plasma. This disorder often remains unrecognized. Heavy menstrual bleeding is a problem faced by girls and women, and it significantly affects their quality of life. Menorrhagia is not the only manifestation of a blood clotting disorder. In most cases, anamnestic data on menstrual bleeding show that a woman has more abundant and prolonged bleeding, which is significant for suspecting the existence of a bleeding disorder. Women face problems owing to the symptoms themselves and other challenges of the reproductive period, primarily concerning planning pregnancy (9). A history of ovarian cysts was detected (52% vs. 22% of controls) in a study of 102 women with vWD, conducted by the United States Centers for Disease Control and Prevention (CDC). In the same study, 30% of the women with vWD suffered from endometriosis, compared to 13% of those in controls (10).

The ten European principles of care for girls and women with congenital bleeding disorders are:

- Equal access and quality of care for all persons, regardless of gender;
- Timely and accurate diagnosis of coagulation disorders in women and girls;
- Awareness of the additional challenges these people face;
- Access to the patient and family, and providing comprehensive care;
- Inclusion of a dedicated gynaecologist and obstetrician in the team;
- Education of women, girls and their families about the menstrual cycle and its regulation;
- Early recognition and control of heavy menstrual bleeding;
- Counselling before conception and access to prenatal diagnostics;
- Providing a comprehensive plan during pregnancy and after birth;
- Inclusion of patients in registries and clinical research.

Coagulation disorders significantly affect the quality of a person's life owing to the way in which they are inherited, the impact of bleeding on the patient's life and the life of the family, the impact on social life, productivity, stress and anxiety. Menstrual bleeding is often not discussed openly in the family circle, so more work should be done to normalize discussions on this topic. Educating the family, healthcare workers and the public about normal and abnormal bleeding patterns can help to create the conditions for an effective diagnosis and therapy of this group of patients (11). A woman experiences approximately 450 menstrual cycles in her lifetime, and the haemostatic challenges of ovulation and menstrual bleeding occur in each instance (12). Education should be adapted to the age and needs of women in different stages of the reproductive period. Adolescent girls are at particular risk of heavy menstrual bleeding due to the immaturity of the ovaries and the high percentage of anovulatory cycles. Women face dilemmas when it comes to family planning. A woman should be introduced to the mechanism of disease inheritance and the risks to the offspring. Pregnancy is a hypercoagulable state. Women with coagulopathies face an increased risk of bleeding complications during pregnancy, childbirth and postpartum. In the case of these women, planning pregnancy should ideally happen before conception (11).

Counselling

This is necessary for the purpose of preparing the patient and her parents for the appearance of the first menstruation. The first signs of puberty appear at the age of 10, on

average. The counselling goals are to explain the risk of bleeding, monitor the volume and length of menstrual bleeding, and the procedure in case of heavy bleeding. As the onset of the first menstruation approaches, insist on the importance of early medical supervision for better efficiency, make a plan of action in case of heavy bleeding, and provide a prescription with therapy and laboratory instruction for haemoglobin determination on the first and third days of menstrual bleeding (13).

Treatment during the First Menstruation and Puberty

1. Take tranexamic acid from the very beginning of the menstruation: 2 tablets of 500 mg 3 times a day,
2. Determine the haemoglobin level on the first and third day of the cycle,
3. Establish contact by phone or e-mail with the selected gynaecologist and haematologist.

The therapy is considered effective and menstrual bleeding is regular:

- if the number of sanitary napkins does not exceed 4/day (+ 1 at night),
- if the haemoglobin level remains > or = 11g/l,
- if menstruation lasts < or = 7 days.

Apply the same protocol during subsequent cycles. If the cycles are irregular, add progestagen therapy from the 16th to the 25th day of the cycle. If the therapy is insufficiently effective: prescribe an estroprogestagen pill of 30 µg, from 2 to 3 pills a day, until the bleeding stops (i.e. over 2 to 3 days) and continue with one pill a day until the end of the pack. Consultation is necessary every six months.

Procedure in Women during Sexual Maturity

If contraception is desired, a combined estroprogestagen pill or an intrauterine device with levonorgestrel should be used. If menstruation is excessive and contraception is not desired, tranexamic acid, 1 g per os, every 6 to 8 hours, is used during the first five days of menstruation, and/or intranasal desmopressin, one dose of spray in both nostrils during the first 2 to 3 days of menstruation, with or without tranexamic acid.

Planning Pregnancy

It is necessary to follow the married couple. Assess the partner's risk and whether he is a carrier of a haemorrhagic disease. In severe forms of the disorder, prevention strategies include genetic counselling. In the case of in vitro fertilization, pre-implantation genetic diagnostics should be performed, if available. After consulting the haematologist, gynaecologist and obstetric team, the married couple must be informed about the risks during pregnancy, especially for the mother and the fetus. If a woman suffering from haemophilia, vWD or a platelet function disorder suspects pregnancy, she should visit her gynaecologist as soon as possible. They will ensure the provision of the best possible care during pregnancy and delivery. Consultation with a haematologist is imperative. If the woman is already pregnant, recommend prenatal diagnostics (biopsy of the chorionic villi, amniocentesis, determining the sex of the child by ultrasound). It is best to make a plan about monitoring the pregnancy and childbirth with the parents. Pregnancy care and pregnancy monitoring are performed in a specialized centre. This also involves the control of haemostasis during childbirth, as well as after childbirth. The birth must take place in a tertiary institution. Tranexamic acid reduces the risk of early and late postpartum bleeding and does not affect breastfeeding. It can also be used for a more extended period after delivery if there is a higher risk of bleeding. The newborns, who may inherit the disorder, are at risk of bleeding during the delivery, especially in instrumental deliveries (11).

Procedure for Women who no Longer Wish to Give Birth

Tranexamic acid and/or intranasal desmopressin can be administered in women during puberty, which is a short-term therapy. An intrauterine device with levonorgestrel is recommended as long-term therapy, and in more severe cases, it is required to resort to endometrial ablation or hysterectomy (14, 15).

The effectiveness of the therapy is not always the same. Caution is needed with prolonged bleeding owing to the risk of functional haemorrhagic ovarian cysts. Progesterone or the birth control pill should be re-prescribed. Monitor dysmenorrhea and prohibit the use of nonsteroidal anti-inflammatory drugs. Recognize neglecting to take the pill and genital infection as the cause of metrorrhagia. Teach the patient to double the pill dose in case of profuse bleeding.

Conclusion

Identification and registration of these patients are essential. Counselling, monitoring and therapy must be instituted from the onset of puberty if a haemostasis disease is known. Otherwise, menarche (first menstrual bleeding) will reveal a latent haemostasis disease. In severe coagulation disorders, bleeding can be very profuse and prolonged and may lead to the need for hospitalization and/or a blood transfusion. Quality of life may be impaired. With well-conducted hormonal therapy and close cooperation between haematologists and gynaecologists, blood transfusions and infusions of platelet factors that carry the risk of alloimmunization can be avoided. Throughout life, it is necessary to monitor and harmonize therapy with the needs of women during the reproductive period.

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SMERNICE ZA PRAĆENJE ŽENA SA POREMEĆAJIMA KOAGULACIJE

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Uprkos napretku u prepoznavanju i lečenju žena sa poremećajima krvarenja, savremena medicinska nauka još nije uskladila dijagnostiku, terapiju i negu sa njihovim potrebama. Sve većem broju žena dijagnostikuju se ovi poremećaji. Pojedine žene koje se jave ginekologu zbog obilnog menstrualnog krvarenja imaju poremećaj koagulacije. Neprepoznavanje ovog poremećaja veoma je uobičajena pojava. Obilno menstrualno krvarenje predstavlja stanje sa kojim se žene sa pomenutim poremećajima sreću od početka reproduktivnog perioda i utiče na kvalitet njihovog života. Takođe, one se suočavaju sa problemom prihvatanja potencijalnih rizika od prenošenja bolesti na dete. Neophodno je pravovremeno prepoznavanje, kao i registracija ovih bolesnica. Važni su i razgovor i savetovanje sa zdravstvenim radnicima, te primena adekvatne terapije koja omogućava suočavanje sa različitim potrebama žene u reproduktivnom periodu.

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***Ključne reči**: menarha, koagulopatije, abnormalna krvarenja iz materice*

Case report

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SHOTGUN INJURY AS A CAUSE OF FLOATING ELBOW: A CASE REPORT

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Floating elbow represents an injury that is a combination of ipsilateral humeral shaft and forearm fractures. Shotgun injury of the elbow is a very severe and complex type of injury, often with complications such as infection, nerve palsy, and range of motion limitation.

We present a case report of a 46-year-old man with a gunshot wound to the right elbow. He sustained an injury of the distal humerus and proximal ulna which resulted in a floating elbow injury. As the initial clinical exam indicated normal neurovascular status, after adequate preoperative preparation, primary surgical treatment of the wound was performed under general endotracheal anesthesia as well as stabilisation of the right elbow with the Mitković external fixator with two pins placed in the humeral shaft and two pins placed in ulna shaft. Two weeks later we performed internal fixation of the mentioned injury.

Surgical treatment of such severe gunshot wounds requires primary treatment with an external fixator with subsequent conversion to internal fixation when the local status of the wound is normal.

Floating elbow injuries should be brought into the correct anatomical reposition as soon as possible with internal fixation because it allows us to have good function of the elbow with the best possible range of motion.

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Key words: *floating elbow, shotgun injury, external fixation, nerve palsy, range of motion*

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Introduction

Non-fatal firearm injuries are often combined with orthopaedic complications like fracture, compartment syndrome, infection, nerve palsies, soft-tissue damage and lead toxicity given the extent of musculoskeletal involvement (1).

The floating elbow is defined as a simultaneous ipsilateral fracture of the humerus and forearm. It is an uncommon injury occurring both in children and in adults (2, 3). There are two major categories of floating joint injuries that have been described in the literature: type 1—skeletal disruption above and below an articulation without direct injury to the intermediate joint and type 2—combined skeletal and direct articular injury. Also, there is a type 3 lesion which includes associated neurovascular damage of overlying soft tissue elements, with or without simultaneous articular involvement as described below (4).

We present a case of floating elbow resulting from a shotgun shooting, its severity, primary care as well as definitive treatment and follow-up of a patient one year after injury.

Case Presentation

A 46-year-old man was admitted to the emergency room due to a shotgun injury to the right elbow. The patient was in a state of traumatic shock, frightened and in severe pain. The orthopedic surgeon was called for a consultation immediately upon admission to the emergency room.

Initial clinical examination showed bleeding from the lateral side of the right elbow, swelling, bruising, inability of motion as well as pathological mobility along with severe pain. After primary lavage, several smaller wounds were observed which indicated shotgun injury. The neurovascular status of the injured extremity was initially normal.

The wound was bandaged, the extremity immobilized, the patient stabilized and referred for

radiographic examination. The radiographs taken at the initial examination showed a supracondylar fracture of the humerus and a fracture of the proximal third of the ulna (Figure 1).

After primary care in the emergency room and diagnostic procedures, patient was admitted to the Clinic for Orthopedic Surgery and Traumatology. Upon the admission, fluid resuscitation, intravenous analgesics and antibiotics were administrated and the patient was prepared for surgery.

After adequate preoperative preparation, the patient was operated on under general endotracheal anesthesia. The wound was thoroughly washed with hydrogen peroxide, saline solution and povidone-iodine solution. The wound was debrided, the swab was taken and the accessible shotgun pellets were removed from it. Then the right elbow was stabilized with the Mitković external fixator with two pins placed in the humeral shaft and two pins placed in the ulna shaft (Figures 2 and 3).

The early postoperative course went normal, the patient was transferred to the intensive care unit where he received antibiotics for a full 72 h (Ceftriaxone 2 g/24 h, Amikacin 1 g/24 h), fluids, analgesics and anticoagulants with daily wound dressing. Afterwards, he was transferred to the Traumatology Department where he was hospitalized for another four days for further care and then discharged home in good general condition with a plan for definitive osteosynthesis in two weeks.

After two weeks patient was readmitted to the Traumatology Department for definitive osteosynthesis of fractures. As the wounds from the shotgun were healing and complete preparation was done, another surgery was performed. Open reduction and fixation of the distal humerus was performed with free screws due to the good position of fracture fragments and the sparing of soft tissue after the initial injury. Osteosynthesis and open reduction of ulna were performed with reconstructive plate due to large comminution of fracture fragments (Figure 4). After a few more days at the Traumatology Department, the patient was discharged home with a sterile swab, good operative wound status and a satisfying range of motion and with a plaster cast.

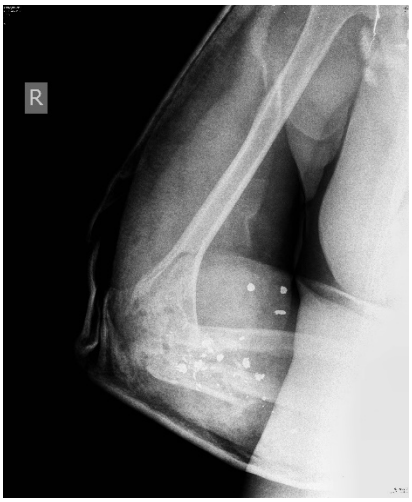

Figure 1. Open elbow dislocation and X-ray of the elbow on admission to the clinic

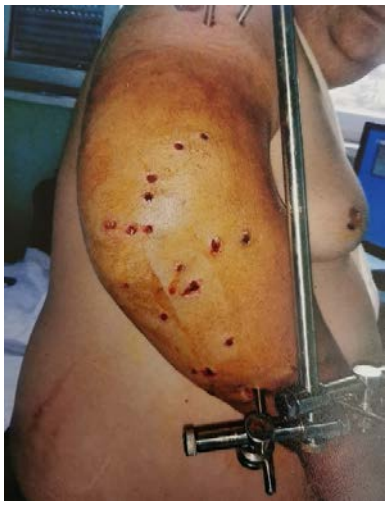

Figure 2. Condition after washing the wounds and external fixation of the elbow

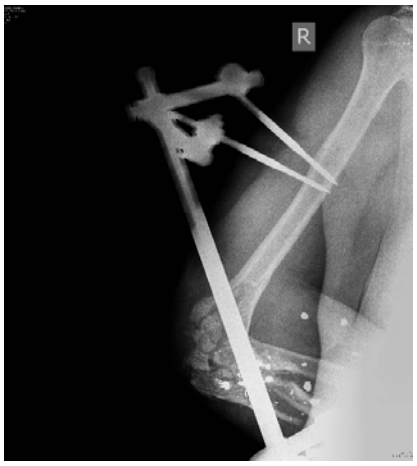

Figure 3. X-ray of the elbow after external fixation

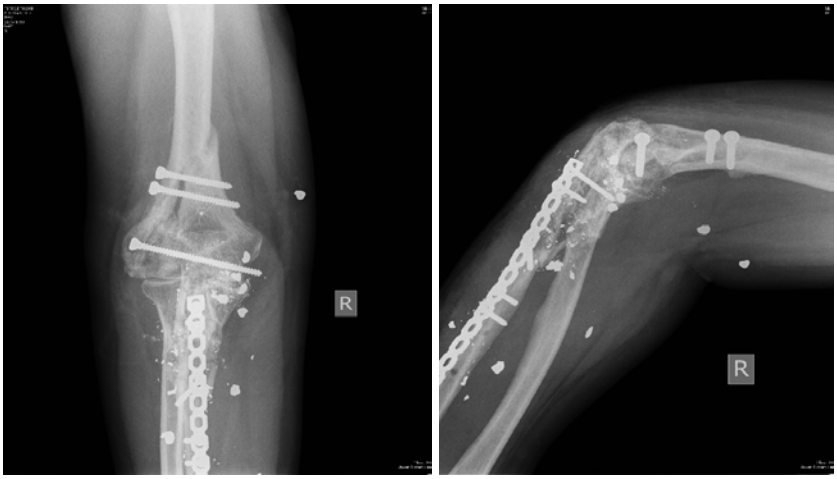

Figure 4. X-ray of the elbow after internal fixation

At the first check-up after 10 days, the plaster cast and sutures were removed, and local status was neat, but the patient complained about weakness in moving the thumb as well as a slight loss of sensation on the dorsum of the hand, which indicated nervus radialis paresis. We started early elbow activation and multivitamin therapy along with analgesics and anticoagulants. Another check-up after two weeks showed slightly better results.

Follow-up visits were scheduled at 2, 6 and 12 months postoperatively and annually thereafter. Two months after surgery, patient was referred to physical therapy. Six month follow-up showed that a slight loss of sensibility on dorsum of the hand was persistant and range of motion was satisfying, so the patient was referred on to another cycle of physical therapy. At 12-month follow-up, the patient was completely recovered with no radial paresis, a full range of motions and neat local status (Figure 5).

Figure 5. Functional outcome 12 months after surgery

Discussion

Floating elbow is a very uncommon injury. Poor functional outcome is very frequent and associated with high morbidity irrespective of the interventions offered (2).

Complications which can occur after floating elbow injury, e.g., infection, myositis ossificans, non-union, and malunion of the humerus or forearm bones, vascular or nerve injury, can lead to poor functional results (3).

We report a case of a 46-year-old man with a gunshot wound to the right elbow. The neurovascular status of the injured extremity was initially normal. After adequate wound irrigation elbow was stabilised with the Mitković external fixator.

Fractures in the upper extremity after a gunshot are mostly treated either conservatively using plaster or splint, or surgically with open reduction and internal fixation (ORIF) using screws and plates, intramedullary nails (IMN) or external fixators. Wounds can be surgically treated and debrided and the bullet may or may not be removed (5).

We assessed that there was a very high risk of infection, so we decided on primary external skeletal fixation and delayed definitive care.

With the Mitković external fixator, it is possible to fix all fractures of the upper extremity, even very complex injuries such as floating elbow. The Mitković external fixator type is excellent in treating fractures caused by firearm injuries because it is easy and quick to apply, provides good stability and enables wound care because of its unilateral type (6).

Most gunshot fractures of the extremities are treated surgically and these patients are always treated with intravenous antibiotics prophylactically (1).

We opted for a combination of two antibiotics (Ceftriaxone 2 g/24 h, Amikacin 1 g/24 h)

There are no prospective, randomized controlled trials investigating two cohorts of patients where one group receives antibiotics and one group does not as seen with the low-velocity gunshot studies. Such a study would really help determine whether antibiotics should be administered prophylactically to all patients presenting with a high-velocity GSW (gunshot wounds) fracture to the extremity. Despite the literature suggesting the use of antibiotics, in light of an absence of high-quality studies, there are no definitive recommendations on antibiotic use (7).

Considering the good healing of the soft tissues, after two weeks the patient underwent another operation for definitive stabilization of the fracture. Open reduction of the humerus fracture and stabilization with free screws was performed, as well as osteosynthesis of the ulna with a plate and screws. In the available literature, fixation with locking plates for stable fixation is mainly shown.

This procedure made the fracture heal, although it was quite an unstable reconstruction (8), but with minimal compromise of soft tissues and minimal risk of infection.

Ten days after the operation, palsy of the radial nerve was observed during a regular check-up.

Reported rates of nerve injury after upper extremity GSWs are highly variable. Traumatic injury to surrounding nerves resulting in clinical palsy after a GSW to the upper extremity can be secondary to direct trauma from the bullet, or indirect trauma such as thermal damage, laceration secondary to fracture fragment displacement, or compression secondary to swelling or subacute scar formation among many other variables (9).

After early physical therapy and vitamin supplementation, there is an improvement in the clinical response.

A common complication after a floating elbow injury is a poor functional outcome (2, 3).

Although the amount of residual gunshot bullet material near the fracture site is more predictive of fracture union rate than comminution (10), delayed healing or non-union did not occur in our case.

The case we present shows an excellent functional outcome 12 months after injury. Good soft tissue healing, fracture healing in good position and almost full range of motion.

Conclusion

Surgical treatment of these severe injuries requires primary treatment with external skeletal fixation with later conversion to internal fixation when there are no local signs of infection. Internal fixation of such an injury requires the best possible repositioning and stable fixation to avoid frequent complications.

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Prikaz slučaja

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„PLUTAJUĆI LAKAT" NASTAO KAO POSLEDICA RANJAVANJA SAČMOM IZ LOVAČKE PUŠKE: PRIKAZ SLUČAJA

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„Plutajući lakat" je povreda koja predstavlja kombinaciju ipsilateralnog preloma nadlakatne kosti i kosti podlaktice. Povreda lakta izazvana hicem iz lovačke puške teška je i složena vrsta povrede, često praćena komplikacijama poput infekcije, paralize nerava i ograničenja obima pokreta.

Predstavljamo slučaj četrdesetšestogodišnjeg muškarca sa prostrelnom ranom desnog lakta. Zadobio je povrede distalnog humerusa i proksimalne ulne, što je rezultiralo povredom „plutajućeg lakta". Budući da je na inicijalnom kliničkom pregledu neurovaskularni status bio normalan, nakon adekvatne preoperativne pripreme urađene su primarna hirurška obrada rane u opštoj endotrahealnoj anesteziji i stabilizacija lakta spoljašnjim fiksatorom po Mitkoviću, sa dva klina u telo humerusa i dva klina u telo ulne. Dve nedelje kasnije urađena je unutrašnja fiksacija navedene povrede.

Hirurško lečenje ovakvih teških prostrelnih povreda zahteva primarni tretman spoljašnjim fiksatorom, sa prevođenjem u unutrašnju fiksaciju onda kada lokalni status rane bude uredan.

Povrede „plutajućeg lakta" treba što pre dovesti u ispravnu anatomsku repoziciju unutrašnjom fiksacijom, s obzirom na to da ona omogućava dobru funkciju lakta sa što većim obimom pokreta.

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***Ključne reči**: plutajući lakat, povreda lovačkom puškom, spoljašnja fiksacija, paraliza nerava, obim pokreta*

Case report **UDC: 616.411-006.32:616.33-006.6**
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GAUCHER DISEASE TYPE 1 AND GASTRIC CANCER: A CASE REPORT

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Gaucher disease (GD is a liposomal storage disease that is inherited in an autosomal recessive manner. The basis of the disease is a mutation of the gene that codes for the enzyme glucocerebrosidase. The clinical division of GB into type 1, 2 and 3 is based on the absence (type 1) or presence (type 2 and 3) of manifestations by the central nervous system. In order to establish a definitive diagnosis, the level of β-glucose cerebrosidase in leukocytes and the value of chitotriosidase in the serum are determined. Genotype analysis is helpful in assessing the type and severity of the disease. Since 1991, Gaucher disease has been treated with enzyme replacement therapy (EST). We present the clinical characteristics of a patient with type 1 Gaucher disease diagnosed in November 2004 in the Hematology Clinic, UKC of Serbia. The patient was a heterozygous carrier of the N307S mutation. In February 2006, treatment was started with imiglucerase (Cerezyme^{R}) IV at a dose of 30 U/kg body weight every two weeks. After 24 months of imiglucerase therapy, a significant improvement in the patient's condition was registered, but she complained of nausea, an urge to vomit and pain in the epigastrium. MSCT of the upper abdomen was performed, and esophagogastroduodenoscopy with a biopsy of changes in the stomach. Pathohistological findings of biopsied changes in the stomach indicated the existence of gastric adenocarcinoma. A total gastrectomy with splenectomy and cholecystectomy was performed. PH finding was adenocarcinoma ventriculi intramucosum (early cancer). After the surgical intervention, the patient continued enzyme replacement therapy with imiglucerase. Patients with GD have an increased risk of developing malignant diseases, most often lymphoproliferative, although solid tumors (hepatocellular carcinoma) have also been described. In our case, to the best of our knowledge, the association of Gaucher disease with gastric cancer has been rarely reported in the literature.

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Key words: *Gaucher disease, enzyme replacement therapy, imiglucerase, gastric cancer*

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Introduction

Gaucher disease (GD) is the most frequent lysosomal storage disease caused by an autosomal recessive mutation in the beta glucocerebrosidase gene. The basis of the disease is a mutation of the gene that codes the enzyme glucocerebrosidase (1–5).

As a result of reduced enzyme synthesis, lack or disruption of enzyme function or saposin C (enzyme activator) deficiency, glucocerebroside accumulates in the macrophages of the liver, spleen, bone marrow, less often in the lungs and other organs, which causes numerous multiorgan complications (hepatomegaly, splenomegaly, anaemia, thrombocytopenia, skeletal and neurological changes) (1, 6–10).

The clinical division of GB into type 1, 2 and 3 is based on the absence (type 1) or presence (type 2 and 3) of manifestations by the central nervous system (1, 10).

Type 1 is the most frequent form and it can vary from asymptomatic forms to the forms with severe complications in childhood and adult period. It is characterized by visceral and skeletal involvement. Clinical manifestations include hepato- and splenomegaly, anaemia, leukopenia, thrombocytopenia, bone changes, and pulmonary disease (1).

Type 2 is the acute and lethal neuronopathic form and type 3 Gaucher disease is the chronic neuronopathic form with visceral, skeletal and cardiac involvement.

The variegated pathology observed in Gaucher disease is not only a consequence of the deposition and mechanical effect of glucocerebroside but also the activation of macrophages and the secretion of cytokines. In the serum of these patients, the level of interleukin 1b, interleukin 6, TNF alpha, soluble interleukin 2 receptor, as well as CD14 was elevated (11−14).

In order to establish a definitive diagnosis, the level of β-glucose cerebrosidase in leukocytes is determined (6, 10). The presence of Gaucher cells in the bone marrow and other tissues is not pathognomonic for Gaucher disease because it can be found in a number of other diseases (acute and chronic lymphoproliferative diseases, chronic granulocytic leukemia, thalassemia). Genotype analysis is helpful in assessing the type and severity of the disease.

In biochemical analyses of patients with Gaucher disease, there are elevated levels of acid phosphatase, ferritin and angiotensin-converting enzyme (ACE) in the serum, which is a consequence of their intense secretion from Gaucher cells and monocyte precursors. In patients with Gaucher disease, a markedly elevated value of the enzyme chitotriosidase, which originates from Gaucher cells, is registered and an indication of macrophage activation and immune response induction (1, 15−18).

Since 1991, Gaucher disease has been treated with enzyme replacement therapy (EST), i.e., replacement of β-glucocerebrosidase with an enzyme obtained by recombinant technology (aglucerase, imiglucerase, velaglucerase, taliglucerase alfa). The therapy is effective, corrects anaemia, thrombocytopenia, and organomegaly, improves bone status and side effects are rare (10, 18−25).

In the serum of patients with Gaucher's disease, the activity of chitotriosidase, a human chitinase produced by tissue macrophages, is typically increased. The level of chitotriosidase is used as a surrogate marker of the total amount of deposited glucocerebroside in the body to assess the effect of EST.

Case presentation

We present the clinical characteristics of a patient with type 1 Gaucher disease, in whom the diagnosis of the disease was established by determining glucocerebrosidase in leukocytes and genotype based on PCR and direct gene sequencing. In this patient, the level of chitotriosidase was monitored as a reliable indicator of the amount of accumulated substrate.

We present the results of monitoring and treatment of a patient who was on enzyme replacement therapy.

In October 2004, a 52-year-old female patient, deaf-mute since birth, was admitted to the Infectious Department of the Health Centre in Prokuplje because of fever (38.5 ^{0}C), weakness and pain in the right hip. On admission, she had accelerated sedimentation (SE 100 mm/h), and mild anaemia (Hgb 117 g/L). In addition, multiple osteolytic lesions were observed on the X-ray image of the right femur, which were interpreted as secondary deposits. The patient was referred to the Clinic of Hematology, University Clinical Centre Niš for further examination. A magnetic resonance imaging (MRI) of the thoracolumbar spine and both femurs was performed. It indicated an Erlenmeyer flask deformity of both femurs, the presence of infarct lesions in the distal third of the diaphysis of the left femur, and altered signal intensity of the vertebral bodies Th9, L1, and L3-changes suggested fat infiltration (Figure 1).

Suspecting the existence of a lipid thesaurus, the patient was referred to the Institute of Haematology, University of Belgrade. Based on the decreased activity of β-glucocerebrosidase in peripheral blood leukocytes (1.2 nmol/h/mg protein), elevated levels of the chitotriosidase enzyme (8788 nmol/ml/h), acid phosphatase (12.6 U/L), ferritin (2359.4 ng/ml), hepatosplenomegaly (confirmed by ultrasound examination of the abdomen, computerized tomography of organs, CT volume of organs—liver 2614 ccm, spleen 539 ccm), with the finding of Gaucher cells in the bone marrow punctate, the patient was diagnosed with Gaucher disease type 1 in November 2004. The type of genetic mutation pAsn409ser (N3075)/p.Ser146Leu(S107) was determined. The patient was a heterozygous carrier of the N307S mutation.

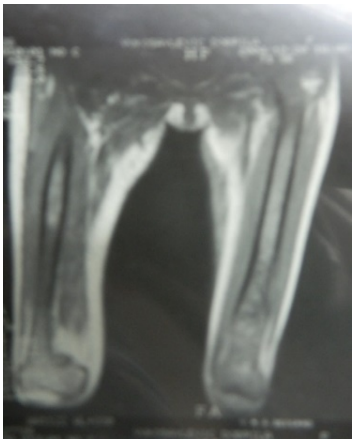
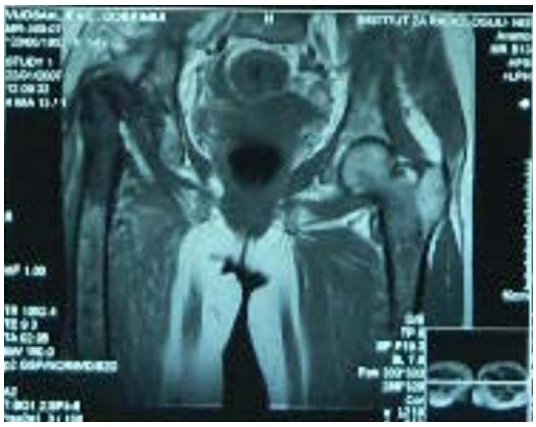
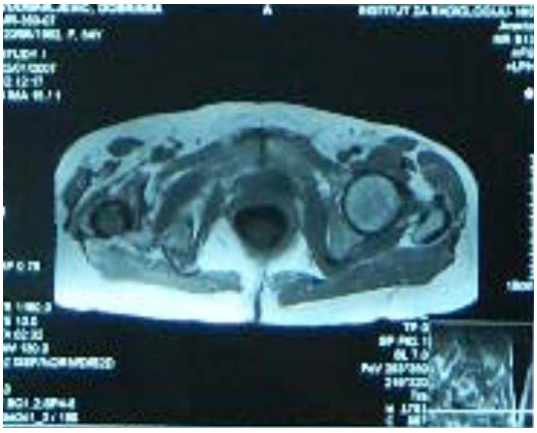


Figure 1. MRI of the femur: Erlenmeyer flask deformity of both femurs





Figures 2 and 3. MRI of the femur and right hip

As a part of the humanitarian program in February 2006, the treatment with imiglucerase (Cerezyme R) was started at a dose of 30 U/kg IV every two weeks. At the time of starting the therapy, the patient was immobile and bedridden, with intense pain in her right hip. She had a mild anaemia (Hgb 106 g/L). The magnetic resonance imaging (MRI) of the femur and right hip showed a fracture of the head of the right femur, and signs of infarction of the upper third of the right femur (Figures 2 and 3). The bone densitometry showed osteopenia, a T-score on the lumbar spine of -2.04, T-score on the hip joint of -0.3 (Figure 4).

In January 2007, after 11 months of imiglucerase therapy, a significant improvement in the patient's condition was registered. The patient moved with the help of a cane, and the pain in the right hip was less intense. Anaemia was corrected (Hgb 135 g/L), and chitotriosidase values decreased (5638 nmol/ml/h), as did acid phosphatase (8.25 U/L). The organ volumetry showed changes in the liver and spleen (liver 1283 ccm, spleen 238 ccm) (Figure 5). The bone densitometry (DEXA) showed osteopenia, a T-score on the lumbar spine of -1.7, T-score on the hip joint of -0.3 (Figure 6).

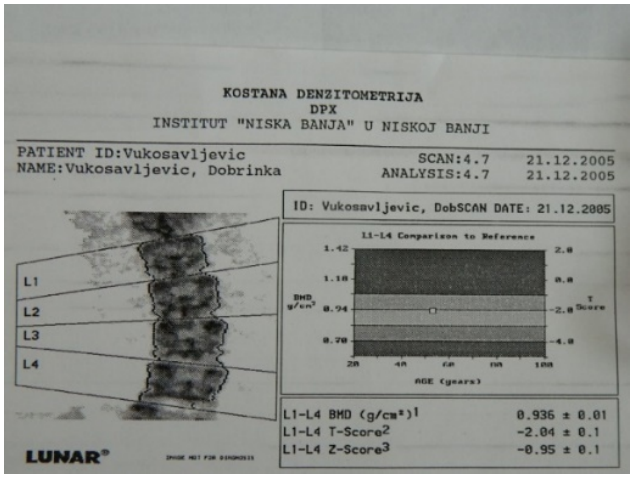


Figure 4. DEXA of the lumbar spine: osteopenia

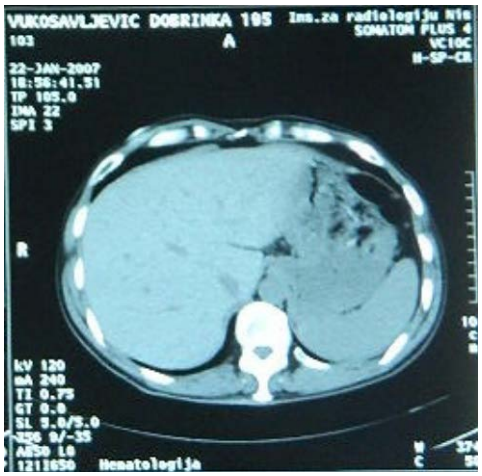


Figure 5. The organ volumetry of the liver and spleen

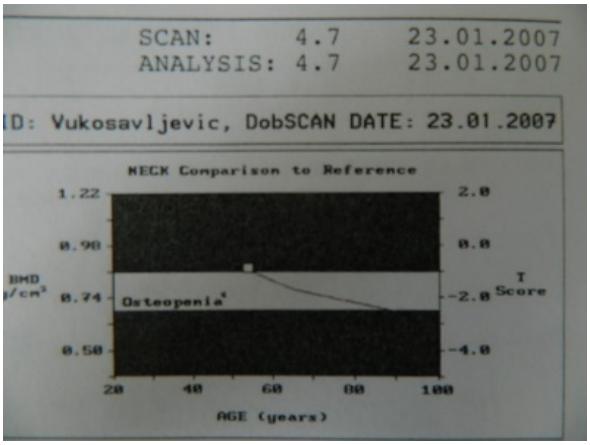


Figure 6. DEXA of the lumbar spine and hip joint—osteopenia

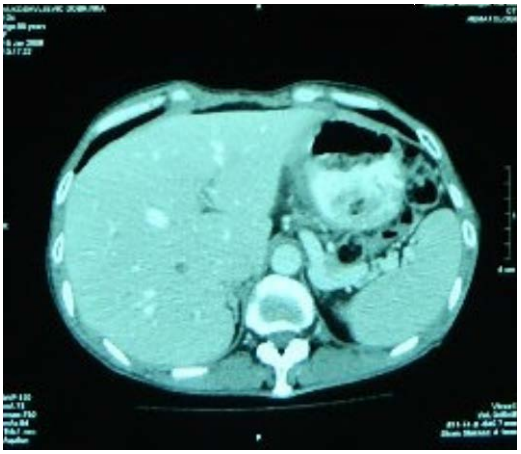


Figure 7. MSCT of the upper abdomen—an expansive change in the stomach

In February 2008, 24 months after the therapy, the patient was mobile and walked without the help of a cane, but she complained of pain, nausea and pain in the epigastrium. Because of the new complaints, an examination of the underlying disease was performed (blood count, biohumoral examination, chitotriosidase value of 3956 nmol/ml/h, echotomography and CT volumetry of the liver and spleen, MRI of the hips and lumbar spine) which indicated the stability of the underlying disease.

Because of the present complaints, in January 2008, an MSCT of the upper abdomen was performed, which indicated an expansive change in the stomach with a secondary spread in the liver (3 focal changes in the VII segment of the liver, the posterior wall of the stomach with irregular contours, greatly thickened in the antropyloric segment (Figure 7). An esophago-gastroduodenoscopy in January 2008 indicated a bizarre ulcer-vegetative change from the antrum to the corpus of the stomach which partially deformed the lumen of the stomach and this change was biopsied. In order to make a precise diagnosis, an MRI of the abdomen was performed in January 2008 which showed a suspect mass intraluminally in the stomach, and the presence of a cyst in the liver. The pathohistological findings of the biopsied changes in the stomach were obtained in January 2008 and indicated gastric adenocarcinoma, PH Gastric microglandular adenocarcinoma, Chronic gastritis with intestinal metaplasia.

In February 2008, the patient underwent total gastrectomy with splenectomy and cholecystectomy at the Clinic of Surgery of the Clinical Center Niš. The pathohistological findings of the operative material were obtained in March 2008. Microscopic findings of the stomach revealed superficial type of early gastric carcinoma

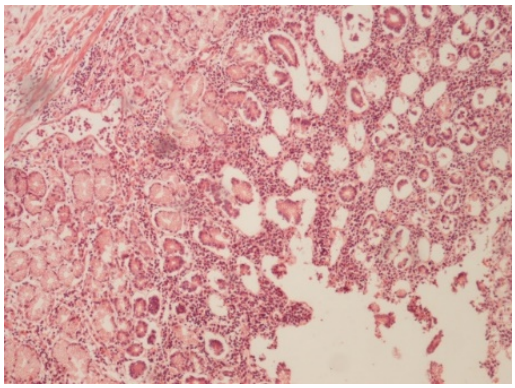
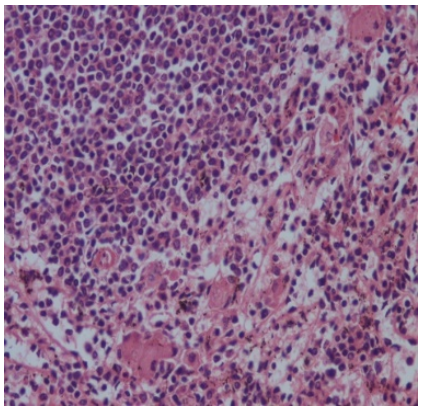
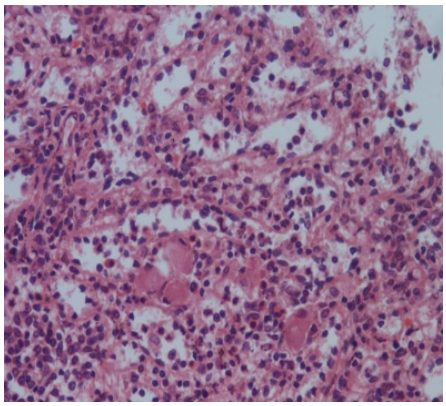


Figure 8. Adenocarcinoma ventriculi intramucosum (early cancer): HE x 150 (Hematoxylin and eosin stained)





Figures 9 and 10. Spleen with Gaucher cells. HE 100, HE X 200

Type 0-IIc surrounded by atrophic gastritis with intestinal metaplasia, chronic atrophic gastritis grade II with atypical foveolar hyperplasia grade I-II, gastric intramucosal adenocarcinoma (early cancer), surrounding lymph nodes without metastatic process (Figure 8), chronic cholecystitis with fibrosis calcification and atrophy, spleen with Gaucher cells (Figure 9, 10).

After the surgical intervention, the patient continued enzyme replacement therapy with imiglucerase in agreement with the responsible member of the Gauche registry.

In December 2010, the patient was in good general condition during the check-up, and she was actively mobile. The pain in the right hip was still present and the patient described it as a pain of low intensity. There were no significant complaints related to the digestive tract. Blood count and hemostasis tests were normal. Chitotriosidase activity was 3956 nmol/ml/h. X-ray and MRI of the hips and lumbar spine showed no significant changes compared to previous findings. Bone densitometry showed worse findings of osteoporosis in the lumbar spine (T-score was -2.7) and the left hip joint (T-score was -2.4). Echocardiography showed preserved global contractile function of the left ventricle, EF was 65%, and mean pressure in the right ventricle was 33 mmHg. The liver was without significant changes compared to the previous finding, determined by CT volumetry (liver volume was 1300 ccm). Electrophoresis and immunofixation of serum proteins were performed on several occasions, always without signs of monoclonal gammopathy.

The patient was on enzyme replacement therapy until 2011, when the therapy was stopped because of the unavailability of the drug due to the termination of the donation. Since 2015, a gradual worsening of the condition has been registered, a decrease in independent mobility, hip pains were more pronounced, there were deformities and swelling of both knees and the patient became bedridden again. Anaemia was registered (Hgb was 10.9g/dl), while leukocytes, platelets and hemostasis tests were normal. X-ray of the pelvis revealed a deformed pelvis. Changes predominated on the right, with deformity of the ipsilateral iliac and pubic bones and ischial axis. Bone structures of the first order were damaged. Changes dominated along the proximal metaphysis and epiphysis of the right femur, as well as in the acetabulum itself. The right hip joint was deformed, joint edges were destroyed, with

irregular bone structure and irregular linear marginal osteosclerosis (Figure 11).

X-ray of the knee showed that the distal half of the femur was deformed, club-like, thinned compact. The bone was inhomogeneous, with traces of darkness, in the distal third it looked like a cluster, which most likely corresponded to bone infarcts. The proximal ends of the tibia were deformed, with signs of fragmentation. The joint crack of both knees was narrowed and deformed, and the contours of the picture were disturbed (Figure 12).

X-ray of the lumbosacral spine showed degenerative changes in the lumbosacral vertebrae, narrowing of the intervertebral space L5-S1 and atrophy of bone tissue with signs of osteoporosis.

Bone densitometry shows severe osteoporosis in the lumbar spine, T-score was -5.2 (Figure 13).

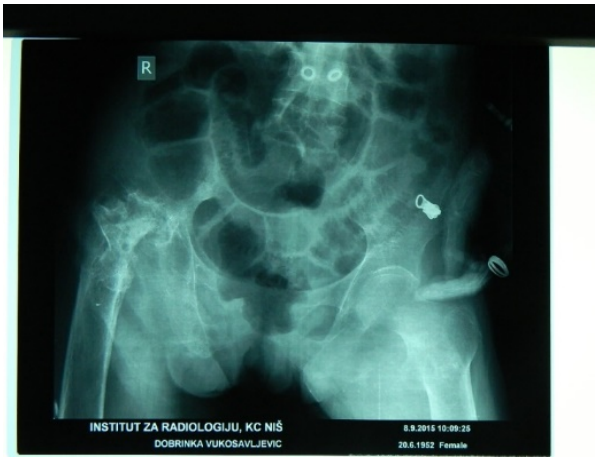


Figure 11. X-ray of the pelvis

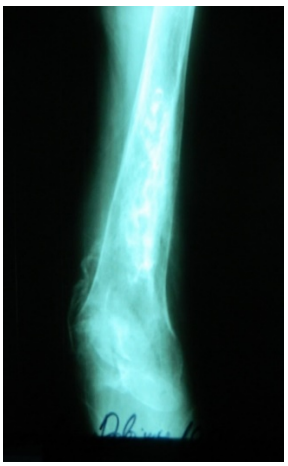


Figure 12. X-ray of the knee

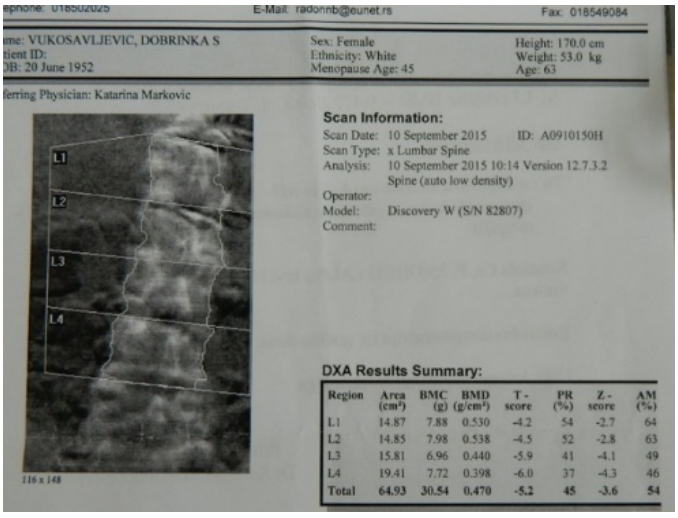


Figure 13. DEXA of the lumbar spine: severe osteoporosis

Discussion and conclusion

This is a case report of a rare association of GD and gastric cancer (26). Patients with GD have an increased risk of developing malignant diseases, most often lymphoproliferative, although solid tumours (hepatocellular carcinoma) have also been described (27–30). The association of GD with multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), chronic lymphocytic leukemia, marginal zone lymphoma and amyloidosis is found in the literature. A statistically increased risk of the

disease has been proven only for multiple myeloma (31–34).

As possible mechanisms of carcinogenesis in patients with Gaucher disease, the constant stimulation of the immune system by accumulated glucocerebroside as well as the carcinogenic action of glucocerebroside and its metabolites are mentioned. Zimran mentions the onset of malignancy as a complication of long-term enzyme therapy and suggests that in mild forms of the disease, treatment is not indicated, especially not with high doses, because the potential harm is greater than the benefit (19, 30, 35).

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GOŠEOVA BOLEST TIP 1 I KARCINOM ŽELUCA: PRIKAZ SLUČAJA

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Gošeova (Gaucher) bolest (GB) jeste lipozomalna bolest nakupljanja koja se nasleđuje autozomno-recesivno. U osnovi bolesti nalazi se mutacija gena koji kodira enzim glukocerebrozidazu. Klinička podela GB-a na tip 1, 2 i 3 zasniva se na odsustvu (tip 1) ili prisustvu (tip 2 i tip 3) manifestacija od strane centralnog nervnog sistema. Sa ciljem postavljanja definitivne dijagnoze određuju se nivo β-glukozocerebrozidaze u leukocitima i vrednost hitotriozidaze u serumu. Analiza genotipa od pomoći je u proceni tipa i težine bolesti. Od 1991. godine Gošeova bolest leči se enzimskom supstitucionom terapijom (EST). U ovom radu prikazuju se kliničke karakteristike bolesnice sa tipom 1 Gošeove bolesti kojoj je bolest dijagnostikovana novembra 2004. godine na Insititutu za hematologiju Univerzitetskog kliničkog centra Srbije. Bolesnica je bila heterozigotni nosilac mutacije N307S. Februara 2006. godine započeto je lečenje imiglucerazom (*Cerezyme*^{R}), sa dozom od 30 U po kilogramu telesne težine i. v. na svake dve nedelje. Iako je posle 24 meseca terapije zabeleženo značajno poboljšanje stanja bolesnice, ona se žalila na mučninu, nagon na povraćanje i bolove u epigastrijumu. Urađeni su multidetektorska kompjuterizovana tomografija (engl. *multislice computed tomography* – MSCT) gornjeg abdomena i ezofagogastroduodenoskopija sa biopsijom promene u želucu. Patohistološki (PH) nalaz promene u želucu ukazao je na postojanje adenokarcinoma želuca. Urađena je totalna gastrektomija sa splenektomijom i holecistektomijom. PH nalaz je pokazao da je posredi *adenocarcinoma ventriculi intramucosum* (*early cancer)*. Bolesnica je posle hirurške intervencije nastavila enzimsku supstitucionu terapiju imiglucerazom. Kod obolelih od GB-a povećan je rizik od nastanka malignih bolesti, najčešće limfoproliferativnih, mada je opisana i pojava solidnih tumora (npr. hepatocelularni karcinom). Prema našim saznanjima, Gošeova bolest udružena sa karcinomom želuca retko se pominje u literaturi.

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***Ključne reči**: Gošeova bolest, enzimska supstituciona terapija, imigluceraza, karcinom želuca*

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