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HEMATOLOGICAL PARAMETERS IN CHILDREN WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION

HEMATOLOŠKI PARAMETRI KOD DECE SA INFEKCIJOM TEŠKOG AKUTNOG RESPIRATORNOG SINDROMA KORONA-VIRUS 2

Dejan DOBRIJEVIĆ[1], Biljana VUČKOVIĆ[2, 3], Jasmina KATANIĆ[1, 4], Goran RAKIĆ[5, 6], Jelena ANTIĆ[7, 8] and Velibor ČABARKAPA[2, 3]

Summary

Introduction. Recently, there has been a need to use more readily available parameters to assess the severe acute respiratory syndrome coronavirus 2 infection in children. **Material and Methods.** A single-center retrospective study included 30 children with severe acute respiratory syndrome coronavirus 2 infection who were admitted to the Isolation Department of the Institute for Child and Youth Health Care of Vojvodina from April to September 2020. A complete blood count with differential was performed. Additionally, systemic inflammatory index, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were calculated. For comparison, age- and sex-matched 30 children negative for severe acute respiratory syndrome coronavirus 2 were included in the study. **Results.** In the period from April to September 2020, 30 laboratory-confirmed cases of coronavirus-19, aged 0 – 17 years, were admitted to the Institute for Child and Youth Health Care of Vojvodina. The age was not a risk factor for the development of coronavirus-19 ($p = 0.707$; OR: 1.018; 95% CI: 0.927 – 1.119). The comparison of hematological parameters of severe acute respiratory syndrome coronavirus 2 status showed that hemoglobin concentration ($p < 0.01$) and hematocrit ($p < 0.01$) were lower, and the percentage of neutrophil granulocytes ($p < 0.05$) was higher among severe acute respiratory syndrome coronavirus 2 positive children. Furthermore, it was found that some severe acute respiratory syndrome coronavirus 2 positive children had a higher ($p < 0.01$), while others had a lower ($p < 0.01$) percentage of lymphocytes. The systemic inflammatory index, the ratio of neutrophils to lymphocytes, and the ratio of platelets to lymphocytes, were not found to be statistically significantly different ($p > 0.05$). **Conclusion.** Low hemoglobin and hematocrit levels, a high percentage of neutrophil granulocytes, and a non-physiological percentage of lymphocytes (both, low and high) may have a diagnostic significance in children with severe acute respiratory syndrome coronavirus 2 infection.

Key words: Hematologic Tests; COVID-19; SARS-CoV-2; Coronavirus Infections; Child; Blood Cell Count; Hematocrit; Hemoglobins; Neutrophils; Lymphocytes

Sažetak

Uvod. U poslednje vreme se javlja potreba za upotrebom lakše dostupnih parametara za procenu SARS-CoV-2 infekcije kod dece. **Materijal i metode.** Sprovedena je retrospektivna studija u koju je uključeno 30 dece sa SARS-CoV-2 infekcijom, primljenih na Odeljenje za izolaciju Instituta za zdravstvenu zaštitu dece i omladine Vojvodine, od aprila do septembra 2020. godine. Pacijentima je određena kompletna krvna slika sa diferencijalnom krvnom slikom. Dodatno su izračunati sistemski inflamatorni indeks, odnos neutrofila i limfocita i odnos trombocita i limfocita. Za poređenje je u studiju uključeno još 30 dece negativne na SARS-CoV-2 sličnog uzrasta i pola. **Rezultati.** U periodu od aprila do septembra 2020. godine, 30 laboratorijski potvrđenih slučajeva COVID-19, uzrasta do 17 godina, primljeno je na Institut za zdravstvenu zaštitu dece i omladine Vojvodine. Uzrast nije bio faktor rizika za razvoj COVID-19 ($p = 0,707$; OR: 1,018; 95% CI: 0,927–1,119). Poređenje hematoloških parametara prema SARS-CoV-2 statusu je pokazalo da su vrednosti hemoglobina ($p < 0,01$) i hematokrita ($p < 0,01$) bile niže, a procenat neutrofilnih granulocita ($p < 0,05$) viši kod dece pozitivne na SARS-CoV-2. Utvrđeno je da su pojedini SARS-CoV-2 pozitivni pacijenti imali viši ($p < 0,01$), dok su drugi imali niži ($p < 0,01$) procenat limfocita. Sistemski inflamatorni indeks, odnos neutrofila i limfocita i odnos trombocita i limfocita nisu se statistički značajno razlikovali ($p > 0,05$). **Zaključak.** Niske vrednosti hemoglobina i hematokrita, visok procenat neutrofilnih granulocita i nefiziološki procenat limfocita (kako viši, tako i niži) mogu imati dijagnostički značaj kod dece sa SARS-CoV-2 infekcijom.

Ključne reči: hematološki testovi; COVID-19; SARS-CoV-2; koronavirus infekcija; dete; kompletna krvna slika; hematokrit; hemoglobin; neutrofili; limfociti

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Abbreviations

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
WHO – World Health Organization
COVID-19 – coronavirus-19 disease
Ig – immunoglobulin
CoVs – coronaviruses
RNA – ribonucleic acid
SARS – severe acute respiratory syndrome
MERS – Middle East respiratory syndrome
PCR – polymerase chain reaction
SII – systemic inflammatory index
NLR – neutrophil-lymphocyte ratio
PLR – platelet-lymphocyte ratio

Introduction

An emerging microbe, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was firstly confirmed in patients with pneumonia in Wuhan, China, in December 2019 [1]. It spread rapidly throughout the whole country and, eventually, to other parts of the world. The global pandemic was declared by the World Health Organization (WHO) on March 11th, 2020. [2] There have been more than 72 million confirmed cases of coronavirus so far, and the death toll exceeds one million, which indicates that this infection is a public health emergency [3]. Coronaviruses (CoVs) are a family of ribonucleic acid (RNA) viruses that replicate in the cytoplasm of infected cells and are prone to mutations, helping them to adapt and to infect the host anew [4]. The CoVs are predominantly responsible for respiratory diseases. So far, there have been two significant outbreaks - severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in 2002 and 2012, respectively [5]. The SARS-CoV-2 causes the coronavirus disease (COVID-19), a form of respiratory and systemic zoonosis, which presents with a wide range of symptoms. While some patients may suffer from serious disease forms, such as SARS, others have mild upper-respiratory-tract symptoms, or they are even asymptomatic. These asymptomatic patients especially contribute to the complexity of disease transmission [6]. Making timely diagnosis and therapeutic decisions is of the utmost importance. Given that at the time a significant number of patients with respiratory symptoms are flooding in and the results of etiological polymerase chain reaction (PCR) tests cannot offer results instantly, it is necessary to utilize other, easier accessible laboratory parameters as criteria for SARS-CoV-2 infection [7]. Currently, the official guidelines (Guidelines of the National Health Commission of China for COVID-19, 5th edition and the WHO interim guidelines) recommend white blood cell count and number of lymphocytes as significant for early diagnosis [8]. Several alterations of hematological parameters have been described in the current literature. It has been noted that in the early stage of the disease onset, total leukocyte count is normal and the lymphocyte count is reduced. The lymphocyte count is found to be significant for the prognosis of patients with COVID-19. Another common laboratory finding is thrombocytosis [9]. Some also suggest that eosinopenia is an important predictor of the outcome [8]. All data were primarily documented from adult cases. The information about hematological abnormalities in children with SARS-CoV-2 infection are very limited worldwide, since the incidence of the disease in the pediatric population is significantly lower than in the adults [9]. Additionally, the interpretation of these results varies to a significant extent [10]. Our study aimed to analyze hematological parameters alterations in children with SARS-CoV-2 infection. The secondary objective of the study was to compare the baseline hematological parameters in SARS-CoV-2 positive children with age- and sex-matched SARS-CoV-2 negative patients.

Material and Methods

A single-center retrospective study included 30 SARS-CoV-2 pediatric patients of both sexes. Patients with COVID-19 admitted to the Isolation Department of the Institute for Child and Youth Health Care of Vojvodina from April to September 2020 were enrolled in the study. The diagnosis of COVID-19 was confirmed by real-time PCR performed on nasopharyngeal and throat swab specimens. The demographic data and the hematological findings from the blood samples collected on the day of admission were recorded. None of the patients received any kind of treatment prior to blood sampling. The samples were tested using a hematology analyzer Siemens Advia 2120 for complete blood count with differential white blood cell count. The following hematological tests were collected: white blood cells count, red blood cells count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelet count, platelet distribution width, plateletcrit, mean platelet volume, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count, lymphocyte percentage, absolute monocyte count, monocyte percentage, absolute eosinophil count, eosinophil percentage, absolute basophil count, and basophil percentage. Furthermore, systemic inflammatory index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) were calculated. For comparative analysis, age- and sex-matched 30 SARS-CoV-2 negative patients were also enrolled in the study. All of them were children with different non-infectious and non-inflammatory diagnosis admitted to the Institute for Child and Youth Health Care of Vojvodina and tested with an immunochromatographic immunoglobulin (IgM/IgG) antibody assay (Innovita COVID-19 IgM/IgG Rapid Test) for COVID-19 prior to admission. Given that pediatric population is very heterogeneous regarding reference ranges, it was not possible to split them into age- and sex-matched subgroups, due to insufficient patient number in both groups. Therefore, hematological values were categorized according to the age- and sex-related hematology reference ranges: ”physiological“, ”below physiological“ and ”above physiological“. Informed consent

Table 1. Age and sex distribution in the control and the COVID-19 group
Tabela 1*. Starosna i polna struktura kontrolne i COVID-19 grupe*

Patient features/*Karakteristike pacijenata*		Total/*Ukupno* (n=60)	Control group/*Kontrolna grupa* (n=30)	COVID-19 group/*COVID-19 grupa* (n=30)	p-value *p-vrednost*
Gender/*Pol*	Female/*Ženski*	35 (58.3%)	17 (56.7%)	18 (60%)	0.793§
	Male/*Muški*	25 (41.7%)	13 (43.3%)	12 (40%)	
Age (years)‡ *Uzrast (godine)*	Total *Ukupno*	5.93 ± 5.44	6.20 ± 5.63	5.67 ± 5.32	0.712†
		5.50 (0.30 – 10.00)	5.50 (0.25 – 10.00)	5.00 (0.31 – 10.25)	
	Female *Ženski*	6.01 ± 6.13	6.80 ± 6.63	5.27 ± 5.70	0.470†
		5.00 (1.50 – 10.00)	6.00 (1.25 – 10.00)	1.50 (1.65 – 9.00)	
	Male *Muški*	5.82 ± 4.42	5.41 ± 4.10	6.27 ± 4.89	0.638†
		6.00 (0.25 – 10.00)	5.00 (0.23 – 10.00)	6.50 (0.18 – 13.50)	

‡ Mean ± standard deviation/median (interquartile range Q1-Q3)/*aritmetička sredina ± standardna devijacija/medijana (interkvartalni opseg: Q1-Q3);* § Chi-square test/*Hi-kvadrat test;* † Independent samples t-test/*Studentov t-test*

Table 2. Comparison of hematological parameters between the control and COVID-19 group
Tabela 2. *Poređenje hematoloških parametara između kontrolne i COVID-19 grupe*

Hematological parameter *Hematološki parametar*	Control group/*Kontrolna grupa* (n=30)			COVID-19 group/*COVID-19 grupa* (n=30)			p-value§ *p-vrednost*
	Physiological value (% of patients)/*Fiziološke vrednosti (% pacijenata)*	Under physiological value (% of patients)/*Ispod fizioloških vrednosti (% pacijenata)*	Above physiological value (% of patients)/*Iznad fizioloških vrednosti (% pacijenata)*	Physiological value (% of patients)/*Fiziološke vrednosti (% pacijenata)*	Under physiological value (% of patients)/*Ispod fizioloških vrednosti (% pacijenata)*	Above physiological value (% of patients)/*Iznad fizioloških vrednosti (% pacijenata)*	
RBC	96.7	0	3.3	73.3	16.7	10.0	0.031
HGB	100	0	0	76.7	23.3	0	**0.005**
HCT	100	0	0	60.0	33.3	6.7	**0.001**
MCV	76.7	13.3	10.0	73.3	16.7	10.0	0.936
MCH	80.0	10.0	10.0	90.0	6.7	3.3	0.502
MCHC	83.3	3.3	13.4	76.7	13.3	10.0	0.363
RDW	76.7	10.0	13.3	73.3	20.0	6.7	0.403
WBC	86.7	10.0	3.3	70.0	16.7	13.3	0.243
Neutr#	86.7	3.3	10.0	63.0	18.5	18.5	0.086
Lymph#	86.7	3.3	10.0	63.0	22.2	14.8	0.065
Mono#	83.3	10.0	6.7	74.1	14.8	11.1	0.690
Eos#	86.7	0	13.3	88.9	0	11.1	0.799
Baso#	93.3	6.7	0	100	0	0	0.172
Neutr%	93.3	6.7	0	66.7	14.8	18.5	**0.021**
Lymph%	93.3	0	6.7	59.3	14.8	25.9	**0.007**
Mono%	76.7	6.7	16.6	66.7	3.7	29.6	0.477
Eos%	83.3	0	16.7	88.9	0	11.1	0.547
Baso%	96.7	0	3.3	92.6	0	7.4	0.492
PLT	83.3	0	16.7	73.3	3.4	23.3	0.467
MPV	57.1	42.9	0	44.8	55.2	0	0.352
PCT	93.3	3.3	3.4	83.3	3.4	13.3	0.373
PDW	53.3	46.7	0	36.7	63.3	0	0.194

Legend/*Legenda:* RBC - Red Blood Cells/*Eritrociti*; HGB - Hemoglobin Concentration/*Koncentracija hemoglobina*; HCT - Hematocrit/*Hematocrit*; MCV - Mean Corpuscular Volume/*Srednja zapremina eritrocita*; MCH - Mean Corpuscular Hemoglobin/*Srednja količina hemoglobina u eritrocitu*; MCHC - Mean Corpuscular Hemoglobin Concentration/*Prosečna koncentracija hemoglobina na litar eritrocita*; RDW - Red Distribution Width/*Raspodela eritrocita po volumenu*; WBC – White Blood Cells/*Leukociti*; Neutr# - Absolute neutrophil count/*Apsolutna vrednost neutrofila*; Lymph# - Absolute lymphocyte count/*Apsolutna vrednost limfocita*; Mono# - Absolute monocyte count/*Apsolutna vrednost mono*cita; Eos# - Absolute eosinophil count/*Apsolutna vrednost eozinofila*; Baso# - Absolute basophil count/*Apsolutna vrednost bazofila*; Neutr% - Neutrophil percentage/*Procenat neutrofila*; Lymph% - Lymphocyte percentage/*Procenat limfocita*; Mono% - Monocyte percentage/*Procenat monocita*; Eos% - Eosinophil percentage/*Procenat eozinofila*; Baso% - Basophil percentage/*Procenat bazofila*; PLT - Platelets/*Trombociti*; MPV - Mean Platelet Volume/*Srednja zapremina trombocita*; PCT – Plateletcrit/*Platelekrit*; PDW - Platelet Distribution Width/*Raspodela trombocita po volumenu*; § Chi-square test and Fisher's exact test/*Hi-kvadrat test i Fišerov test*
The values in bold are statistically significant/*Boldovane vrednosti su statistički značajne*

Table 3. Comparison of hematological indices and ratios between the control and COVID-19 group
Tabela 3. *Poređenje hematoloških indeksa i odnosa između kontrolne i COVID-19 grupe*

Index/Ratio *Indeks/Odnos*	Control group (n=30) *Kontrolna grupa (n=30)*	COVID-19 group (n=30) *COVID-19 grupa (n=30)*	p-value/*p-vrednost*†
SII‡	419.45 ± 264.06 358.85 (252.75 – 633.03)	1128.76 ± 1785.54 370.65 (160.29 – 1082.31)	0.578
NLR‡	1.53 ± 0.85 1.40 (0.95 – 1.97)	3.14 ± 3.73 1.45 (0.42 – 4.88)	0.662
PLR‡	109.99 ± 44.46 100.92 (73.81 – 133.06)	169.63 ± 132.71 130.08 (70.06 – 244.93)	0.138

SII - Systemic inflammatory index/*Sistemski inflamatorni indeks*; NLR - Neutrophil-Lymphocyte ratio/*Odnos neutrofila i limfocita*; PLR - Platelet-Lymphocyte ratio/*Odnos trombocita i limfocita;* ‡ Mean ± standard deviation/median (interquartile range: Q1-Q3)/*Aritmetička sredina ± standardna devijacija/medijana (interkvartalni opseg: Q1-Q3);* † Independent samples t-test/*Studentov t-test*

was waived because of the retrospective nature of the study and the analysis was based on anonymous laboratory data. Statistical analysis (descriptive and inferential) was performed using the Statistical Package for the Social Sciences version 26.0 software. For categorical variables, Chi-square test and Fisher's exact test were performed, for continuous variables with normal distribution t-test, and for non-normally distributed continuous variables Mann-Whitney U test were used. Before running any test for continuous variables, homogeneity of variance, i.e. normal distribution within each group, was checked. Binary logistic regression was used to determine risk factors for COVID-19. The study was approved by the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina.

Results

In total, 30 cases with SARS-CoV-2 infection were admitted to the Institute for Child and Youth Health Care of Vojvodina between April and September 2020, with an average age of 5.67 ± 5.32 years and a median age of 5.00 years; 60% of them were females, with a mean age of 5.27 ± 5.70 years and a median of 1.50 years, and 40% were males, with a mean age of 6.27 ± 4.89 years and a median of 6.50 years. In regard to the SARS-CoV-2 status, there was no statistically significant difference in gender and age ($p > 0.05$) **(Table 1)**. Binary logistic regression analysis showed that age was not a risk factor for COVID-19 ($p = 0.707$; OR: 1.018; 95% CI: 0.927 – 1.119). No confounding factors were identified. A statistically significant difference was found between the test groups in hemoglobin concentration ($p < 0.01$) and hematocrit ($p < 0.01$) which were lower, while the percentage of neutrophils ($p < 0.05$) was higher among SARS-CoV-2 positive children. Furthermore, it was determined that some patients had a higher lymphocyte percentage ($p < 0.01$), while others had a lower lymphocyte percentage ($p < 0.01$) **(Table 2)**. Comparison of hematological parameters according to SARS-CoV-2 status showed no statistically significant difference regarding white blood cell count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelet count, platelet distribution width, plateletcrit, mean platelet volume, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, monocyte percentage, absolute eosinophil count, eosinophil percentage, absolute basophil count, and basophils percentage ($p > 0.05$). The SII, NLR, PLR were not found to be significant ($p > 0.05$) **(Table 3)**.

Discussion

Considering the global incidence and mortality risk of COVID-19, rapid and accurate diagnosis and therapeutic decisions are of utmost importance [11]. Real-time PCR tests provide definitive diagnosis of SARS-CoV-2 infection, but given that a lot of patients with respiratory symptoms are flooding in and laboratory capacities are limited and insufficient, the time it takes to get PCR tests results may be prolonged [12]. Consequently, there is a need to utilize other, easier accessible laboratory parameters as criteria for SARS-CoV-2 infection. The clinical hematology laboratory plays an important role by providing markers useful for quick assessment and triage of COVID-19 patients [1, 13]. In our study, 30 children with average age of 5.67 years and 40% males, tested positive for SARS-CoV-2 by real-time PCR. In a multicenter, multinational study conducted by Götzinger et al., the mean age was 5.0 years and 53% of patients were male [14]. Another study by Tagarro et al. showed a mean age of 3.3 years and 44% of the patients were male [15]. Furthermore, Cai et al. revealed that 40% of all patients were male and with a mean age of 6.17 years [16]. Thus, it can be said that our study is similar regarding the age-sex distribution in comparison to other researches in pediatric population. During the COVID-19 infection, patients are in hypermetabolic state and oxygen demands of peripheral tissues are increasing. Low hemoglobin concentration leads to decreased ability of patients' body to support these increased demands [17]. Additionally, anemic children are two times more susceptible to lower respiratory tract infections [18]. In our study, low hemoglobin concentration and hematocrit val-

ues were found in SARS-CoV-2 positive children. The same result was noted in Lu et al. study [19]. Although neutrophilia is usually not present in viral infections, it can be found during the early phase of infection. However, it remains unclear whether it is the result of virus-induced cytopathy or host response to viral infection [20]. In our study group, the percentage of neutrophils was found to be higher in SARS-CoV-2 positive children. Even though neutrophilia has been commonly reported in adult population with COVID-19 [21], there is still not enough data to support this in pediatric population. Reactive lymphocytosis commonly occurs in patients with viral infections and it is more likely to begin in children than in adults [22], but in conditions like COVID-19, natural killer cells and T-cells become exhausted and their count starts decreasing which leads to lymphopenia [23]. Therefore, both increased and decreased lymphocyte count can be present in COVID-19 patients. We have determined that some patients had higher percentage of lymphocytes, while others had lower percentage of lymphocytes. The study of Xu et al. showed the same findings [24]. The SII, NLR and PLR are inflammation-related indicators [25, 26]. Eren et al. reported that low values of SII and NLR may have diagnostic properties in SARS-CoV-2 positive patients [26]. In our study, none of these indicators were found to be significant. This result is expected considering that children in our study group presented with mild to moderate symptoms.

Conclusion

Our results show that low hemoglobin/hematocrit, high percentage of neutrophils and non-physiological lymphocyte percentage (both, low and high) may have diagnostic properties in children with severe acute respiratory syndrome coronavirus 2 infection.

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020;382(13):1199-207.

2. Johns Hopkins University and Medicine. Coronavirus Resource Center [Internet]. Baltimor: Johns Hopkins University and Medicine. 2021 [cited 2021 Feb 12]. Available from: https://coronavirus.jhu.edu/.

3. COVID-19 coronavirus pandemic [Internet]. 2021 [cited 2021 Feb 12]. Available from: Https://www.worldometers.info/coronavirus/.

4. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424-32.

5. Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus disease 2019–COVID-19. Clin Microbiol Rev. 2020;33(4):1-48.

6. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:m606.

7. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med. 2020;58(7):1135-8.

8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

9. Tiwari N, Nath D, Madan J, Bajpai P, Madan U, Singh S. Novel insights into the hematological parameter abnormalities in pediatric COVID-19 cases: observation from a preliminary study of 11 pediatric COVID-19 cases in a tertiary care center of north India. Saudi Journal of Pathology and Microbiology. 2020;5(5):276-84.

10. Ma H, Hu J, Tian J, Zhou X, Li H, Laws MT, et al. A single-center, retrospective study of COVID-19 features in children: a descriptive investigation. BMC Med. 2020;18(1):123.

11. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China - key questions for impact assessment. N Engl J Med. 2020;382(8):692-4.

12. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):1-8.

13. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020;42(Suppl 1):11-8.

14. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-61.

15. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. JAMA Pediatr. In press. doi:10.1001/jamapediatrics.2020.1346.

16. Jiehao C, Jin X, Daojiong L, Zhi Y, Lei X, Zhenghai Q, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020;71(6):1547-51.

17. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz Z, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol. 2020;35(8):763-73.

18. Mourad S, Rajab M, Alameddine A, Fares M, Ziade F, Merhi BA. Hemoglobin level as a risk factor for lower respiratory tract infections in Lebanese children. N Am J Med Sci. 2020;2(10):461-6.

19. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, et al. Symptomatic infection is associated with prolonged duration of viral shedding in mild coronavirus disease 2019: a retrospective study of 110 children in Wuhan. Pediatr Infect Dis J. 2020;39(7):95-9.

20. Camp JV, Jonsson CB. A role for neutrophils in viral respiratory disease. Front Immunol. 2017;8:550.

21. Henry B, Cheruiyot I, Vikse J, Mutua V, Kipkorir V, Benoit J, et al. Lymphopenia and neutrophilia at admission predicts severity and mortality in patients with COVID-19: a meta-analysis. Acta Biomed. 2020;91(3):1-16.

22. Riley LK, Rupert J. Evaluation of patients with leukocytosis. Am Fam Physician. 2015;92(11):1004-11.

23. Fathi N, Rezaei N. Lymphopenia in COVID-19: therapeutic opportunities. Cell Biol Int. 2020;44(9):1792-7.

24. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020;26(4):502-5.

25. Geng Y, Shao Y, Zhu D, Zheng X, Zhou Q, Zhou W, et al. Systemic Immune-Inflammation Index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis. Sci Rep. 2016;6:39482.

26. Usul E, San I, Bekgoz B, Sahin A. Role of hematological parameters in COVID-19 patients in the emergency room. Biomark Med. 2020;14(13):1207-15.

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ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES - A PRELIMINARY STUDY

PROCENA KVALITETA ŽIVOTA POVEZANOG SA ZDRAVLJEM PEDIJATRIJSKIH PACIJENATA OBOLELIH OD DIJABETESA MELITUS TIP 1 – PRELIMINARNO ISTRAŽIVANJE

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Summary

Introduction. Diabetes mellitus is a chronic disease that affects all aspects of life of pediatric patients, especially the psychological aspect, and hence the health-related quality of life. The aim of the study was to evaluate the effects of sociodemographic and clinical factors of pediatric patients with type 1 diabetes mellitus on self-assessment of health-related quality of life. **Material and Methods.** The research was conducted as a cross-sectional study. The sample included 37 pediatric patients aged 8 to 18 years, who were diagnosed with the type 1 diabetes mellitus six months or longer before enrollment into the study. The research instruments used in the study were the Serbian version of child-friendly EuroQol-5D-Y youth questionnaire and medical history data (gender, age, time since diagnosis - in years, glycosylated hemoglobin values, type of insulin therapy). **Results.** The total score of general health on the visual analogue scale was 80.54 on average (standard deviation - 20.87). A negative correlation was found between the total score on the visual analogue scale and the duration of diabetes ($\rho = -0.329$, $p < 0.05$). The statistical significance of the difference in the distribution of respondents' responses in relation to the type of insulin therapy was confirmed in the domain "Feeling of concern" ($\chi 2\ (2) = 7.19$, $p < 0.05$). **Conclusion.** The key determinants that influenced the self-assessment of the health-related quality of life in pediatric patients with type 1 diabetes mellitus are duration of the disease and the use of insulin analogues.

Key words: Diabetes Mellitus, Type 1; Quality of Life; Child; Adolescent; Surveys and Questionnaires; Diagnostic Self Evaluation; Health Status; Glycated Hemoglobin A; Insulin

Sažetak

Uvod. Dijabetes melitus je hronično oboljenje koje utiče na sve aspekte života pedijatrijskog pacijenta-posebno na psihološki i samim tim na kvalitet života uslovljen zdravljem. Cilj rada je bio da se proceni uticaj sociodemografskih i kliničkih karakteristika pedijatrijskih pacijenata obolelih od dijabetesa melitus tip 1 na samoprocenu kvaliteta života uslovljenog zdravljem. **Materijal i metode.** Istraživanje je sprovedeno kao studija preseka. Uzorak je obuhvatio 37 pedijatrijskih pacijenata uzrasta od osam do 18 godina, kojima je dijabetes tip 1 dijagnostikovan pre šest meseci ili duže pre uključivanja u studiju. Korišćeni instrumenti istraživanja su srpska verzija upitnika za mlade *EuroQol-5D-Y* i dokumentacioni list za prikupljanje podataka o pacijentu (pol, uzrast, vreme proteklo od postavljanja dijagnoze – u godinama, vrednost glikoziliranog hemoglobina i vrsta insulinske terapije). **Rezultati.** Ukupna ocena opšteg zdravstvenog stanja na vizuelno analognoj skali prosečno je iznosila 80,54 (standardna devijacija = 20,87). Zapažena je negativna korelacija između ukupnog skora na vizuelno analognoj skali i dužine trajanja dijabetesa ($\rho = -0.329$, $p < 0,05$). Statistička značajnost razlike distribucije odgovora ispitanika u odnosu na vrstu insulinske terapije potvrđena je u domenu *Osećaj zabrinutosti* ($\chi^2\ (2) = 7,19$, $p < 0,05$). **Zaključak.** Ključne determinante koje su uticale na samoprocenu kvaliteta života uslovljenog zdravljem pedijatrijskih pacijenata obolelih od dijabetesa melitus tip 1 su: dužina trajanja bolesti i upotreba insulinskih analoga.

Ključne reči: dijabetes melitus, tip 1; kvalitet života; dete; adolescent; istraživanja i upitnici; samoprocena; zdravstveni status; glikozilizirani hemoglobin; insulin

Introduction

The concept of health-related quality of life (HRQOL), as a subset of patient-reported health outcomes, has been the subject of research of many studies, since improvement of HRQOL is certainly the ultimate goal of modern therapeutic regimens. The HRQOL is closely related and affected by the disease itself, process of health care provision, health promotion, patient adherence, satisfaction with therapy effects, and provision of pharmaceutical services [1].

Type 1 diabetes mellitus (T1DM) is a chronic disease that affects all aspects of a pediatric patient's life, especially the psychological aspect and thus the HRQOL [2–4]. The life of these chronically ill chil-

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Abbreviations
HRQOL – health-related quality of life
T1DM – type 1 diabetes mellitus
HbA1c – glycosylated hemoglobin
VAS – visual analogue scale
CGM – continuous glucose monitoring
EQ-5D-Y – EuroQol-5D instrument, version EQ-5D-Y

dren is specific, because management of T1DM is often complex and requires a high degree of patient and family involvement, decision making and regular glucose monitoring, injections of insulin and dose adjustments, carbohydrate estimation, therapy adjustments according to physical activity, emotional status, illness or infections, alcohol intake. Children with T1DM rate their own HRQOL as similar to their healthy peers [2–5], but they report disease specific problems, which are described in the literature [2, 6–20]. Previous studies highlighted that several factors are associated with poor metabolic control and worse HRQOL in children with T1DM such as: female gender, older adolescents, lower family income, social minority status, single parenthood, and lower level of adherence to treatment [2, 3].

The analysis of the National Diabetes Registry of Serbia for 2010 [21], 2014 [22], and 2017 [23], showed a large annual increase of newly diagnosed pediatric patients with T1DM, especially in those aged 5 – 9 and 10 – 14 years. Todorović et al. found that during the ten-year period (from January 2007 to January 2017), 501 children with newly diagnosed T1DM were hospitalized at the Mother and Child Healthcare Institute of Serbia "Dr. Vukan Čupić" [6]. Therefore, the aim of the study was to assess the HRQOL in pediatric patients with T1DM and its association with sociodemographic (age, gender, and time since diagnosis in years) and clinical factors (glycosylated hemoglobin (HbA1c) levels and type of insulin therapy). The following hypothesis was made: age, duration of diabetes (in years) and HbA1c% are negatively associated with HRQOL. In addition, female gender and pediatric patients receiving insulin analogues are even more likely to have suboptimal HRQOL in at least one domain.

Material and Methods

An observational cross-sectional study was conducted at the Mother and Child Health Care Institute of Serbia "Dr. Vukan Čupić" in the period from May 30, 2019 to July 4, 2019. The study protocol was approved by the Hospital Ethics Committee (No. 8/21 May 21, 2019) and was performed in accordance with the Declaration of Helsinki. A permission for using the Serbian version of child-friendly EuroQol-5D instrument (version EQ-5D-Y) (youth) was obtained from the EuroQol team.

The study included pediatric T1DM patients aged from 8 to 18 years, with multiple daily injections of insulin. Exclusion criteria were: children younger than 8 years at the time of recruitment, T1DM diagnosis made during the previous 6 months, subjects with cognitive problems, and children and adolescents with other types of diabetes. The eligible patients were recruited by a medical doctor after medical examination. According to the ethical requirements, every pediatric patient and his/her parent were informed about the study objectives in writing and signed informed consent was obtained from both of them. The pediatric patients filled out the EQ-5D-Y instrument in a separate room to provide a suitable environment and privacy. Their parents were allowed to be present as well as researchers if they had problems and ambiguities with filling out the questionnaire. The survey included EQ-5D-Y instrument, documentation sheet (to collect demographic and clinical characteristics of patients) and informed consent of the patients/parents. Each of these documents was identically coded for each patient.

Basic characteristics of patients were presented dividing patients into two predetermined groups (8 – 12.9 and 13 – 18 years) following the classification of the Teens Eating for Energy and Nutrition at School study [24]. The quality of life of patients was compared between groups in respect to years when the diagnosis of T1DM was confirmed. Patients were divided into groups: 0 – 4.9; 5 – 9.9; 10 – 14.9; and 15 – 18 years, according to the form of the National Diabetes Registry in Serbia [21–23].

Socio-demographic and clinical data were collected from the electronic medical data records (Heliant Health Information System). The sociodemographic data of patients included: gender, age, and time since diagnosis in years. Clinical data included: HbA1c% values and type of insulin therapy.

The levels of HbA1c% (as an indicator of metabolic control of disease and risk of acute and chronic complications of T1DM) were measured by immunoturbidimetric method using automatic Roche Cobas c 501analyzer, in the biochemical laboratory of the Mother and Child Health Care Institute of Serbia "Dr. Vukan Čupić". The analyses were performed by a medical biochemistry specialist. According to the levels of HbA1c%, pediatric patients were divided into four groups: group with ideal metabolic control (HbA1c < 5.7%), group with good metabolic control (HbA1c% = 5.8 – 7.4%), group with unstable metabolic control (with HbA1c% = 7.5 – 8.5%) and group of patients with poor metabolic control (HbA1c% > 8.5%).

The child-friendly instrument EQ-5D-Y was used to assess the HRQOL. It consists of self-reported EQ-5D-Y descriptive system and a visual analogue scale (VAS). The descriptive system covers 5 domains/dimensions: mobility, self-care, usual activities, pain-discomfort, and anxiety/depression. The responses were graded using a 3-level Likert scale (no problems, moderate, and serious problems). The VAS describes the general health status on a scale from 0 (the worst health status) to 100 (the best possible health status). The self-reported EQ-5D-Y instrument is more comprehensible and suitable version than EQ-5D for children and adolescents, and it is an acceptable, valid and reliable in-

strument for evaluating the HRQOL in children and adolescents with T1DM [25–28].

All data were analyzed using descriptive statistics. The relationship between nominal data was analyzed using the Chi-square test of independence. The interval data analysis was done using the t-test of independent samples, one-way analysis of variance, and correlation analysis. Data analysis was performed using the Statistical Package for the Social Sciences for Windows (version 23.0, 2015.) and Microsoft Office Excel 2010.

Results

Thirty-seven pediatric patients participated in the study. On average, they were aged 13.97 years (SD = 3.00, range: 8 – 18 years), and 63.89% of them were female. The average T1DM duration was 4.59 years (SD = 3.35, range 0.5 – 12.9 years). The lowest number of patients had ideal metabolic control, as opposed to good control of the T1DM disease. The data on therapy are presented in **Table 1** as well as the level of metabolic control in T1DM patients.

The results of patients' quality of life are presented in **Table 2** as health profile. Data are presented according to age groups, gender, and type of insulin therapy. The most frequent answer noted in every EQ-5D-Y domain was "no problems".

Most children and adolescents stated that they did not have health problems in EQ-5D-Y dimensions, but when it comes to their therapy, children and adolescents who received insulin analogues reported significant worry/sadness/unhappiness (χ^2 (2) = 7.19, p= 0.02).

The total VAS EQ-5D-Y score was 80.54 on average (SD = 20.87). The difference in mean values of VAS EQ-5D-Y scores in different age groups was not statistically significant; the same goes for gender, metabolic control, age at diagnosis (years), and type of insulin therapy (**Table 3**).

A statistically significant negative correlation was found between the duration of diabetes and the VAS score (ρ = -0.33, p < 0.05). Opposite to this result, the correlation between the HbA1c% and VAS scores was not statistically significant (ρ = 0.15, p = 0.39).

Discussion

The assessment of HRQOL is increasingly recognized as an important measure of the overall treatment outcome of pediatric patients suffering from T1DM [29, 30]. To the best of the authors' knowledge, this is the first study in the Republic of Serbia that assesses the HRQOL in children and adolescents with T1DM.

Results of hypothesis test

The following hypothesis was tested: age, duration of diabetes in years and HbA1C% values and female gender are negatively associated with HRQOL, pediatric patients who received insulin ana-

Table 1. Clinical data of pediatric patients
Tabela 1. *Klinički podaci pedijatrijskih pacijenata*

	Total *Ukupno*		8 - 12.9 years *8 – 12,9 godina*		13 - 18 years *13 – 18 godina*	
	No/*Broj*	% *Procenat*	No/*Broj*	% *Procenat*	No/*Broj*	% *Procenat*
Type of insulin/*Vrste insulina*						
Short-acting human insulin/*Humani insulin kratkog dejstva* (Actrapid)	12	32.43	4	10.80	8	21.60
Intermediate-acting human insulin/*Humani insulin srednje dugog dejstva* (Insulatard)	5	13.51	2	5.40	3	8.10
Fast-acting insulin analogue/*Insulinski analog brzodelujući* (Insulin glulizin (*Apidra*)	2	5.40	0	0.00	2	5.40
Fast-acting insulin analogue/*Insulinski analog brzodelujući* (Insulin aspart (*NovoRapid*)	22	59.45	5	13.51	17	45.95
Long-acting insulin analogue/*Insulinski analog dugog dejstva* (Insulin glargin (*Lantus*)	11	29.72	0	0.00	11	29.72
Long-acting insulin analogue/*Insulinski analog dugog dejstva* (Insulin detemir (*Levemir*)	15	40.54	6	16.21	9	24.32
Long-acting insulin analogue/*Insulinski analog dugog dejstva* (Insulin degludek (*Tresiba*)	4	10.80	2	5.40	2	5.40
Metabolic control of T1DM/*Metabolička kontrola T1DM*						
Ideal/*Idealna* (HbA1c < 5.7%)	5	13.51	2	5.40	3	8.10
Good/*Dobra* (HbA1c% = 5.8 – 7.4%)	15	40.54	4	10.80	11	29.72
Unstable/*Nestabilna* (HbA1c% = 7.5 to 8.5%)	10	27.03	2	5.40	8	21.60
Poor/*Loša* (HbA1c% > 8.5%)	6	16.21	2	5.40	4	10.80

Legenda: TIDM - Tip 1 dijabetesa melitus, HbA1C - Glikozilirani hemoglobin

Table 2. Health profile of pediatric patients in regard to different EQ-5D-Y domains and age groups, gender and type of insulin therapy
Tabela 2*. Zdravstveni profil pedijatrijskih pacijenata u odnosu na EQ-5D-Y domene, starosne grupe, pol i vrstu insulinske terapije*

EQ-5D-Y domains *EQ-5D-Y domeni*	Answer *Odgovor*	Age groups *Starosne grupe*		Gender *Pol*		Type of insulin therapy *Vrsta insulinske terapije*			All patients/*Ukupan broj pacijenata*
		8 - 12.9	13 - 18	Male *Muški*	Female *Ženski*	Human *Humani*	Analogues *Analozi*	Combination* *Kombinacija**	
		No (%) *Broj (%)*	No (%) *Broj (%)*	No (%) *Broj (%)*	No (%) *Broj (%)*	No (%) *Broj (%)*	No (%) *Broj (%)*	No (%) *Broj (%)*	N (%) *Broj (%)*
Mobility *Pokretljivost*	No problems *Nemam problema*	10 (27.03)	24 (64.86)	14 (37.83)	20 (54.05)	7 (18.91)	21 (56.75)	6 (16.21)	34 (91.87)
	Some problems *Imam nekih problema*	0 (0.00)	3 (8.10)	0 (0.00)	3 (8.10)	0 (0.00)	3 (8.10)	0 (0.00)	3 (8.10)
	A lot of problems *Imam mnogo problema*	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Looking after myself *Vođenje brige o sebi*	No problems *Nemam problema*	10 (27.03)	25 (67.56)	14 (37.83)	21 (56.75)	7 (18.91)	22 (59.45)	6 (16.21)	35 (94.59)
	Some problems *Imam nekih problema*	0 (0.00)	2 (5.40)	0 (0.00)	2 (5.40)	0 (0.00)	2 (5.40)	0 (0.00)	2 (5.40)
	A lot of problems *Imam mnogo problema*	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Doing usual activities *Obavljanje uobičajenih aktivnosti*	No problems *Nemam problema*	9 (24.32)	23 (62.16)	13 (35.13)	19 (51.35)	6 (16.21)	20 (54.05)	6 (16.21)	32 (86.48)
	Some problems *Imam nekih problema*	0 (0.00)	4 (10.80)	0 (0.00)	4 (10.80)	0 (0.00)	4 (10.80)	0 (0.00)	4 (10.80)
	A lot of problems *Imam mnogo problema*	1 (2.70)	0 (0.00)	1 (2.70)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.70)
Having pain or discomfort *Imam bol ili nelagodnost*	No problems *Nemam problema*	8 (21.60)	21 (56.75)	12 (32.43)	17 (45.94)	15 (40.54)	19 (51.35)	5 (13.51)	20 (54.05)
	Some problems/*Imam nekih problema*	2 (5.40)	6 (16.21)	2 (5.40)	6 (16.21)	2 (5.40)	5 (13.51)	1 (2.70)	8 (21.60)
	A lot of problems *Imam mnogo problema*	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Feeling worried, sad or unhappy *Osećaj zabrinutosti tuge ili nesreće*	Not worried, sad or unhappy *Nisam zabrinut, tužan ili nesrećan*	6 (16.21)	15 (40.54)	8 (21.60)	13 (35.13)	1 (2.70)	15 (40.54)	5 (13.51)	21 (56.75)
	A bit worried, sad or unhappy/*Pomalo sam zabrinut, tužan ili nesrećan*	4 (10.80)	12 (32.43)	6 (16.21)	10 (27.03)	6 (16.21)	9 (24.32)	1 (2.70)	16 (43.24)
	Very worried, sad or unhappy *Veoma sam zabrinut, tužan ili nesrećan*	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

*Combination of short-acting human insulin and a long-acting analogue: insulin detemir
**Kombinacija humanog insulina kratkog dejstva i insulinskog analoga dugog dejstva*

logues are even more likely to have suboptimal HRQOL in at least one domain.

Among the most important results, no statistically significant difference was found between the VAS EQ-5D-Y score and age, gender, HbA1c levels and type of insulin therapy. A statistically significant association between the total VAS EQ-5D-Y score and the duration of diabetes (negative correlation) was confirmed, that is, longer duration of T1DM was associated with a lower overall VAS EQ-5D-Y score, and vice versa.

Pediatric patients showed relatively few health problems in EQ-5D-Y domains and they were not statistically significant; however, when they were observed from the aspect of therapy, children and adolescents who injected insulin analogues reported significantly higher concerns.

The age of our subjects at the time of disease onset is in agreement with results of many researchers [31–38].

The duration of diabetes in our patients was similar to the study of Murillo et al. [3]. In another

Table 3. VAS EQ-5D-Y scores of different groups of pediatric patients
Tabela 3*. VAS EQ-5D-Y skor u odnosu na različite grupe pedijatrijskih pacijenata*

VAS EQ-5D-Y *Vizuelno analogna skala EQ-5D-Y*	Average (SD)/*Prosek* (*Standardna devijacija*)	Range *Raspon*	Stat. test *Stat. test*
Total score/*Ukupan skor*	80.54 (20.87)	4 – 100	
Age groups/*Starosne grupe*			
Group of patients 8–12.9 years/*Grupa pacijenata 8 – 12,9 godina*	87.50 (11.61)	65 - 100	t = 1.24
Group of patients 13–18 years/*Grupa pacijenata 13 – 18 godina*	77.96 (23.04)	4 - 100	p > 0.05
Gender/*Pol*			
Male patients/*Muški pacijenti*	84.71 (14.69)	51 - 100	t = 0.94
Female patients/*Ženski pacijenti*	78.00 (23.82)	4 - 100	p > 0.05
Metabolic Control/*Metabolička kontrola*			
Ideal metabolic control/*Idealna metabolička kontrola*	91.00 (12.45)	70 - 100	
Good metabolic control/*Dobra metabolička kontrola*	78.00 (24.90)	4 - 100	F= 1.03
Unstable metabolic control/*Nestabilna metabolička kontrola*	77.00 (20.06)	30 - 100	p > 0.05
Poor metabolic control/*Loša metabolička kontrola*	90.00 (6.32)	80 - 95	
Age at diagnosis (in years)/*Starost kada je dijagnostikovana bolest (u godinama)*			
0 – 4.9	83.30 (12.52)	65 - 95	
5 – 9.9	74.08 (26.34	4 - 95	F = 1.32
10 – 14.9	80.69 (19.29)	30 - 100	p > 0.05
15 – 18	100.00 (0.00)	100 - 100	
Type of insulin therapy/*Vrsta insulinske terapije*			
Human insulin/*Humani insulin*	88.57 (12.15)	70 - 100	
Analogues/*Analozi*	75.21 (23.37)	4 - 100	F = 2.47
Combination of short-acting human insulin and a long-acting analogue: insulin detemir/*Kombinacija humanog insulina kratkog dejstva i dugodelujućeg analoga: insulin detemir*	92.50 (6.89)	80 - 100	p > 0.05

study of AlBuhairan et al. [29] the average duration of T1DM was longer (6.9 years) in population aged form 12 to 18 years, and even longer (10.1 years) in the study of Naughton et al. [30] in population aged from 10 to 16 years.

According to the results of this study, the largest number of pediatric patients received a fast-acting analogue, insulin aspart (NovoRapid) and the most commonly used long-acting insulin analogue, insulin detemir (Levemir). Using the χ^2 independence test, the statistical significance of the difference in the distribution of respondents' responses to different domains of EQ-5D-Y in relation to the type of insulin therapy was in the domain "Feeling of concern". Other examined differences in the distribution of responses showed no statistical significance in the given sample. In the most compatible study by Murillo et al. [3] 21.6% of children and adolescents reported feeling anxiety or depression.

In our study, a statistically significant negative correlation was found between the overall VAS EQ-5D-Y score and the duration of diabetes mellitus. This result is consistent with the results of the study conducted by Kalyva et al. [39], where the duration of diabetes was identified as one of the five significant predictors of HRQOL in both the generic and diabetes-specific questionnaires in pediatric patients.

However, in our study, a statistically significant difference in the mean values of VAS EQ-5D-Y scores was not confirmed related to patients' gender, age, type of insulin therapy, and metabolic control. Nevertheless, in a study by AlBuhairan et al. [29] the results indicate that significant predictors of quality of life were gender and age of respondents, and female respondents reported lower quality of life, while younger adolescents (13 – 15 years of age) achieved better VAS EQ-5D-Y scores in relation to older teenagers (16 – 18 years of age), and these results are consistent with the results of Murillo et al. [3] and Naughton [30]. Al-Hayek [40] assessed the quality of life of adolescents with T1DM, using the DMPediatric Quality of Life Inventory 3.0 Diabetes Module (PedsQL 3.0 DM) and found that female gender is one of the predictors of poorer HRQOL in at least one domain, that is similar to the conclusion of Kalyva et al. [39].

The highest VAS EQ-5D-Y scores were reported by our patients diagnosed with the disease at 15 – 18 years of age, while the lowest scores were found in pediatric patients diagnosed at the age of 5 – 9.9 years. However, statistically significant differences between mean values in different patient groups were not found. Opposite to these results, the study of Kalyva et al. [39] indicated that the age when the

diagnosis of diabetes was confirmed was a significant predictor of better HRQOL.

In our study, a correlation between the HbA1c and the total VAS EQ-5D-Y score was not confirmed, which contradicts the results obtained by the authors Kalyva [39] and Murillo et al. [3]. Also, in a review by Cameron et al. [41] it was confirmed that poorer metabolic disease control in adolescents is positively correlated with poorer QOL, which is consistent with the conclusions of numerous authors: AlBuhairan [29], Naughton [30], Al-Hayek [40], Alvarado-Martel [42] and Samardžic et al. [43].

The comparison of mean VAS EQ-5D-Y scores with respect to the type of insulin therapy was examined by one-factor analysis of variance and the difference was not statistically significant. However, the highest VAS EQ-5D-Y score was found in subjects receiving a combination of short-acting human insulin and a long-acting analogue followed by human insulin and insulin analogue therapy.

It should be noted that all our respondents had the opportunity to point out what would, in their opinion, significantly improve their HRQOL, and they all reported that they needed continuous glucose monitoring (CGM). Since November 2020, the National Health Insurance Fund provides CGM sensors ("List of aids" that came into force on 14th November, 2020) to all pediatric patients with diabetes [44]. A possible limitation of the present study is the small number of patients, from one tertiary-care center, but the results are comparable with other studies [3, 29, 30, 39–43].

Conclusion

In summary, this preliminary report suggests that health-related quality of life in Serbian children and adolescents with type 1 diabetes mellitus is similar to that in the general population of the same age and gender from Serbia and different countries. Among the most important results is that no statistically significant difference was found between the visual analogue scale EQ-5D-Y score and variables: age, gender, glycosylated hemoglobin values, and type of insulin therapy.

A statistically significant association between the total visual analogue scale EQ-5D-Y score and the duration of diabetes mellitus (negative correlation) was confirmed, with a longer duration of type 1 diabetes mellitus and a lower overall visual analogue scale EQ-5D-Y score, and vice versa. Higher concerns were reported by pediatric patients receiving insulin analogue therapy.

The present study provides initial data on the childhood population with type 1 diabetes mellitus. Similar studies need to be done in different pediatric hospitals. In the Republic of Serbia, there are no translated and culturally adapted disease-specific instruments for measuring health-related quality of life of pediatric patients with type 1 diabetes mellitus so it is the next task that needs to be done.

References

1. Karimi M, Brazier J. Health, health–related quality of life, and quality of life: what is the difference? Pharmacoeconomics. 2016;34(7):645-9.

2. Delamater AM, de Wit M, McDarby V, Malik J, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2014. Psychological care of children and adolescents with type 1 diabetes. Pediatr Diabetes. 2014;(Suppl 20):232-44.

3. Murillo M, Bel J, Pérez J, Corripio R, Carreras G, Herrero X, et al. Health-related quality of life (HRQOL) and its associated factors in children with type 1 Diabetes mellitus (T1DM). BMC Pediatr. 2017;17(1):16.

4. Miranda Velasco MJ, Domínguez Martín E, Arroyo Díez FJ, Méndez Pérez P, González de Buitrago Amigo J. Calidad de vida relacionada con la salud en la diabetes mellitus tipo 1. An Pediatr (Barc). 2012;77(5):329-33.

5. Nieuwesteeg A, Pouwer F, van der Kamp R, van Bakel H, Aanstoot HJ, Hartman E. Quality of life of children with type 1 diabetes: a systematic review. Curr Diabetes Rev. 2012;8(6):434-43.

6. Todorović S, Milenković T, Mitrović K, Plavšić L, Panić-Zarić S, Vuković R. High prevalence of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes in Belgrade, Serbia: 10-year tertiary centre experience. Health Care. 2019;48(4):7-14.

7. Ješić MD, Milenković T, Mitrović K, Todorović S, Zdravković V, Ješić MM, et al. Problems in diabetes management in school setting in children and adolescent with type 1 diabetes in Serbia. Vojnosanit Pregl. 2016;73(3):273-6.

8. Ješić MD, Ješić MM, Stanisavljević D, Zdravković V, Bojić V, Vranješ M, et al. Ketoacidosis at presentation of type 1 diabetes mellitus in children: a retrospective 20-year experience from a tertiary care hospital in Serbia. Eur J Pediatr. 2013;172(12):1581-5.

9. Ješić M, Ješić M, Sajić S, Bogićević D, Buljugić S, Maglajlić S. The effect of metabolic and hormonal parameters on microalbuminuria in adolescents with type 1 diabetes mellitus. Srp Arh Celok Lek. 2013;141(5-6):315-9.

10. Viaene AS, Van Daele T, Bleys D, Faust K, Massa GG. Fear of hypoglycemia, parenting stress, and metabolic control for children with type 1 diabetes and their parents. J Clin Psychol Med Settings. 2017;24(1):74-81.

11. Driscoll KA, Raymond J, Naranjo D, Patton SR. Fear of hypoglycemia in children and adolescents and their parents with type 1 diabetes. Curr Diab Rep. 2016;16(8):77.

12. Große J, Hornstein H, Manuwald U, Kugler J, Glauche I, Rothe U. Incidence of diabetic ketoacidosis of new-onset type 1 diabetes in children and adolescents in different countries correlates with human development index (HDI): an updated systematic review, meta-analysis, and meta-regression. Horm Metab Res. 2018;50(3):209-22.

13. Manuwald U, Schoffer O, Hegewald J, Große J, Kugler J, Kapellen TM, et al. Ketoacidosis at onset of type 1 diabetes in children up to 14 years of age and the changes over a period of 18 years in Saxony, Eastern-Germany: a population based register study. PLoS One. 2019;14(6):e0218807.

14. Kordonouri O, Klingensmith G, Knip M, Holl RW, Aanstoot HJ, Menon PS, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Other complications and diabetes - associated conditions in children and adolescents. Pediatr Diabetes. 2014;(Suppl 20):270-8.

15. Babiker A, Datta V. Lipoatrophy with insulin analogues in type 1 diabetes. Arch Dis Child. 2011;96(1):101-2.

16. Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab. 2013;39(5):445-53.

17. Picard S, Bonnemaison-Gilbert E, Leutenegger E, Barat P. Optimization of insulin regimen and glucose outcomes with short-term real-time continuous glucose monitoring (RT-CGM) in type 1 diabetic children with sub-optimal glucose control on multiple daily injections: the pediatric DIACCOR study. Arch Pediatr. 2019;26(2):95-101.

18. Ly TT, Anderson M, McNamara KA, Davis EA, Jones TW. Neurocognitive outcomes in young adults with early-onset type 1 diabetes: a prospective follow-up study. Diabetes Care. 2011;34(10):2192-7.

19. Ferguson SC, Blane A, Wardlaw J, Frier BM, Perros P, McCrimmon RJ, et al. Influence of an early-onset age of type 1 diabetes on cerebral structure and cognitive function. Diabetes Care. 2005;28(6):1431-7.

20. Persson S, Dahlquist G, Gerdtham UG, Steen Carlsson K. Impact of childhood-onset type 1 diabetes on schooling: a population-based register study. Diabetologia. 2013;56(6):1254-62.

21. Institute of Public Health of Serbia "Dr Milan Jovanović Batut". Serbian diabetes registry - incidence and mortality of diabetes in Serbia 2010 [Internet]. 2010 [cited 2020 Jun 24]. Available from: http://www.batut.org.rs/download/publikacije/Registar%20za%20dijabetes%20u%20Srbiji%202010.pdf.

22. Institute of Public Health of Serbia "Dr Milan Jovanović Batut". Serbian diabetes registry – incidence and mortality of diabetes in Serbia 2014 [Internet]. 2014 [cited 2020 Jun 24]. Available from: http://www.batut.org.rs/download/publikacije/2014IzvestajDijabetes.pdf.

23. Institute of Public Health of Serbia "Dr Milan Jovanović Batut". Serbian diabetes registry - incidence and mortality of diabetes in Serbia 2017 [Internet]. 2017 [cited 2020 Jun 24]. Available from: http://www.batut.org.rs/download/publikacije/2017Izvestaj%20dijabetes.pdf.

24. Anderson BJ, Laffel LM, Domenger C, Danne T, Phillip M, Mazza C, et al. Factors associated with diabetes-specific health related quality of life in youth with type 1 diabetes: the global TEENs study. Diabetes Care. 2017;40(8):1002-9.

25. EuroQol Research Foundation. EQ-5D-Y user guide, how to apply, score, and present results from the EQ-5D-Y [Internet]. 2020 [updated 2020 Sep; cited 2020 Oct 1]. Available from: https://euroqol.org/wp-content/uploads/2019/10/EQ-5D-Y-User-Guide.pdf.

26. Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res. 2010;19(6):875-86.

27. Robles N, Rajmil L, Rodriguez-Arjona D, Azuara M, Codina F, Raat H, et al. Development of the web-based Spanish and Catalan versions of the Euroqol 5D-Y (EQ-5D-Y) and comparison of results with the paper version. Health Qual Life Outcomes. 2015;13:(72).

28. Mayoral K, Rajmil L, Murillo M, Garin O, Pont A, Alonso J, et al. Measurement properties of the online EuroQol-5D-Youth instrument in children and adolescents with type 1 diabetes mellitus: questionnaire study. J Med Internet Res. 2019;21(11):e14947.

29. Al Buhairan F, Nasim M, Al Otaibi A, Shaheen NA, Al Jaser S, Al Alwan I. Health related quality of life and family impact of type 1 diabetes among adolescents in Saudi Arabia. Diabetes Res Clin Pract. 2016;114:173-9.

30. Naughton MJ, Yi-Frazier JP, Morgan TM, Seid M, Lawrence JM, Klingensmith GJ, et al. Longitudinal associations between sex, diabetes self-care, and health-related quality of life among youth with type 1 or type 2 diabetes mellitus. J Pediatr. 2014;164(6):1376-83.e1.

31. Harjutsalo V, Sjöberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet. 2008;371(9626):1777-82.

32. Dabelea D. The accelerating epidemic of childhood diabetes. Lancet. 2009;373(9680):1999-2000.

33. Forlenza GP, Rewers M. The epidemic of type 1 diabetes: what is it telling us? Curr Opin Endocrinol Diabetes Obes. 2011;18(4):248-51.

34. Peng H, Hagopian W. Environmental factors in the development of type 1 diabetes. Rev Endocr Metab Disord. 2006;7(3):149-62.

35. Berhan Y, Waernbaum I, Lind T, Möllsten A, Dahlquist G; Swedish Childhood Diabetes Study Group. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. Diabetes. 2011;60(2):577-81.

36. DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med. 2006;23(8):857-66.

37. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. Lancet. 2009;373(9680):2027-33.

38. Piffaretti C, Mandereau-Bruno L, Guilmin-Crepon S, Choleau C, Coutant R, Fosse- Edorh S. Trends in childhood type 1 diabetes incidence in France 2010–2015. Diabetes Res Clin Pract. 2019;149:200-7.

39. Kalyva E, Malakonaki E, Eiser C, Mamoulakis D. Health-related quality of life (HRQoL) of children with type 1 diabetes (T1DM): self and parental perception. Pediatr Diabetes. 2011;12(1):34-40.

40. Al-Hayek AA, Robert AA, Abbas HM, Itani MB, Al-Saeed AH, Juhani AE, et al. Assessment of health-related quality of life among adolescents with type 1 diabetes mellitus in Saudi Arabia. Saudi Med J. 2014;35(7):712-7.

41. Cameron FJ, de Beaufort C, Aanstoot HJ, Hoey H, Lange K, Castano L, et al. Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach. Pediatr Diabetes. 2013;14(7):473-80.

42. Alvarado-Martel D, Velasco R, Sánchez-Hernández RM, Carrillo A, Nóvoa FJ, Wägner AM. Quality of life and type 1 diabetes: a study assessing patients' perceptions and self-management needs. Patient Prefer Adherence. 2015;9:1315-23.

43. Samardzic M, Tahirovic H, Popovic N, Popovic-Samardzic M. Health related quality of life of Montenegro children and adolescents with type 1 diabetes. Relationship between

metabolic control and quality of life. J Pediatr Endocrinol Metab. 2016;29(6):663-8.

44. Republički fond za zdravstveno osiguranje. Lista pomagala [Internet]. 2020 [cited 2020 Dec 3]. Available from: https://www.rfzo.rs/download/pravilnici/pomagala/Lista%20pomagala%20od%2014.11.2020..pdf.

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ENDOVASCULAR REVASCULARIZATION OF CAROTID ARTERY STENOSIS

ENDOVASKULARNA REVASKULARIZACIJA SUŽENJA KAROTIDNE ARTERIJE

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Summary

Introduction. Endovascular revascularization is a peripheral artery disease therapy used to improve blood flow in blood vessels. The objective of this study was to analyze the types and prevalence of comorbidities in patients with indications for carotid artery revascularization, as well as early results of endovascular carotid artery revascularization in relation to periprocedural complications. **Material and Methods.** This retrospective study was conducted from October 2014 to October 2019 and included 96 patients. Descriptive and comparative statistical analysis was performed in all patients, male and female, and those with both symptomatic and asymptomatic carotid diseases. **Results.** The study included 96 patients, of whom 69.8% were male and 30.2% were female. A successful endovascular procedure was performed in 89.6% of patients, while in 10.4% of patients the procedure failed. The distribution of patients by sex, age and the duration of procedure, showed a statistically significant difference ($p < 0.05$) in the age ($p = 0.0003$) and duration of the procedure ($p = 0.022$). The comparison of two groups of patients, with symptomatic and asymptomatic carotid atherosclerotic disease, hyperlipoproteinemia ($p = 0.015$) showed a statistically significant difference ($p < 0.05$) between the two groups. **Conclusion.** Endovascular revascularization has a high success rate in the treatment of atherosclerotic disease of the carotid arteries as well as low periprocedural morbidity and mortality. The analysis of gender-related differences, we concluded that endovascular revascularization lasts significantly longer in female patients, and that the average age is significantly higher in male patients compared to females. We also concluded that hyperlipoproteinemia is a major risk factor for carotid artery disease.

Key words: Carotid Stenosis; Stroke; Cerebral Revascularization; Endovascular Procedures; Treatment Outcome; Stents; Atherosclerosis; Minimally Invasive Surgical Procedures: Risk Factors; Comorbidity

Sažetak

Uvod. Endovaskularna revaskularizacija podrazumeva rekonstrukciju obolelog krvnog suda metodama koje se koriste da poboljšaju protok krvi kroz krvni sud. Cilj rada bila je analiza komorbiditeta po tipu i učestalosti javljanja kod pacijenata sa indikacijom za revaskularizaciju karotidnih arterija, kao i analiza ranih rezultata endovaskularne revaskularizacije karotidnih arterija u odnosu na periproceduralne komplikacije. **Materijal i metode.** Retrospektivna studija između oktobra 2014. i oktobra 2019. godine obuhvatila je 96 pacijenata. Rađena je deskriptivna i komparativna statistika za celu populaciju između grupe muškog i ženskog pola i simptomatske i asimptomatske karotidne bolesti. **Rezultati.** Istraživanjem je obuhvaćeno 96 bolesnika, od kojih je 69,8% bilo muškog, dok je 30,2% bilo ženskog pola. Uspešno izvršena endovaskularna procedura je urađena kod 89,6% bolesnika, dok kod 10,4% bolesnika procedura nije uspela. Poređenjem pacijenata po polu, starosti ($p = 0,0003$) i trajanja procedure ($p = 0,022$) pokazala se statistički značajna razlika ($p < 0,05$). Poređenjem dve grupe pacijenata sa simptomatskom i asimptomatskom karotidnom aterosklertoskom bolešću, hiperlipoproteinemija, ($p = 0,015$) pokazala se takođe statistički značajna razlika ($p < 0,05$). **Zaključak.** Endovaskularnom revaskularizacijom se postiže visok uspeh lečenja aterosklerotske bolesti karotidnih arterija, praćena je malim periproceduralnim morbiditetom i mortalitetom. Analizom rezultata po polu, zaključili smo da endovaskularna revaskularizacija značajno duže traje kod pacijenata ženskog pola i da je prosečna starost značajno veća kod pacijenata muškog pola u odnosu na ženski pol. Zaključili smo i da hiperlipoproteinemija ima značajnu ulogu u simptomatologiji karotidne bolesti, kao i da je hiperlipoproteinemija značajan faktor rizika za bolest karotidne arterije.

Ključne reči: karotidna stenoza; moždani udar; cerebralna revaskularizacija; endovaskularne procedure; ishod lečenja; stentovi; ateroskleroza; minimalno invazivne hirurške procedure; faktori rizika; komorbiditet

Introduction

Endovascular revascularization is a peripheral artery disease therapy that involves reconstruction of diseased blood vessels in order to improve blood flow [1]. Carotid disease commonly manifests as atherosclerotic stenosis, which can lead to ischemic stroke with a high mortality, and revascularization has shown its place in its prevention [2]. Ischemic cerebrovascular disease (ICVD) has a very high mortality rate, and the fact that it is a neurological disease with the highest degree of disability is equally serious [3]. Cerebrovascular insult (CVI) or stroke is the third

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Abbreviations

ICVD – ischemic cerebrovascular disease
CVI – cerebrovascular insult
CEA – carotid endarterectomy
CAS – carotid artery stenting
HTA – arterial hypertension
HLP – hyperlipoproteinemia
COPD – chronic obstructive pulmonary disease
PAOD – peripheral arterial occlusive disease
CMP – cardiomyopathy

leading cause of death in developed countries, after heart disease and malignancies [4].

Carotid revascularization for prevention of ischemic stroke can be surgical or endovascular revascularization [5]. Surgical treatment involves carotid endarterectomy (CEA), and involves direct access to a blood vessel followed by complete removal of atherosclerotic plaque [6]. Endovascular treatment involves placement of a stent in the carotid artery, carotid stenting (CAS) and it is a less invasive method compared to surgical treatment [7]. Surgical revascularization is the method of choice for the treatment of carotid artery stenosis, but in high-risk patients (several associated diseases) who are contraindicated for CEA, with stenosis of a surgically inaccessible place, restenosis after CEA, the best choice is endovascular treatment. Endovascular treatment of carotid arteries is a minimally invasive branch of vascular surgery using percutaneous transluminal angioplasty (PTA) and CAS [1]. Stents are metal cylinders of mesh structure, designed to keep the lumen of the artery open by preventing the progression of plaque into the lumen. Some of the embolic protection devices during endovascular revascularization are distal occlusion balloons and distal filters [8].

The aim of this research was to analyze risk factors and comorbidities in patients with indicated endovascular revascularization of carotid arteries, and to analyze early results of endovascular revascularization in relation to periprocedural complications.

Material and Methods

The retrospective study included 96 patients who were treated with endovascular revascularization at the Clinical Center of Vojvodina in the period from October 2014 to October 2019 (5 years). The data on patients were collected from medical records of the Department of Interventional Radiology, Center for Radiology, and at the Clinic of Vascular and Endovascular Surgery of the Clinical Center of Vojvodina in Novi Sad (computer database, operative protocol, accompanying clinical and radiological documentation, discharge lists). All endovascular interventions were performed in the angio-hall of the Department of Interventional Radiology, Center for Radiology, by a team of interventional radiologists, vascular surgeons and anesthesiologists. Carotid revascularizations were performed according to the guidelines of the European Society for Vascular and Endovascular Surgery [9].

In order to analyze the results of the endovascular revascularization, the following parameters were analyzed:

1. Before the treatment:
– Gender and age of patients,
– Associated diseases (arterial hypertension (HTA), diabetes mellitus, hyperlipoproteinemia (HLP), chronic obstructive pulmonary disease (COPD), cardiomyopathy (CMP), and other vascular and cardiac diseases, nicotinism, obesity),
– Clinical stage of extracranial cerebrovascular disease,
– Degree of carotid artery stenosis or restenosis.
2. After the treatment:
– Duration of the surgical procedure,
– The amount of heparin given during the procedure,
– Postoperative complications,
– Procedural success rate (%).

In addition to the medical history data and clinical examination, accurate diagnosis was made by a combination of duplex ultrasound, multislice computed tomographic angiography (MSCTA) and magnetic resonance angiography (MRA). After the diagnostic algorithm and morphological assessment of suitability for endovascular treatment of the carotid artery were performed, each intervention was done under local anesthesia. The functionality of the reconstruction was determined by physical examination and duplex ultrasound. Other vascular and cardiac diseases include the following diseases: pectoral angina, valvular heart disease, valvular aortic disease, extrasystolic ventricular arrhythmia, pulmonary artery hypertension, peripheral arterial occlusive disease (PAOD), myocardial infarction and chronic renal failure. Carotid restenosis or restenosed carotid artery, involves stenosis of the artery that had already been treated with one of the surgical or endovascular methods. Each endovascular procedure was performed with distal filter protection as well as predilatation of the carotid artery wall.

Descriptive and comparative statistics were done for all the patients, with sex distribution and symptomatic and asymptomatic distribution of patients. As part of the descriptive statistics, the following parameters were used: statistical mean and median, minimum and maximum values, and standard deviation. To compare differences in the intensity of impressions between the tested groups for non-parametric attributes, we used the Pearson χ^2-test.

Results

The study included 96 patients, of whom 67/96 (69.8%) were male, while 29/96 (30.2%) were female. The average age of patients was 67.2 years; the oldest patient was 79 years old, and the youngest 42 years old. The most common comorbidities in the entire group of patients were: HTA in 71.87% of patients, followed by CMP in 53.12% of patients. Non-insulin-dependent diabetes mellitus (NIDDM) affected 28.2% and HLP 26.04% of all patients. The COPD was present in 15.62%, nicotinism in 16.66%, insulin-dependent diabetes mellitus (IDDM) in 4.16% of patients. Only

2.08% patients were obese. Other vascular and cardiac diseases were found in 54.16% of patients. Other concomitant cardiac and vascular diseases were present in 54.2% of patients, of which PAOD was present in 16.7% and myocardial infarction in 15.6% of patients. Pectoral angina was present in 14.6% of the total number of patients, while 5.2% patients suffered from chronic renal insufficiency.

Based on the medical history data and clinical examination, 51/96 (53.1%) patients had a symptomatic carotid disease, while in the rest of 45/96 (46.9%) patients it was asymptomatic. In patients with symptomatic carotid disease, CVI occurred in 33/51 patients, transient ischemic attack (TIA) in 14/51, while reversible ischemic neurological deficit (RIND) occurred in 4/51 patients.

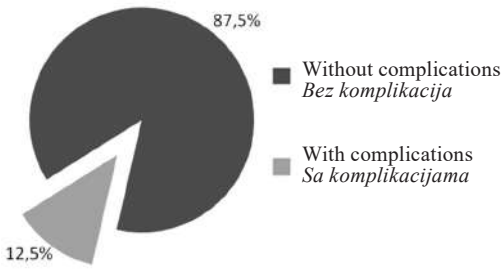
Treatment of restenosed artery was done in 26% of patients, while in the remaining 71/96 (74%) patients the stenosis was primary. The degree of the artery stenosis, which was determined by diagnostic methods, was divided into stenosis of less than 90% and of more than 90% of the normal lumen of the artery. Artery stenosis less than 90% was found in 71.9% of patients, while more than 90% was found in 28.1%. Contralateral significant stenosis, i.e. greater than 70% of the artery on the opposite side from the planned endovascular revascularization, was present in 17/96 (17.7%) patients. Right carotid artery stenting was indicated in 50/96 (52.1%) patients, while slightly less was indicated in the left carotid artery, in 46/96 (47.9%) patients. The endovascular procedure went smoothly in 84/96 (87.5%) patients **(Graph 1)**, while complications occurred in 12/96 (12.5%). Transient carotid spasm occurred in 6/12 patients. In 2/12, a hematoma occurred at the access site. Transient hemodynamic instability (hypotension and bradycardia) occurred in 2/12 patients. Two out of 12 patients had moderate neurological deficits (i.e. transient loss of vision in one eye). One of 12 patients had iatrogenic rupture of the femoral and iliac arteries. Complications were present in 8/67 (11.9%) males, while in females they were present in 4/29 (13.8%) patients. The average amount of heparin applied for anticoagulant action was 5800 IU (maximum amount was 10000, minimum 2500 IU).

Tehnically successful endovascular procedure was performed in 89.6% of patients, while in 10.4% the

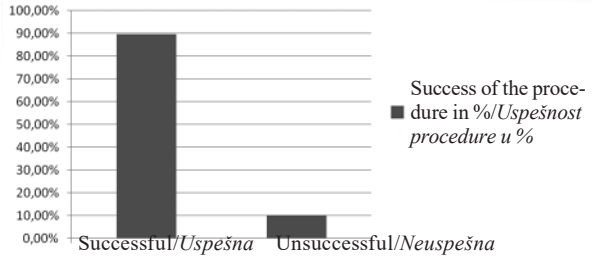
Table 1. Comparative statistics of comorbidities and other parameters with gender distribution
Tabela 1. *Komparativna statistika komorbiditeta i drugih parametara u odnosu na pol*

Gender/*Pol*	Male/*Muški*			Female/*Ženski*			*p*
	No/*Br.*	Mean *Srednja*	Standard deviation *Standardna devijacija*	No/*Br.*	Mean *Srednja*	Standard deviation *Standardna devijacija*	
Age (years)/*Starost (godine)*	67	69.164	7.470	29	62.448	9.276	0.0003
Heparin (IU)/*Heparin (ij)*	56	5723.214	1310.516	20	6175.000	1640.563	0.220
Duration of procedure (min.) *Trajanje procedure (min.)*	27	73.926	19.729	11	90.000	16.125	0.022
HTA	47			22			0.746
NIDDM/*IZNDM*	25			2			0.173
IDDM/*IZDM*	3			1			0.710
HLP	17			8			0.979
Nicotinism	10			6			0.691
COPD/*HOBP*	12			3			0.528
CMP	40			11			0.082
Other diseases/*Druge bolesti*	38			14			0.590
Asympt. – Sympt. *Asimp – Simptomat.*	31-36			14-15			0.967
Left–Right side *Leva – desna strana*	32-35			14-15			0.860
Protection/*Zaštita*	61			26			0.868
Predilation/*Predilatacija*	4			5			0.174
Complications/*Komplikacije*	8			4			0.933
Preliminary examination *Preliminarni pregled*	5			5			0.282
70 – 90%	46			23			0.413
> 90%	21			6			0.413

Legend/*Legenda:* HTA = arterial hypertension/*arterijska hipertenzija*; NIDDM/IZNDM = non-insulin-dependent diabetes mellitus/*insulin-nezavisan dijabetes melitus*; IDDM/IZDM = insulin-dependent diabetes mellitus/*insulin-zavisan dijabetes melitus*; HLP = hyperlipoproteinemia/*hiperlipoproteinemija*; Nicotinism = smoking/*pušenje*; COPD/HOBP = chronic obstructive pulmonary disease/*hronična opstruktivna bolest pluća*; CMP = cardiomyopathy/*kardiomiopatija*; Other diseases/*Druge bolesti* = other cardiac and vascular diseases/*druge kardijalne i vaskularne bolesti*; Asympt.-Sympt. = asymptomatic-symptomatic disease/*asimptomatska – simptomatska bolest*; 70–90% = stenosis above 70% and below 90%/*suženje iznad 70% a ispod 90%*; > 90% = stenosis above 90%/*suženje iznad 90%*



Graph 1. The incidence of complications during the intervention
Grafikon 1. *Prisustvo komplikacija tokom intervencije*



Graph 2. Success rate of endovascular revascularization
Grafikon 2. *Uspešnost endovaskularne revaskularizacije*

procedure failed **(Graph 2)**. In 3/10 patients the procedure failed due to unfavorable separation of internal carotid artery from common carotid artery (a sharp angle), in 2/10 patients due to carotid artery occlusion, in 1/10 due to iatrogenic artery rupture at the access site, in 2/10 due to difficult passage through aortic arch, in 1/10 due to unfavorable morphology of the brachial tree, while in 1/10 patient the procedure failed due to pseudoaneurysmatic dilatation and significant artery stenosis in the petrous region. Failed procedures were present in 5/67 (7.5%) males and in 5/29 (17.2%) female patients **(Table 1)**.

In both male and female patients, the age ($p = 0.0003$) and duration of the procedure ($p = 0.022$) showed a statistically significant difference ($p < 0.05$) **(Table 2)**.

In the groups of patients with symptomatic and asymptomatic carotid atherosclerotic disease, hyperlipoproteinemia ($p = 0.015$) showed a statistically significant difference ($p < 0.05$).

Table 2. Comparative statistics of comorbidities and other parameters in relation to symptoms of carotid disease
Tabela 2*. Komparativna statistika komorbiditeta i drugih parametara u odnosu na simptomatologiju karotidne bolesti*

Asympt./*Sympt.*/Asimpt./*Simptomat.*	Asymptomatic/*Asimptomatski*			Symptomatic/*Simptomatski*			p
	No/*Br.*	Mean *Srednja*	Standard deviation *Standardna devijacija*	N	Mean *Srednja*	Standard deviation *Standardna devijacija*	
Age/*Starost*	45	68.822	8.105	51	65.647	8.802	0.070
Heparin	33	5984.848	1481.579	43	5732.558	1355.539	0.442
Duration/*Trajanje*	17	81.824	22.269	21	75.952	18.001	0.374
Gender (male - female) *Pol (muški - ženski)*		31-14			36-15		0.967
HTA		33			36		0.943
NIDDM/*IZNDM*		17			14		0.389
IDDM/IZDM		3			1		0.741
HLP		6			19		0.015
Nicotinism		6			10		0.583
COPD/*HOBP*		7			8		0.792
CMP		29			22		0.060
Other diseases/*Druge bolesti*		28			24		0.200
Left–Right side/*Leva – desna strana*		20-25			26-25		0.664
Protection/*Zaštita*		43			44		0.228
Predilation/*Predilatacija*		4			5		0.844
Complications/*Komplikacije*		8			4		0.246
Preliminary examination *Preliminarni pregled*		6			4		0.586
70 – 90%		33			36		0.943
> 90%		12			15		0.943

Legend/*Legenda:* HTA = arterial hypertension/*arterijska hipertenzija*; NIDDM/IZNDM = Non-insulin-dependent diabetes mellitus/*insulin nezavisan dijabetes melitus*; IDDM/IZDM = insulin-dependent diabetes mellitus/*insulin zavisan dijabetes melitus*; HLP = hyperlipoproteinemia/*hiperlipoproteinemija*; Nicotinism = smoking/*pušenje*; COPD/HOBP = chronic obstructive pulmonary disease/*hronična opstruktivna bolest pluća*; CMP = cardiomyopathy/*kardiomiopatija*; Other diseases/*Druge bolesti* = other cardiac and vascular diseases/*druge kardijalne i vaskularne bolesti*; Asympt.-Sympt. = asymptomatic-symptomatic disease/*asimptomatska – simptomatska bolest*; 70% - 90% = stenosis above 70% and below 90%/*suženje iznad 70% a ispod 90%*; > 90% = stenosis above 90%/*suženje iznad 90%*

Discussion

The study included 96 patients, 69.8% male and 30.2% female, which is in agreement with the available literature data [10]. The mean age of patients was 67.2 years, which is lower compared to the literature data, where the average age is 75.6 years [1].

The obtained results on the prevalence of HTA, diabetes mellitus, and CMP are in line with the global data [11], while the prevalence of HLP in our patients is significantly lower than in T. Reiff et al. where it was present in 66.6% [10].

In 53.1% of patients, carotid disease was symptomatic, which is consistent with the literature where symptomatic carotid disease was present in 52.2% [12]. Treatment of restenosed artery was present in 26.0% of patients, while in 74.0% of patients the stenosis was primary, which is not in accordance with the available literature data where treatment of restenosed artery was present only in 11% [13]. Significant carotid stenosis of the opposite side from the planned endovascular revascularization was present in 17.7% of patients, which is consistent with the literature [14].

Right carotid stenting was more often indicated (52.1%) compared to the left carotid artery, while the left side was slightly higher in the literature (50.6%) [14]. The endovascular procedure was done without complications in 87.5% of patients, while complications occurred in 12.5%, which is in line with the percentage of complications in the world literature [15]. No patients died during the stent placement, which is not in agreement with the literature data, where death occurred in 0.7% of patients [14]. Technically successful endovascular procedure was performed in 89.6% of patients, while in 10.4% the procedure failed. In the literature data, failed stent placement was reported somewhat less frequently, only in 2.1% [16].

In the groups of male and female patients, age ($p = 0.0003$) showed a statistically significant difference ($p < 0.05$). This indicates that the average age of male patients was 69.2 years, while in female patients it was 62.4 years. These data show that the female patients were treated about 7 years earlier than the male patients. However, these data were not found in the available literature.

In the groups of male and female patients, the duration of the procedure ($p = 0.022$) showed a statistically significant difference ($p < 0.05$). This indicates that the average duration of the procedure in males was 74 minutes, while in females it was 90 minutes. This information was not found in the available literature.

The comparison of two groups of patients, with symptomatic and asymptomatic carotid atherosclerotic disease, HLP ($p = 0.015$) showed a statistically significant difference ($p < 0.05$). This shows that HLP largely accounts for the symptomatology. This data has been found in the available literature [10], which proves that the reduction of HLP by using statins also reduces the consequences of carotid disease.

Conclusion

We concluded that endovascular revascularization has a high success rate in the treatment of atherosclerotic disease of the carotid arteries and it is associated with low periprocedural morbidity and mortality.

The analysis of gender-related differences, we concluded that endovascular revascularization lasts significantly longer in female patients, and that the average age is significantly higher in male patients compared to females. We also concluded that hyperlipoproteinemia is a major risk factor for carotid artery disease.

References

1. Faggioli G, Pini R, Mauro R, Freyrie A, Gargiulo M, Stella A. Contralateral carotid occlusion in endovascular and surgical carotid revascularization: a single centre experience with literature review and meta-analysis. Eur J Vasc Endovasc Surg. 2013;46(1):10-20.

2. Halliday A, Bulbulia R. Stenting or surgery for carotid stenosis? The largest trial in the world nears completion. Eur J Vasc Endovasc Surg. 2019;58(2):159-60.

3. Chandra A, Stone CR, Du X, Li WA, Huber M, Bremer R, et al. The cerebral circulation and cerebrovascular disease III: stroke. Brain Circ. 2017;3(2):66-77.

4. Mandić M, Rančić N. Risk factors for stroke. Med Pregl. 2011;64(11-12):600-5.

5. Cole TS, Mezher AW, Catapano JS, Godzik J, Baranoski JF, Nakaji P, et al. Nationwide trends in carotid endarterectomy and carotid artery stenting in the post-CREST era. Stroke. 2020;51 (2):579-87.

6. Manojlović V, Popović V, Nikolić D, Milošević Đ, Pasternak J, Budakov N. Completeness of circle of Willis in asymptomatic and symptomatic extracranial carotid disease. Med Pregl. 2016;69(11-12):351-5.

7. Müller M, Lyrer PA, Brown MM, Bonati LH. Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis. Stroke. 2021;52(1):e3-5.

8. Texakalidis P, Letsos A, Kokkinidis DG, Schizas D, Karaolanis G, Giannopoulos S, et al. Proximal embolic protection versus distal filter protection versus combined protection in carotid artery stenting: a systematic review and meta-analysis. Cardiovasc Revasc Med. 2018;19(5 Pt A):545-52.

9. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelinesof the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55(1):3-81.

10. Reiff T, Amiri H, Rohde S, Hacke W, Ringleb PA. Statins reduce peri-procedural complications in carotid stenting. Eur J Vasc Endovasc Surg. 2014;48(6):626-32.

11. de Weerd M, Greving JP, de Jong AW, Buskens E, Bots ML. Prevalence of asymptomatic artery stenosis according to age and sex: systematic review and metaregression analysis. Stroke. 2009;40(4):1105-13.

12. Hussain MA, Mamdani M, Tu JV, Saposnik G, Khoushhal Z, Aljabri B, et al. Impact of clinical trial results on the temporal trends of carotid endarterectomy and stenting from 2002 to 2014. Stroke. 2016;47(12):2923-30.

13. Lindström D, Jonsson M, Formgren J, Delle M, Rosfors S, Gillgren P. Outcome after 7 years of carotid artery stenting and endarterectomy in Sweden - single centre and national results. Eur J Vasc Endovasc Surg. 2012;43(5):499-503.

14. Brott T, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11-23.

15. Bisdas T, Egorova N, Moskowitz AJ, Sosunov EA, Marin ML, Faries PL, et al. The impact of gender on in-hospital outcomes after carotid endarterectomy or stenting. Eur J Vasc Endovasc Surg. 2012;44(3):244-50.

16. Zhang X, Ma H, Li L, Zou J, Jiao Y, Zhang X, et al. A meta-analysis of transfemoral endovascular treatment of common carotid artery lesions. World Neurosurg. 2019;123:89-94.

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REVIEW ARTICLES
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NEUROCOGNITIVE CHANGES IN CANCER PATIENTS AS A CURRENT CHALLENGE IN PSYCHO-ONCOLOGY

NEUROKOGNITIVNE PROMENE KOD ONKOLOŠKIH PACIJENATA KAO AKTUELNI IZAZOV U PSIHOONKOLOGIJI

Aleksandra KOVAČ[1, 5], Vojislava BUGARSKI IGNJATOVIĆ[1, 2], Snežana TOVILOVIĆ[3], Jasmina BOBAN[4, 5] and Duško KOZIĆ[4, 5]

Summary

Introduction. Along with a high intensity emotional distress, cancer patients often face neurocognitive changes that are particularly pronounced after chemotherapy. **Clinical features of neurocognitive deficits in non-central nervous system cancer patients.** So far**,** studies have demonstrated that neurocognitive changes most often occur in domains of executive functions, attention and concentration, working memory, information processing speed and visuospatial abilities, but there is still no definite protocol for the diagnosis and management of this condition. **Potential causal mechanisms and risk factors.** Apart from chemotherapy, there are other factors associated with the development and manifestation of neurocognitive deficits in cancer patients: genetic, biological, psychological and socio-demographic. **Assessment of cancer-related cognitive impairments.** When assessing potential cognitive impairments, it is beneficial to combine neuropsychological test battery and self-report questionnaires for the assessment of cognitive and affective status, as well as modern neuroimaging methods that will indicate neural (structural and functional) changes underlying neurocognitive deficit. **The role of psychosocial factors: implications for future research**. In addition to cognitive reserve and emotional status, the patient's personal characteristics may very likely play an important role in explaining neurocognitive functioning and neurocognitive adaptation of cancer patients upon completion of treatment. **Conclusion.** Further studies are needed to elucidate the mechanisms underlying neurocognitive changes in cancer patients, with special emphasis on the contribution of psychosocial factors. Based on the novel findings, adequate and timely cognitive rehabilitation treatment will be provided for patients suffering from malignant diseases.

Key words: Neurocognitive Disorders; Cancer Survivors; Psycho-Oncology; Neuropsychology; Neuroimaging; Cognitive Dysfunction; Affective Symptoms; Chemotherapy-Related Cognitive Impairment; Psychological Distress; Personality

Sažetak

Uvod. Uz visok intenzitet emocionalnog distresa, onkološki pacijenti često se suočavaju sa neurokognitivnim promenama koje postaju naročito izražene nakon hemioterapije. **Kliničke manifestacije neurokognitivnog deficita kod pacijenata koji nemaju tumor centralnog nervnog sistema.** Dosadašnje studije su pokazale da se kognitivne smetnje najčešće javljaju u domenima egzekutivnih funkcija, pažnje i koncentracije, radne memorije, brzine procesiranja informacija i vizuospacijalnih sposobnosti, te za iste još uvek ne postoji krajnje definisan protokol dijagnostike i lečenja. **Potencijalni etiološki mehanizmi i faktori rizika.** Pored hemioterapije, važnu ulogu u nastanku i manifestaciji neurokognitivnog deficita kod onkoloških pacijenata imaju i drugi: genetski, biološki, psihološki i sociodemografski faktori. **Metode procene neurokognitivnog deficita kod onkoloških pacijenata.** Za procenu eventualnog neurokognitivnog oštećenja najbolje je koristiti kombinaciju koja uključuje neuropsihološku dijagnostiku i inventare za samoprocenu kognitivnog i afektivnog statusa, kao i savremene metode neuroimidžing dijagnostike koje će ukazati na neuralne (strukturalne i funkcionalne) promene koje leže u osnovi neurokognitivnog deficita. **Uloga psihosocijalnih faktora - smernice za buduća istraživanja.** Pored kognitivne rezerve i afektivnog statusa, potencijalnu ulogu u objašnjenju neurokognitivnog funkcionisanja i neurokognitivne adaptacije po završenom lečenju vrlo verovatno mogu imati i karakteristike ličnosti obolelih. **Zaključak.** Neophodne su nove studije koje će omogućiti dalje rasvetljavanje mehanizama koji leže u osnovi neurokognitivnih promena kod onkoloških pacijenata, sa posebnim akcentom na doprinos psihosocijalnih faktora, a na osnovu kojih će dalje biti omogućen i adekvatan i pravovremeni kognitivno-rehabilitacioni tretman obolelih od malignih bolesti.

Ključne reči: neurokognitivni poremećaji; onkološki bolesnici; psiho-onkologija; neuropsihologija; neuroimidžing; kognitivni poremećaji; afektivni simptomi; kognitivni poremećaji uzrokovani hemoterapijom; psihološki poremećaj; ličnost

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Abbreviations
CNS – central nervous system
DNA – deoxyribonucleic acid
fMRI – functional magnetic resonance imaging
CRCI – chemotherapy-related cognitive impairment
COMT – catechol-O-methyltransferase
BDNF – brain-derived neurotrophic factor

Introduction

Emotional distress, anxiety, depression and adjustment disorders have long been recognized as significant psychological concomitants of malignant diseases, but recently the attention of clinicians and researchers has also been drawn to cognitive impairment in cancer patients. The phenomenon known as "chemobrain" was noted by systematic studies focusing on side effects caused by different cytostatic drugs and it includes a sense of mental fatigue and other cognitive changes reported by those suffering from malignant diseases. Studies have demonstrated that not only can difficulties in cognitive functioning occur during and directly after chemotherapy, but can also be present before the beginning of treatment, but also for years after cancer treatment ends [1, 2]. The onset of neurocognitive deficits, although mainly provoked by cytostatic agents affecting the central nervous system (CNS), appears to be influenced by other factors as well; this has resulted in recent introduction of the term cancer-related cognitive impairment (CRCI) used for this phenomenon [3]. Furthermore, as these neurocognitive changes are often subtle in intensity, their recognition requires more complex diagnostics, which makes it difficult not only to determine their etiology and mechanisms of manifestation, but also developing suitable therapeutic approaches. Although many questions in this area remain open, neuroscience with its interdisciplinary approach is certainly making a significant progress in elucidating different aspects of this phenomenon.

Clinical features of neurocognitive deficits in non-central nervous system cancer patients

Previous studies have shown that cognitive impairment most often occurs in the domain of executive functions, attention and concentration, memory, and information processing speed [1–3]. The data on the incidence of cognitive deficits in cancer patients vary from one-third to more than one-half, depending on methodological aspects of the respective studies [4]. The CRCI has most frequently been investigated in patients suffering from breast cancer, but research shows that cognitive changes may occur in patients with other non-CNS cancers as well, i.e. testicular, gynecologic, prostate, colorectal cancer, non-Hodgkin's and Hodgkin's lymphoma [3, 4]. Despite the fact that cognitive difficulties are most pronounced directly after completion of chemotherapy [1], mild cognitive problems may persist for years. In comparison with patients treated only with local therapy, breast cancer and lymphoma survivors treated with systemic chemotherapy scored significantly lower in the domains of verbal memory and psychomotor functioning even ten years after completing the treatment [4]. Also, in some survivors, cognitive difficulties manifest as a subjective sense of impaired cognitive functioning, which does not necessarily correlate with cognitive achievement on neuropsychological tests which remain the same, or with affective symptoms often associated with cognitive difficulties. A possible explanation for this discrepancy is that the perceived cognitive difficulties, despite good results on neuropsychological tests, may be a consequence of neurofunctional disturbances that follow brain damage due to treatment [5]. Neurocognitive deficit, especially when pronounced, along with impaired memory, manifests in the form of planning and decision making difficulties, problems in organization, difficulties in acquiring new skills, or with multitasking, problems with finding the appropriate word or naming objects, but also with emotion regulation deficits. Today, many patients return to work after completing treatment and their cognitive difficulties become more evident in the context of heightened demands with a potential of provoking additional psychosocial distress. Many cancer survivors report cognitive impairments being burdensome for years, affecting their self-confidence and social relationships, forcing them to use compensatory strategies in adjusting to work requirements [3]. It is undeniable that intact cognitive functions are extremely important for the quality of life of cancer patients and treatment outcome. More recent studies suggest that cognitive impairment not only affects adherence but also the course and outcome of malignant disease, since it increases the risk of mortality in older patients up to six times [6]. Unfortunately, there are still no well-defined protocols for prevention and treatment of neurocognitive deficits in cancer patients. The up-to-date research findings point to the benefits of physical activity, cognitive-behavioral therapy and cognitive rehabilitation, while neurostimulating, neuroprotectant and antineuroinflammatory therapeutic agents, along with some antidepressants and antidementia drugs, are still in the testing phase [3]. This implies that the timely and adequate detection of potential neurocognitive deficits is of crucial importance in the treatment of cancer patients and should be included in clinical protocols.

Potential causal mechanisms and risk factors

Although passing of chemotherapy through the hematoencephalic barrier was earlier thought to be impossible, today it is assumed that even a low concentration of many cytostatic agents, especially platinum-based chemotherapy, can penetrate the blood-brain barrier (BBB) and thus lead to damage of the neural progenitor cells and oligodendrocytes, as well as hippocampal neurons [5, 7]. Apart from these direct effects, neurocognitive deficits in oncology patients can be provoked by indirect mech-

anisms such as metabolic and hormonal changes brought on by treatment, by activation of inflammatory cytokines, genetic polymorphism, fatigue and other bodily damage, as well as certain psychological factors [3]. Negative impact on cognitive functions seems to be most frequently realized through proinflammatory mediators and cytokines (e.g. tumor necrosis alpha, interleukin-6). One of the hypothesis is that by entering the brain peripheral proinflammatory mediators and cytokines stimulate glial cells to release central cytokines, which in turn cause local neuronal injury resulting in different cognitive symptoms [8]. Furthermore, not only does chemotherapy seem to take effect through cytokines that compromise the metabolism of key neurotransmitters involved in the regulation of sleep, learning, memory and mood (e.g. noradrenaline, serotonin and dopamine) [9], but a similar effect, although not as intense, can be caused by the tumor itself alongside different treatment modalities and processes, psychological and emotional distress, that all provoke systemic inflammation and compromise the immune system during a malignant disease [8]. Also, elevated oxidative stress, i.e. oxygen free radicals that are released during cytostatic therapy, can lead to deoxyribonucleic acid (DNA) damage in neurons, and the oxidative damage of DNA can be associated with lower levels of cognitive functioning and lower frontal lobe gray matter density, as well as poorer functional magnetic resonance imaging (fMRI) activity for years after completion of chemotherapy treatment [10]. Hormonal therapy used in the treatment of breast cancer in patients with estrogen positive receptors, which acts through blocking and lowering hormonal levels, is also linked to poorer cognitive functioning, since, among its other effects, it can lead to the reduction of cholinergic activity, decrease the serotonin receptors' activity and most probably accelerate the cell aging process due to the antioxidative effect of estrogen [11], while one of the mechanisms that explains the development of CRCI is exactly accelerated aging. Among the predisposing factors for CRCI, there are also findings about the apolipoprotein E gene ε4 (ApoE4) that codes catechol-O-methyltransferase (COMT), and the brain-derived neurotrophic factor (BDNF) involved in neural reparation and long-term potentiation. Studies aimed at establishing the importance of these genes in the etiology of CRCI have shown that breast cancer and lymphoma survivors with at least one ε4 allele score significantly lower in domains of visual memory and spatial abilities, as well as in the domain of psychomotor functioning, compared to persons who are not carriers of this allele [12]. Compared to COMT Met carriers, COMT Val carriers score lower on tests assessing attention, verbal fluency and motor speed [13], while carriers of the BDNF Met allele are more resilient to CRCI, especially in the domain of verbal fluency and multitasking ability [14]. The patients' age and cognitive reserve capacity are factors that contribute to their cognitive achievement, in the way that older patients and those with lower education levels score significantly lower on neuropsychological tests after the completion of chemotherapy treatment, e.g. have poorer results on information processing speed [15]. Etiologic factors for the occurrence of cognitive deficit in patients seem to vary, i.e. different patients are vulnerable to different mechanisms [9], making the approach to this phenomenon even more complex.

The assessment of cancer-related cognitive impairment

As there is still no general agreement on the affected cognitive domains and underlying neural changes, and due to the discrepancy that is sometimes registered between subjective and objective measures, in the process of diagnosing CRCI it is best to use a combination of neuropsychological assessment, self-reports, and neuroimaging whenever possible.

Neuropsychological assessment

According to the International Cognition and Cancer Task Force, a neuropsychological battery of tests is the "gold standard" for the assessment of CRCI [16]. Although there is still no standardized test battery for the assessment of this phenomenon, in order to achieve more research cohesion, authors recommend using tests aimed at assessing key cognitive domains in which the impairment is registered: e.g. Hopkins Verbal Learning Test-Revised for verbal learning and memory, Controlled Oral Word Association Test, or the Multilingual Aphasia Examination for speeded lexical fluency and Trail Making Test for processing speed, out of which the last two also cover some aspects of executive function, with a recommendation to use additional tests for the assessment of working memory [16]. Other instruments that can be used in assessing CRCI include Mini-Mental State Examination, Montreal Cognitive Assessment Scale, Rey Auditory Verbal Learning Test, Rey Complex Figure Test, selected subtests from the Wechsler Memory Scale, and The Wisconsin Card Sorting Test [2, 6, 17]. Due to the many methodological limitations of cross-sectional studies, it is recommended to use a longitudinal design with mandatory baseline cognitive assessments prior to chemotherapy [16], since up to one third of patients may manifest a cognitive deficit even before starting the treatment [1]. Moreover, each neuropsychological assessment must include an assessment of affective status, especially when it comes to cancer patients, whose diagnosis and demanding treatment, already carries a high prevalence of psychological distress, which can affect their cognitive functions as well [18–21]. There are a number of instruments appropriate for this purpose, e.g. the Depression, Anxiety and Stress Scales, Positive and Negative Affect Schedule, Beck Depression Inventory-II, Beck Anxiety Inventory, and Spielberger's State-Trait Anxiety Inventory [1, 20, 21]. Fatigue and sociodemographic factors should also be taken into account for the neurocognitive assessment, especially if we consider the fact that

the elderly population, along with CRCI, is at a higher risk for other neurodegenerative processes [22].

Self-report assessment

Self-report questionnaires provide insight into how patients perceive their problem and how they function in everyday situations. The discrepancy registered between the achievement on a neuropsychological battery of tests and self-report instruments is often linked to mood changes, but quite possibly also with compensatory strategies patients use when confronted with cognitive demands [9]. This is probably even more pronounced in individuals with a higher cognitive reserve, since they are presumed to be more capable of activating alternative neural networks, thus succeeding to function as before in spite of significant structural damage [23], although with a subjective sense of putting in more cognitive effort. The most frequently used instruments include Functional Assessment of Cancer Therapy - Cognitive Function and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [3], more precisely the cognitive functioning subscale of this questionnaire, which assesses cognitive aspects of the quality of life. Additionally, the Behavior Rating Inventory of Executive Function - Adult Version, as one of the more ecologically valid complementary instrument for assessing behavioral aspects of executive functions [24], can be applied when performing a more complex examination [17,21].

Neuroimaging assessment and findings

The most valuable data on structural and functional changes and mechanisms that are the core feature of the patients' neurocognitive deficits come from neuroimaging studies. However, the potentials of multimodal magnetic resonance imaging in defining the exact pathophysiology and underlying biological mechanisms are not yet fully exploited. The fMRI has shown that chemotherapy, particularly anthracycline-based therapy compared to non-anthracycline protocols, is the risk factor for cognitive deficits in patients with breast cancer. The affected brain areas include the left precuneus connections with the frontal, hippocampal, and lateral parietal regions, and on the neurocognitive level, they are primarily reflected in verbal memory impairment (immediate and delayed recall) [25]. Also, this method identifies reduced activity in brain areas responsible for the executive deficits which is most often seen in cancer patients after chemotherapy treatment, e.g. decreased activity of the dorsolateral prefrontal cortex, as well as significantly lower functional connectivity of anterior cingulate cortex [26]. Furthermore, negative effects of chemotherapy on executive function networks that support higher level cognition can persist for years upon completion of treatment [26]. This is also supported by findings obtained by voxel-based morphometry that point to significantly reduced grey matter volume in the left middle frontal gyrus and the left superior frontal gyrus in patients treated with chemotherapy, which is followed by self-reported difficulties in executive functions, primarily in the domain of initiation [27]. Some studies have found a reduced hippocampal volume in patients treated with chemotherapy, which is linked to poorer ability to access episodic autobiographical memories [28]. Along with the reduced grey matter volume in different regions, diffusion tensor imaging in breast cancer patients treated by chemotherapy also registered alterations in white matter microstructure, e.g. significant increases in mean diffusivity and radial diffusivity in the genu of the corpus callosum, decreased fractional anisotropy values in corpus callosum, frontal, parietal, and occipital white matter tracts, and a larger decline in white matter integrity in the right superior longitudinal fasciculus and corticospinal tract, which is followed by significant difficulties in cognitive and physical functioning, as well as disturbances in the domain of attention and verbal memory [29]. Magnetic resonance spectroscopy results, although rare, have thus far pointed to lower levels of N-acetyl aspartate in deep white matter of the left cerebral hemisphere in breast cancer patients treated with high-dose chemotherapy [30], lower N-acetyl-aspartate/creatinine ratio [31] and lower N-acetyl-aspartate and choline and N-acetyl-aspartate and myo-inositol ratios in breast cancer patients treated with chemotherapy [32]. Increased myo-inositol and choline, with decreased levels of N-acetyl-aspartate in the prefrontal cortex have been linked to subjective memory difficulties, but not to perceived difficulties in executive functions [32]. Although it is still unclear to what extent structural and functional brain changes are reversible, the persistence of some despite the later improved neurocognitive functioning, suggests a significant role of brain plasticity in alleviating the possible negative effects of chemotherapy on cognition [5].

The role of psychological and social factors: implications for future research

Cognitive reserve and cognition

The fact that the neurotoxic effects of chemotherapy and the malignant disease and its treatment in general, will not have the same intensity on all patients' cognitive functions, speaks in favor of the existence of factors that increase the risk and make the patients more vulnerable to negative side-effects of the illness and treatment, while other factors may act protectively. We have already described some of these factors, and what remains to be elaborated further is the role and the importance of cognitive reserve on the patients' neurocognitive functioning. The concept of cognitive reserve can explain the frequent discrepancy between brain damage and its clinical manifestation, i.e. cognitive reserve is an individual's ability to efficiently use the existing neural networks in response to cognitive demands even in case of brain injury [23]. The brain is thought to have combat strategies to overcome the injury by using either the existing approach to cognitive information processing or by developing novel compensatory strategies. This implies that the individuals with

higher cognitive reserve capacity, which can be restored throughout the course of life (including a wealth of intellectual and occupational activities and knowledge acquired during life), are more apt in dealing with brain damage compared to those with a lower cognitive reserve [23]. This is also supported by studies that demonstrate that in dealing with age-related brain pathology or Alzheimer's disease, individuals with a higher cognitive reserve remain without visible symptoms much longer than those with a low cognitive reserve, who manifest the symptoms at an earlier stage [33]. Likewise, patients with breast cancer and lower cognitive reserve prior to treatment, upon its completion manifest more difficulties in the domain of information processing and executive functions [15, 34]. A single proxy or a combination of proxies are often used for measuring the construct, which primarily includes variables of socio-economic status such as education level and occupation, but also cognitively stimulating activities that summarize one's experience. The premorbid intelligence quotient is also a commonly used proxy [23, 33]. It is suggested that socioeconomic status affects brain development and cognition, through different prenatal factors, quality of parental care and intensity of cognitive stimulation, which all later reflects differences in language processing and executive functions (particularly in the domains of working memory and inhibitory control), but differences can also be seen in emotional processing [35]. Physical activity has been found to be a significant protective factor of cognitive functioning in cancer patients treated with chemotherapy as well, e.g. patients who increased their physical activities showed significant improvement in cognitive health [17]. Lately, there is a tendency to design and apply an all encompassing questionnaire that would cover all the complexity of this construct; however, due to the existing methodological and measurement challenges, the authors who systematically studied the quality of the existing questionnaire for assessment of cognitive reserve agreed that a final recommendation for one specific questionnaire cannot be made [36].

Personality, stress, anxiety, depression and cognition

Emotional distress and mood disorders are well known psychological factors that affect cognitive functions, and these have to be controlled during neuropsychological assessment, while the importance of other factors, including the personality, remains insufficiently explored up to date. Studies so far have demonstrated that intense and chronic stress, as well as increased cortisol level associated with stress, weaken prefrontal networks and contribute to hippocampal volume reduction and decrease neurogenesis in adults, so it is a risk factor for difficulties in higher-level cognitive processes and executive function [37, 38]. Anxiety resulting from insufficient control of intrusive thoughts intensifies a person's focus on negative stimuli and affects executive functions, especially working memory [39], while depression is linked to deficits in executive function, memory, attention and concentration [40]. Long lasting psychological distress is generally associated with cognitive deterioration and increases the risk for the development of dementia [41]. The psycho-oncology research findings indicate that compared to non-chemotherapy patients, chemotherapy patients have higher levels of stress, anxiety and depression as well as more neurocognitive disturbances associated with them [21, 42]. Emotional distress associated with CRCI or its intensification, have been registered, for instance, in the domains of verbal memory and concentration, speed of information processing and executive functions [42]. Preliminary results of our study that combined neuropsychological assessment and magnetic resonance neuroimaging, point to the atrophy of nucleus accumbens following chemotherapy treatment in breast cancer patients [43], which can be linked to the previously registered affective state but also to deficits in the domain of executive functions which are significantly associated with the intensity of patients' emotional distress [21]. Since basic personality dimensions are strong determinants of behavioral, emotional and cognitive patterns and since they generally affect one's lifestyle, personal interests and health related behaviors [44], i.e. adaptation to cancer and its treatment [45], and considering the common neural substrates of certain aspects of personality and cognitive functions [46], we believe that they can be important factors of vulnerability, but also the factors of resilience, in the context of neurocognitive adaptation of cancer patients, thus significantly contributing to the cognitive reserve. The most recent studies indicate that high neuroticism, i.e. increased tendency toward experiencing distress and low conscientiousness, i.e. poorer organizational abilities and tendency toward less disciplined and responsible behavior, are strongly associated with cognitive health and increased risk for mild cognitive impairment and dementia [47, 48]. Also, openness to experience, characterized by intellectual curiosity and eagerness to search for new and different experiences, which strengthens one's cognitive reserve through numerous cognitive activities, has proven to be a factor of resilience to cognitive decline in older adulthood [49]. The findings from our study support the importance of personality traits for neurocognitive functioning of cancer patients, point to a significant correlations between high neuroticism and difficulties in the domain of behavioral regulation, and between low conscientiousness and difficulties in the domain of metacognition in breast cancer patients prior to chemotherapy treatment [50]. We also found increased vulnerability for manifestation of executive function deficits in patients with a high negative affectivity as a personality trait [21]. Certainly, these findings require further longitudinal research.

Conclusion

As demonstrated, cancer-related cognitive impairment is a phenomenon with multiple clinical aspects. However, the answers to numerous questions

on the etiology and mechanisms that predispose someone to develop and manifest it are still lacking. Along with factors associated with the malignant disease and its treatment, biological and genetic factors, as well as specific socio-demographic characteristics, the question on the significance of psychological factors as determinants of both vulnerability and resilience to neurocognitive deficits after chemotherapy treatment still remain open. Since the most effective strategy for preventing and treating neurocognitive deficits in cancer patients is still in research phase, shedding light on the role of psychological factors would contribute not only to prevention and timely recognition of neurocognitive deficits in the most vulnerable patients, but also to the development and implementation of different cognitive-behavioral interventions and cognitive rehabilitation programs with the aim of improving neurocognitive functioning and quality of life of cancer patients. Taking this into account, intense collaboration of neuro-radiology and clinical psychology specialists is needed to clarify the etiological mechanisms and possible treatment for cancer-related cognitive impairment, by correlating findings obtained by modern neuroimaging methods and neuropsychological diagnostics. A cooperation with all other specialists involved in the diagnostics, treatment, and rehabilitation of cancer patients is also required.

References

1. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. 2010;116(14):3348-56.

2. Koppelmans V, Breteler MM, Boogerd W, Seynaeve C, Gundy C, Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. J Clin Oncol. 2012;30(10):1080-6.

3. Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. Ann Oncol. 2019;30(12):1925-40.

4. Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol. 2002;20(2):485-93.

5. Wigmore P. The effect of systemic chemotherapy on neurogenesis, plasticity and memory. Curr Top Behav Neurosci. 2013;15:211-40.

6. Libert Y, Dubruille S, Borghgraef C, Etienne AM, Merckaert I, Paesmans M, et al. Vulnerabilities in older patients when cancer treatment is initiated: does a cognitive impairment impact the two-year survival? PLoS One. 2016;11(8):e0159734.

7. Andres AL, Gong X, Di K, Bota DA. Low-doses of cisplatin injure hippocampal synapses: a mechanism for 'chemo' brain? Exp Neurol. 2014;255:137-44.

8. Wang XM, Walitt B, Saligan L, Tiwari AFY, Cheung CW, Zhang ZJ. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. Cytokine. 2015;72(1):86-96.

9. Asher A, Myers JS. The effect of cancer treatment on cognitive function. Clin Adv Hematol Oncol. 2015;13(7):441-50.

10. Conroy SK, McDonald BC, Smith DJ, Moser LR, West JD, Kamendulis LM, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Cancer Res Treat. 2013;137(2):493-502.

11. Mandelblatt JS, Hurria A, McDonald BC, Saykin AJ, Stern RA, VanMeter JW, et al. Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? Semin Oncol. 2013;40(6):709-25.

12. Ahles TA, Saykin AJ, Noll WW, Furstenberg CT, Guerin S, Cole B, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology. 2003;12(6):612-9.

13. Small BJ, Rawson KS, Walsh E, Jim HS, Hughes TF, Iser L, et al. Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. Cancer. 2011;117(7):1369-76.

14. Ng T, Teo SM, Yeo HL, Shwe M, Gan YX, Cheung TY, et al. Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. Neuro Oncol. 2016;18(2):244-51.

15. Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol. 2010;28(29): 4434-40.

16. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011;12(7):703-8.

17. Floyd R, Dyer AH, Kennelly SP. Non-pharmacological interventions for cognitive impairment in women with breast cancer post-chemotherapy: a systematic review. J Geriatr Oncol. In press. Doi: https://doi.org/10.1016/j.jgo.2020.05.012.

18. Kovač A, Popović-Petrović S, Nedeljković M, Kojić M, Tomić S. Post-operative condition of breast cancer patients after surgery from standpoint of psycho-oncology: preliminary results. Med Pregl. 2014;67(1-2):43-8.

19. Popović-Petrović S, Kovač A, Kovač N, Tovilović S, Novakov I, Ćulibrk D. Secondary lymphedema of the arm, the perception of disease, self-efficacy, and depression as determinants of quality of life in patients with breast cancer. Vojnosanit Pregl. 2018;75(10):961-7.

20. Kovač A, Tovilović S, Bugarski-Ignjatović V, Popović-Petrović S, Tatić M. The role of cognitive emotion regulation strategies in health related quality of life of breast cancer patients. Vojnosanit Pregl. 2020;77(10):1032-40.

21. Kovač A, Bugarski-Ignjatović V, Tovilović S, Kozić D, Trifunović J, Popović-Petrović S, et al. The impact of negative affect and emotional distress on executive functions in breast cancer patients. In: 1st PSU-UNS joint conference on medical science and technology: book of abstracts; 2018 Mar 5-7; Krabi, Thailand. Hat Yai District: Faculty of Medicine, PSU and UNS; 2018. p. 101-2.

22. Lange M, Rigal O, Clarisse B, Giffard B, Sevin E, Barillet M, et al. Cognitive dysfunctions in elderly cancer patients: a new challenge for oncologists. Cancer Treat Rev. 2014;40(6):810-7.

23. Stern Y, Barnes CA, Grady C, Jones RN, Raz N. Brain reserve, cognitive reserve, compensation, and maintenance: operationalization, validity, and mechanisms of cognitive resilience. Neurobiol Aging. 2019;83:124-9.

24. Roth RM, Isquith PK, Gioia GA. BRIEF-A: Behavior Rating Inventory of Executive Function - Adult Version. Lutz: Psychological Assessment Resources; 2005.

25. Kesler SR, Blayney DW. Neurotoxic effects of anthracycline- vs nonanthracycline-based chemotherapy on cognition in breast cancer survivors. JAMA Oncol. 2016;2(2):185-92.

26. Miao H, Li J, Hu S, He X, Partridge SC, Ren J, et al. Long-term cognitive impairment of breast cancer patients after chemotherapy: a functional MRI study. Eur J Radiol. 2016;85(6):1053-7.

27. McDonald BC, Conroy SK, Smith DJ, West JD, Saykin AJ. Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. Brain Behav Immun. 2013;30(Suppl 0):S117-25.

28. Kesler S, Janelsins M, Koovakkattu D, Palesh O, Mustian K, Morrow G, et al. Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain Behav Immun. 2013;30(Suppl 0):S109-16.

29. Chen BT, Ye N, Wong CW, Patel SK, Jin T, Sun CL, et al. Effects of chemotherapy on aging white matter microstructure: a longitudinal diffusion tensor imaging study. J Geriatr Oncol. 2020;11(2):290-6.

30. Stouten-Kemperman MM, de Ruiter MB, Koppelmans V, Boogerd W, Reneman L, Schagen SB. Neurotoxicity in breast cancer survivors ≥10 years post-treatment is dependent on treatment type. Brain Imaging Behav. 2015;9(2):275-84.

31. de Ruiter MB, Reneman L, Boogerd W, Veltman DJ, Caan M, Douaud G. Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging. Hum Brain Mapp. 2012;33(12):2971-83.

32. Kesler SR, Watson C, Koovakkattu D, Lee C, O'Hara R, Mahaffey ML, et al. Elevated prefrontal myo-inositol and choline following breast cancer chemotherapy. Brain Imaging Behav. 2013;7(4):501-10.

33. Tucker AM, Stern Y. Cognitive reserve in aging. Curr Alzheimer Res. 2011;8(4):354-60.

34. Kesler SR, Kent JS, O'Hara R. Prefrontal cortex and executive function impairments in primary breast cancer. Arch Neurol. 2011;68(11):1447-53.

35. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. Nat Rev Neurosci. 2010;11(9):651-9.

36. Kartschmit N, Mikolajczyk R, Schubert T, Lacruz ME. Measuring Cognitive Reserve (CR) - a systematic review of measurement properties of CR questionnaires for the adult population. PLoS One. 2019;14(8):e0219851.

37. Lucassen PJ, Oomen CA. Stress, hippocampal neurogenesis and cognition: functional correlations. Front Biol (Beijing). 2016;11(3):182-92.

38. Arnsten AF. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015;18(10):1376-85.

39. Lukasik KM, Waris O, Soveri A, Lehtonen M, Laine M. The relationship of anxiety and stress with working memory performance in a large non-depressed sample. Front Psychol. 2019;10:4.

40. Kaser M, Zaman R, Sahakian BJ. Cognition as a treatment target in depression. Psychol Med. 2017;47(6):987-9.

41. Simard M, Hudon C, van Reekum R. Psychological distress and risk for dementia. Curr Psychiatry Rep. 2009;11(1):41-7.

42. Cheung YT, Shwe M, Chui WK, Chay WY, Ang SF, Dent RA, et al. Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. Ann Pharmacother. 2012;46(12):1645-55.

43. Boban J, Trifunović J, Kovač A, Kozić D. Chemobrain: uloga magnetnorezonantne volumetrije u detekciji promena nakon citostatske terapije karcinoma dojke. In: Drugi srpski senološki kongres: zbornik sažetaka; 2019 maj 24-25; Novi Sad, Srbija. Novi Sad: Senološko Udruženje Srbije i Centar za KME Medicinskog fakulteta u Novom Sadu; 2019. p. 40.

44. Joyner C, Rhodes RE, Loprinzi PD. The prospective association between the five factor personality model with health behaviors and health behavior clusters. Eur J Psychol. 2018;14(4):880-96.

45. Macía P, Gorbeña S, Gómez A, Barranco M, Iraurgi I. Role of neuroticism and extraversion in the emotional health of people with cancer. Heliyon. 2020;6(7):e04281.

46. Kabbara A, Paban V, Weill A, Modolo J, Hassan M. Brain network dynamics correlate with personality traits. Brain Connect. 2020;10(3):108-20.

47. Terracciano A, Stephan Y, Luchetti M, Albanese E, Sutin AR. Personality traits and risk of cognitive impairment and dementia. J Psychiatr Res. 2017;89:22-7.

48. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Five-factor model personality traits and cognitive function in five domains in older adulthood. BMC Geriatr. 2019;19(1):343.

49. Franchow EI, Suchy Y, Thorgusen SR, Williams P. More than education: openness to experience contributes to cognitive reserve in older adulthood. J Aging Sci. 2013;1(2):1-8.

50. Bugarski-Ignjatović V, Kovač A, Smederevac S, Tovilović S, Trifunović J. Personality traits and executive functions in breast cancer patients. In: Popov B, editor. Current trends in psychology: book of abstracts; 2019 Oct 24-27; Novi Sad, Serbia. Novi Sad: Faculty of Philosophy; 2019. p. 204-6.

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NOVEL BIOPHOTONICS-BASED TECHNIQUES IN DENTAL MEDICINE – A LITERATURE REVIEW

NOVE TEHNIKE ZASNOVANE NA BIOFOTONICI U DENTALNOJ MEDICINI – PREGLED LITERATURE

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Summary

Introduction. Biophotonics deals with interactions between light and biological matter, integrating knowledge of physics, chemistry, engineering, biology, and medicine for solving specific biomedical or life science problems. Due to the ability to provide non-invasive, highly sensitive tissue information and inducing specific localized tissue ablation, biophotonics-based technologies may be of utmost importance in improving dental healthcare. The aim of this review article is to give an overview of contemporary biophotonics-based technologies and their applications in dental research and clinical practice. **Various applications of biophotonics-based technologies.** Biomedical imaging techniques (nonlinear microscopy methods and optical coherence tomography), photo-mechanical methods (digital holographic interferometry, photo-elasticity, digital image correlation, Moiré interferometry), optical spectroscopy techniques (Raman and Fourier transform infrared spectroscopy, Brillouin light scattering spectroscopy), fiber Bragg grating sensors, photodynamic therapy, photo-biostimulation, and femtosecond laser applications are presented in this paper. **Conclusion.** In accordance with the modern tendencies of prevention and timely diagnosis of oral diseases, biophotonics may be considered the leading scientific discipline on the path of progress of dental medicine and technology. Therefore, this paper provides an overview of modern methods based on biophotonics and summarizes their applicability focusing on the field of dental medicine.

Key words: Optics and Photonics; Lasers; Microscopy; Optical Imaging; Dentistry; Mouth Diseases

Sažetak

Uvod. Biofotonika se bavi interakcijom svetlosti sa biološkom materijom, integrišući znanja iz fizike, biologije, hemije, tehnike i medicine za rešavanje određenog biomedicinskog ili prirodnonaučnog problema. Zbog mogućnosti neinvazivnog pružanja visokoosetljivih informacija o tkivu i indukovanja specifične lokalizovane ablacije tkiva, tehnologije zasnovane na biofotonici mogu imati ogromnu vrednost za poboljšanje stomatološke zdravstvene zaštite. Cilj ovog preglednog rada je da se pruži prikaz savremenih tehnologija zasnovanih na biofotonici i njihove primene u stomatološkim istraživanjima i kliničkoj praksi. **Različite primene tehnika zasnovanih na biofotonici**. Tehnike biomedicinskog snimanja (metode nelinearne mikroskopije i optička koherentna tomografija), fotomehaničke metode (digitalna holografska interferometrija, fotoelastičnost, digitalna korelacija slike, Muarova (*Moire*) interferometrija), tehnike optičke spektroskopije (*Raman* i Furijeova (*Fourier*) infracrvena spektroskopija, Briluanova (*Brillouin*) spektroskopija), fiber Bragovi (*Bragg*) senzori, fotodinamička terapija, fotobiostimulacija i primena femtosekundnog lasera predstavljeni su u ovom radu. **Zaključak.** U skladu sa savremenim tendencijama prevencije i pravovremene dijagnostike oralnih oboljenja, biofotonika se može smatrati vodećom naučnom disciplinom na putu napretka dentalne medicine i tehnologije. Stoga, ovaj rad pruža pregled savremenih metoda zasnovanih na biofotonici i rezimira njihovu primenljivost usredsređujući se na oblast dentalne medicine.

Ključne reči: optika i fotonika; laseri; mikroskopija; optički imidžing; stomatologija; bolesti usta

Introduction

Biophotonics, defined as a field of biomedical optics, is a novel interdisciplinary scientific approach, relating to the interaction of light with biological matter [1]. Accordingly, biophotonics integrates physics, chemistry, engineering, biology, and medicine for solving specific biomedical or life science problems [2]. It combines optical methods for studying and manipulating biological specimens at the subcellular, cellular, tissue, and organ levels, while covering biomedical diagnosis, research, and therapy [3]. From a general viewpoint, photonics is defined as "the technology of generating and harnessing light and other forms of radiant energy whose quantum unit is the photon" [4]. It includes all light-based optical technologies used for information processing and transfer, measurement of changes in physical parameters, as well as physically modifying material characteristics [5]. Ever

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Abbreviations

2PEF – two-photon excited fluorescence
SHG – second harmonic generation
DHI – digital holographic interferometry
FTIR – Fourier transform infrared
BLS – Brillouin light scattering
FOS – fiber optic-based sensors
PDT – photodynamic therapy

since the first demonstration of lasers in 1960, a concentrated source of monochromatic light, photonics has emerged as an indispensable tool for basic life science research [6].

In contemporary dental practice, the principal priorities are early diagnosis and prevention of common oral diseases, as well as the preservation of tooth tissue as much as possible during treatment [7]. The potential of biophotonics-based technologies to provide noninvasive highly sensitive tissue information and induce specifically localized tissue processing may therefore be of immense value [8, 9]. On the other hand, the ability to identify clinically relevant information much earlier than actual signs and symptoms of a disease appear indicates one of their most beneficial features, due to the possibility of performing preventive or minimally invasive treatment procedures [10]. The aim of this review article is to give an overview of contemporary biophotonics-based techniques and their applications in dental research and clinical practice.

Various applications of biophotonics-based techniques

Different ways to classify the application of biophotonics-based techniques have been suggested, albeit very few of them in the field of dental medicine [2, 5, 10–12]. The most convenient approach would probably be the one proposed by Kishen and Asundi [10], with a wide-ranging categorization into research and clinical applications, subdivided into diagnostics and therapeutic approaches **(Table 1)**.

Biomedical imaging techniques

Nonlinear microscopy methods, such as two-photon excited fluorescence (2PEF), second harmonic generation (SHG), and coherent anti-Stokes Raman spectroscopy (CARS) are widely used imaging techniques for studying a variety of biological materials [9, 13, 14]. Recently introduced in dental research practice for investigating internal tooth tissue structure and caries diagnosis, 2PEF, and SHG as noninvasive imaging modalities, provide in situ information of the examined samples without the need for histological tissue sectioning [15, 16]. Moreover, relying on the intrinsic properties of specimens (2PEF images are generated by excitation of tissue fluorophores, while SHG signal is produced by non-centrosymmetric molecules such as collagen), the use of sample labeling is unnecessary [15]. Also, these research modalities can provide three-dimensional information due to their inherent tomographic capabilities [10].

Another optical imaging technique able to provide high-resolution noninvasive images of internal microstructure in living tissues is optical coherence tomography [17]. Unlike 2PEF and SHG, it performs cross-sectional tomographic imaging in situ and in real-time by measuring back-scattered or back-reflected light [17]. At first, applied in ophthalmology for obtaining corneal and retinal images, it is currently well established in dentistry for caries diagnostics, soft tissue analysis, dental materials investigation, etc. [17–19].

Photo-mechanics

In general, photo-mechanics is a scientific discipline that uses optical methods for studying the mechanical response of various structures under an impact of load [20–22]. It includes several non-destructive, highly sensitive (submicron range) techniques such as digital holographic interferometry (DHI), photo-elasticity, digital image correlation, and Moiré interferometry that can provide full-field stress and strain information of specimens in situ [23].

The DHI is a laser optic technique suitable for the submicron measurement of surface deformations in a contactless and non-destructive manner [24]. The basic principle of holographic interferometry considers recording sample images (holograms) at two states, before and after mechanical load, and interference of the resulting holograms visualizing the displacement field of the object [25–27]. By using a digital camera connected to a computer interface in DHI, fast and simple recording and reconstruction of the holographic images in real-time is possible [24]. As for photo-elasticity, it is based on the interference of polarized light transmitted by experimentally loaded models simulating dental structures, providing information on stress distribution and intensity [28]. However, these models are made of light-polarizing material, with obvious difficulty to mimic the variation of biological structure [23]. On the other hand, digital image correlation is a less sensitive method than photo-elasticity, but it is not limited in terms of material and it is easy to use when compared to other optical methods [23].

Table 1. Applications of biophotonics-based techniques in dental medicine
Tabela 1. *Primena tehnologija zasnovanih na biofotonici u dentalnoj medicini*

Diagnostics/*Dijagnostika*	Therapy/*Terapija*	Research/*Istraživanje*
Biomedical imaging *Biomedicinski imidžing*	Photodynamic therapy/*Fotodinamička terapija*	Photo-mechanics/*Fotomehanika*
	Photo-biostimulation/*Fotobiostimulacija*	Optical spectroscopy/*Optička spektroskopija*
	Photo-thermal effects/*Foto-termalni efekti*	Fiber optic sensors/*Fiber optički senzori*

Moiré interferometry is an optical method viable for studying elastic, viscoelastic, and plastic deformations of both isotropic and anisotropic materials [29]. The main advantage of this method is its capability of measuring in-plane deformations (unlike DHI), particularly corresponding to hard tooth tissue functional load [23]. With its high sensitivity, spatial resolution, and clarity, Moiré interferometry is recommended for investigating dental mechanical strain, as well as deformations caused by thermal or hydro (e.g. moisture change, water loss) alterations in tooth tissue [29–31].

Optical spectroscopy methods

The interaction of light (electromagnetic radiation) with matter can lead to a variety of phenomena such as absorption, scattering, reflection, and emission, presenting the basis of optical spectroscopy [1, 10]. Considering different regions of the electromagnetic spectrum that can be employed in spectroscopy for the structural analysis of biological material, various experimental techniques have been developed. Ultraviolet-visible spectroscopy, fluorescence spectroscopy, infrared and Raman spectroscopy, as well as Brillouin light scattering spectroscopy are some of the techniques that may be applied in dental research practice [10, 32].

Raman and Fourier transform infrared (FTIR) spectroscopy are complementary research techniques most frequently used for non-destructive imaging of hard dental tissues and studying dental materials' chemical composition, especially the degree of conversion (DC) [33, 34]. It is commonly perceived that the main advantage of Raman spectroscopy compared to FTIR is its ability to provide a material examination in their native state, but the recent advances in FTIR spectroscopy also allow sample analysis with minimal preparation [34]. In contemporary dental research practice, FTIR has proved to be a useful technique for rapid and precise investigation of chemical structural properties of natural and synthetic materials at the molecular scale [34–37]. On the other hand, the use of Raman spectroscopy has significantly increased due to the advances in instrumentation and technique (e.g. implementation of miniature fiber optical probes) [38–40]. By expanding its field of application into oral hard and soft tissue pathology diagnosis, as well as identification of oral microbial flora, Raman spectroscopy can be considered an important diagnostic tool in the early detection and prognosis of oral diseases [33].

Brillouin light scattering spectroscopy (BLS) measures spectral changes of coherent incident light caused by its interaction with inherent density fluctuations of matter [32]. The frequency shift and linewidth of spectra are linked to the stiffness and viscosity of the material. Unlike standard mechanical tests, BLS is non-invasive and non-destructive. Recently, researchers have performed the first study of hard dental tissues and materials using BLS [16, 32]. By measuring different Brillouin frequency shifts and linewidths of spectra in healthy and decayed dentinal samples, BLS showed the potential to be used as a micro-precise diagnostic laser-based tool in dental medicine to differentiate healthy dentin from a carious lesion, as well as to examine tissue-material interfaces precisely and non-destructively [16, 32]. Based on the research outcomes, a fiber-optic diagnostic tool with a microscopic precision based on BLS could be developed for in situ clinical use in dental practice.

Fiber optic sensors

Optical fibers offer the advantage of adaptability of light beam manipulation providing an optical passage for illuminating inaccessible areas, or for using high-energy laser beams at a specific location for tissue cutting [10]. The progress from conventional sensors to fiber optic-based sensors (FOS), provided a highly sensitive, safe, rapid, and minimally invasive diagnostic method [41]. Being a suitable method for real-time assessment of local temperature and tooth biomechanical behavior, as well as for measurement of dental material polymerization kinetics, fiber Bragg grating sensors seem to be the most convenient and appealing type of FOS in dental medicine [42, 43].

Therapeutic applications

Photodynamic therapy (PDT) is a relatively new treatment modality, still in the early stage of development within the field of dental medicine [44]. Defined as "the light-induced inactivation of cells, microorganisms or molecules" [45], PDT provides an alternative treatment of elimination of malignant cells or pathogenic microorganisms, while overcoming the problems of bacterial, fungal, and viral resistance. However, PDT has a few disadvantages, such as a period of consequent skin photosensitivity due to the accumulation of photosensitizing agents in the target tissue, and a limited ability to penetrate deep tissues [44]. Although having a few limitations, PDT with its non-invasive approach and non-resistant broad-ranging spectrum of action against pathogens can be considered a promising therapeutic tool in dentistry [44].

Photo-biostimulation or low-level laser therapy is another non-invasive treatment modality used in several fields of contemporary dental practice [46–48]. By using low-powered laser light biological interaction is induced, in particular reduction of pain mediators and inflammatory cells leading to an acceleration of pain relief and healing [49]. In the field of orthodontics, it was found that intraoral application of low-level laser therapy reduced the treatment time, supposedly by increasing cellular metabolic activity and favoring bone remodeling [46]. Moreover, photo-biostimulation can be used to reduce pain severity and duration, as well as swelling after dental implant surgery [49].

With the recent introduction of high power and high repetition rate femtosecond lasers significant progress towards precise and effective tooth tissue ablation was achieved, compared to cavity preparation using a conventional erbium laser [8]. Utilizing proper laser parameters for efficient dental ablation, femtosecond lasers cause no collateral thermo-mechanical damage to the surrounding tooth tissue, whereas beneficial tooth surface roughness is achieved [8, 50]. Therefore, based on "cold" tooth tissue ablation and machining precision at the submicron and nano levels, femtosec-

ond laser may become an advanced alternative laser system for tooth cavity preparation [50].

Conclusion

Bearing in mind constant efforts to accomplish prevention and early diagnosis of oral diseases, as well as non-invasive treatment measures in modern dental practice, biophotonics should be the leading scientific discipline to provide advancements in dental medicine and technology. In the light of such trends, this paper has provided an overview of contemporary biophotonics-based techniques and summarized their applicability focusing on the field of dental medicine.

References

1. Bordin-Aykroyd S, Brito R, Leavitt WP, Raz G, Lynch E. Biophotonics: an introduction to new laser users. EC Dent Sci. 2019;18(9):2171-86.
2. Tsia KK, editor. Understanding biophotonics: fundamentals, advances, and applications. Boca Raton: CRC Press; 2015. p. 1-4.
3. Marcu L, Boppart SA, Hutchinson MR, Popp J, Wilson BC. Biophotonics: the big picture. J Biomed Opt. 2017;23(2):1-7.
4. Fuller PWW. An introduction to high speed photography and photonics. Imaging Science Journal. 2009;57(6):293-302.
5. Gerd K. Biophotonics: concepts to application. Singapore: Springer Science; 2016. p. 1–22.
6. Luke AM, Mathew S, Altawash MM, Madan BM. Lasers: a review with their applications in oral medicine. J Lasers Med Sci. 2019;10(4):324-9.
7. Innes NPT, Chu CH, Fontana M, Lo ECM, Thomson WM, Uribe S, et al. A century of change towards prevention and minimal intervention in cariology. J Dent Res. 2019;98(6):611-7.
8. Petrov T, Pecheva E, Walmsley AD, Dimov S. Femtosecond laser ablation of dentin and enamel for fast and more precise dental cavity preparation. Mater Sci Eng C Mater Biol Appl. 2018;90:433-8.
9. Lin PY, Lyu HC, Hsu CY, Chang CS, Kao FJ. Imaging carious dental tissues with multiphoton fluorescence lifetime imaging microscopy. Biomed Opt Express. 2011;2(1):149-58.
10. Kishen A, Asundi A. Fundamentals and applications of biophotonics in dentistry. London: Imperial College Press; 2007.
11. Prasad PN. Introduction to biophotonics. Hoboken, New Jersey: John Wiley; 2003. p. 1-11.
12. Meglinski I. Biophotonics for medical applications. Cambridge: Elsevier; 2015.
13. Rabasović MD, Pantelić DV, Jelenković BM, Ćurčić SB, Rabasović MS, Vrbica MD, et al. Nonlinear microscopy of chitin and chitinous structures: a case study of two case-dwelling insects. J Biomed Opt. 2015;20(1):016010.
14. Bukara K, Jovanic S, Drvenica IT, Stancic A, Ilic V, Rabasovic MD, et al. Mapping of hemoglobin in erythrocytes and erythrocyte ghosts using two photon excitation fluorescence microscopy. J Biomed Opt. 2017;22(2):026003.
15. Cloitre T, Panayotov IV, Tassery H, Gergely C, Levallois B, Cuisinier FJ. Multiphoton imaging of the dentine-enamel junction. J Biophotonics. 2013;6(4):330-7.
16. Lainović T, Margueritat J, Blažić L, Pantelić D, Rabasović MD, Krmpot AJ, et al. Mapping mechanical properties and structure of dentin by Brillouin spectroscopy and nonlinear optical microscopy. In: Larin KV, Scarcelli G, editors. Optical elastography and tissue biomechanics VI. Bellingham, Washington: SPIE; 2019. p. 1088018.
17. Machoy M, Seeliger J, Szyszka-Sommerfeld L, Koprowski R, Gedrange T, Woźniak K. The use of optical coherence tomography in dental diagnostics: a state-of-the-art review. J Healthc Eng. 2017;2017:7560645.
18. Maia AM, de Freitas AZ, de L Campello S, Gomes AS, Karlsson L. Evaluation of dental enamel caries assessment using quantitative light induced fluorescence and optical coherence tomography. J Biophotonics. 2016;9(6):596-602.
19. Han SH, Sadr A, Tagami J, Park SH. Internal adaptation of resin composites at two configurations: influence of polymerization shrinkage and stress. Dent Mater. 2016;32(9):1085-94.
20. Pantelić D, Vasiljević D, Blažić L, Savić-Šević S, Murić B, Nikolić M. Biomechanical model produced from light-activated dental composite resins: a holographic analysis. Phys Scr. 2013;T157:014021.
21. Pantelić D, Blažić L, Savić-Šević S, Murić B, Vasiljević D, Panić B, et al. Holographic measurement of dental tissue contraction and stress, due to postpolymerization reaction. Acta Phys Pol A. 2007;112(5):1157-60.
22. Puskar T, Jevremovic D, Blazic L, Vasiljevic DM, Pantelic D, Muric B, et al. Holographic interferometry as a method for measuring strain caused by polymerization shrinkage of dental composite. Contemp Mater. 2010;1(1):105-11.
23. Li FC, Kishen A. Deciphering dentin tissue biomechanics using digital moiré interferometry: a narrative review. Opt Lasers Eng. 2018;107:273-80.
24. Pantelić DV, Grujić DŽ, Vasiljević DM. Single-beam, dual-view digital holographic interferometry for biomechanical strain measurements of biological objects. J Biomed Opt. 2014;19(12):127005.
25. Pantelić D, Savić-Šević S, Vasiljević D, Murić B, Blažić L, Nikolić M, et al. Holographic measurement of a tooth model and dental composite contraction. Materials and Manufacturing Processes. 2009;24(10-11):1142-6.
26. Blažić L, Pantelić D, Savić-Šević S, Murić B, Belić I, Panić B. Modulated photoactivation of composite restoration: measurement of cuspal movement using holographic interferometry. Lasers Med Sci. 2011;26(2):179-86.
27. Pantelić D, Blažić L, Savić-Šević S, Panić B. Holographic detection of a tooth structure deformation after dental filling polymerization. J Biomed Opt. 2007;12(2):024026.
28. Tiossi R, de Torres EM, Rodrigues RCS, Conrad HJ, de Mattos M da GC, Fok ASL, et al. Comparison of the correlation of photoelasticity and digital imaging to characterize the load transfer of implant-supported restorations. J Prosthet Dent. 2014;112(2):276-84.
29. Wood JD, Wang R, Weiner S, Pashley DH. Mapping of tooth deformation caused by moisture change using moiré interferometry. Dent Mater. 2003;19(3):159-66.
30. Lim H, Li FC, Friedman S, Kishen A. Residual microstrain in root dentin after canal instrumentation measured with digital moiré interferometry. J Endod. 2016;42(9):1397-402.

31. Shrestha A, Messer HH, Asundi A, Kishen A. Effect of hydration on the strain gradients in dental hard tissues after heat and cold application. J Endod. 2010;36(10):1643-7.

32. Lainović T, Margueritat J, Martinet Q, Dagany X, Blažić L, Pantelić D, et al. Micromechanical imaging of dentin with Brillouin microscopy. Acta Biomater. 2020;105:214-22.

33. Ramakrishnaiah R, Rehman GU, Basavarajappa S, Al Khuraif AA, Durgesh BH, Khan AS, et al. Applications of Raman spectroscopy in dentistry: analysis of tooth structure. Appl Spectrosc Rev. 2015;50(4):332-50.

34. Lopes CCA, Limirio PHJO, Novais VR, Dechichi P. Fourier transform infrared spectroscopy (FTIR) application chemical characterization of enamel, dentin and bone. Appl Spectrosc Rev. 2018;53(9):747-69.

35. Khan AS, Khalid H, Sarfraz Z, Khan M, Iqbal J, Muhammad N, et al. Vibrational spectroscopy of selective dental restorative materials. Appl Spectrosc Rev. 2017;52(6):507-40.

36. Daugherty MM, Lien W, Mansell MR, Risk DL, Savett DA, Vandewalle KS. Effect of high-intensity curing lights on the polymerization of bulk-fill composites. Dent Mater. 2018;34(10):1531-41.

37. Zorzin J, Maier E, Harre S, Fey T, Belli R, Lohbauer U, et al. Bulk-fill resin composites: polymerization properties and extended light curing. Dent Mater. 2015;31(3):293-301.

38. Wang Z, Zheng W, Hsu SC, Huang Z. Optical diagnosis and characterization of dental caries with polarization-resolved hyperspectral stimulated Raman scattering microscopy. Biomed Opt Express. 2016;7(4):1284-93.

39. Mitić Ž, Stolić A, Stojanović S, Najman S, Ignjatović N, Nikolić G, et al. Instrumental methods and techniques for structural and physicochemical characterization of biomaterials and bone tissue: a review. Mater Sci Eng C Mater Biol Appl. 2017;79:930-49.

40. Han GJ, Kim JM, Cho BH, Hwang Y, Kim HY. Improved resin-to-dentin bond strength and durability via nonthermal atmospheric pressure plasma drying of etched dentin. Eur J Oral Sci. 2019;127(2):170-8.

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41. Roriz P, Carvalho L, Frazão O, Santos JL, Simões JA. From conventional sensors to fibre optic sensors for strain and force measurements in biomechanics applications: a review. J Biomech. 2014;47(6):1251-61.

42. Vinagre A, Ramos J, Alves S, Messias A, Alberto N, Nogueira R. Cuspal displacement induced by bulk fill resin composite polymerization: biomechanical evaluation using fiber bragg grating sensors. Int J Biomater. 2016;2016:7134283.

43. Rajan G, Raju R, Jinachandran S, Farrar P, Xi J, Prusty BG. Polymerisation shrinkage profiling of dental composites using optical fibre sensing and their correlation with degree of conversion and curing rate. Sci Rep. 2019;9(1):3162.

44. Stájer A, Kajári S, Gajdács M, Musah-Eroje A, Baráth Z. Utility of photodynamic therapy in dentistry: current concepts. Dent J (Basel). 2020;8(2):43.

45. Gursoy H, Ozcakir-Tomruk C, Tanalp J, Yilmaz S. Photodynamic therapy in dentistry: a literature review. Clin Oral Investig. 2013;17(4):1113-25.

46. Caccianiga G, Paiusco A, Perillo L, Nucera R, Pinsino A, Maddalone M, et al. Does low-level laser therapy enhance? Results from a randomized pilot study. Photomed Laser Surg. 2017;35(8):421-6.

47. Pawar SS, Pujar MA, Makandar SD, Khaiser MI. Postendodontic treatment pain management with low-level laser therapy. Journal of Dental Lasers. 2014;8(2):60-3.

48. Suresh S, Merugu S, Mithradas N. Low-level laser therapy: a biostimulation therapy in periodontics. SRM Journal of Research in Dental Sciences. 2015;6(1):53-6.

49. Caccianiga G, Perillo L, Portelli M, Baldoni M, Galletti C, Gay-Escoda C. Evaluation of effectiveness of photobiostimulation in alleviating side effects after dental implant surgery. A randomized clinical trial. Med Oral Patol Oral Cir Bucal. 2020;25(2):e277-82.

50. Chen H, Li H, Sun Y, Wang Y, Lü PJ. Femtosecond laser for cavity preparation in enamel and dentin: ablation efficiency related factors. Sci Rep. 2016;6:20950.

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TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION AND DIADYNAMIC CURRENT THERAPY IN THE MANAGEMENT OF ACUTE LOW BACK PAIN

TRANSKUTANA ELEKTRIČNA NERVNA STIMULACIJA I TERAPIJA DIJADINAMIČKIM STRUJAMA U TRETMANU AKUTNOG LUMBALNOG BOLA

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Summary

Introduction. Although transcutaneous electrical nerve stimulation and diadynamic currents are widely used in the treatment of painful conditions, their effectiveness in acute low back pain is still controversial. The aim of this study was to evaluate the therapeutic effects of transcutaneous electrical nerve stimulation and diadynamic current therapy in patients with acute low back pain. The study was designed as a single-blind randomized controlled trial. **Material and Methods.** A total of 60 patients with acute low back pain, recruited from physiotherapy referrals, were included in the study. Thirty consecutive patients randomized to receive transcutaneous electrical nerve stimulation were in the experimental group, and 30 patients treated with diadynamic current were included in the control group. The primary outcome variable, measured at days 1 and 10 was pain intensity, measured using a visual analogue scale. Secondary outcome measures were lumbosacral spine flexibility (measured by Schober test), lumbar paraspinal muscle tone evaluated by palpation of the affected paraspinal muscles, and hip range of motion during the straight leg raise test in the supine position. **Results.** All the parameters in each group showed significant improvements after 10 days of physical therapy ($p < 0.01$). Statistical analysis showed that there were significant differences between the groups in pain relief and sensitivity of paraspinal muscles after the treatment, mostly due to the experimental group ($p < 0.01$). **Conclusion**. In conclusion, transcutaneous electrical nerve stimulation and diadynamic current therapy can be used in rehabilitation of patients with acute low back pain, but transcutaneous electrical nerve stimulation seems to have better pain modulation effect than diadynamic current therapy.

Key words: Transcutaneous Electric Nerve Stimulation; Electric Stimulation Therapy; Low Back Pain; Acute Pain; Pain Management; Pain Measurement; Treatment Outcome; Rehabilitation

Sažetak

Uvod. Iako se transkutana električna stimulacija nerva i dijadinamička struja široko koriste u lečenju bolnih stanja, njihova efikasnost u akutnom lumbalnom sindromu je i dalje kontroverzna. Cilj ove studije bio je da se proceni terapeutski efekat transkutane električne stimulacije nerva i terapija dijadinamičkim strujama kod pacijenata sa akutnim lumbalnim sindromom. Ispitivanje je dizajnirano kao jednostruko slepa randomizovana kontrolisana studija. **Materijal i metode.** U istraživanje je bilo uključeno ukupno 60 pacijenata sa akutnim lumbalnim sindromom regrutovanim po preporukama za fizioterapiju. Trideset pacijenata kojima je sekvencijalno dodeljeno da primaju transkutanu električnu stimulaciju predstavljalo je eksperimentalnu grupu, a 30 pacijenata koji su lečeni dijadinamičkom strujom uključeni su u kontrolnu grupu. Primarna promenljiva ishoda izmerena tokom prvog i desetog dana bila je intenzitet bola, izmeren pomoću vizuelne analogne skale. Sekundarne mere ishoda bile su fleksibilnost lumbosakralne kičme (mereno Šober testom), tonus lumbalnih paraspinalnih mišića procenjen palpacijom zahvaćenih paraspinalnih mišića i opseg pokreta kuka pomoću dizanja ekstendirane noge u u ležećem položaju. **Rezultati**. Svi parametri u svakoj grupi pokazali su značajna poboljšanja nakon 10 dana fizikalne terapije ($p < 0,01$). Statističke analize su pokazale da postoje značajne razlike među grupama u ublažavanju bolova i osetljivosti paraspinalnih regiona nakon tretmana, jer je primena transkranijalne električne stimulacije dala bolje rezultate ($p < 0,01$). **Zaključak.** Transkutana električna stimulacija nerva i dijadinamička struja mogu se koristiti u programu rehabilitacije pacijenata sa akutnim lumbalnim bolom, mada se čini da transkutana električna stimulacija ima bolji efekat modulacije bola od dijadinamičke struje.

Ključne reči: TENS; elektroterapija; lumbalni bol; akutni bol; kontrola bola; merenje jačine bola; ishod lečenja; rehabilitacija

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Abbreviations

TENS – transcutaneous electrical nerve stimulation
DDC – diadynamic current
LBP – low back pain
SLRT – straight leg raise test
VAS – visual analogue scale

Introduction

Low back pain (LBP) is among the most common and costly socioeconomic and health problems with a prevalence of 65 to 80% over one's lifetime [1–3].

Improvements in pain and disability as well as return to work occur in the first month after an initial episode, but LBP is a recurrent problem and 50% of the active workforce experience back pain every year [4]. In most cases, a precise pathoanatomic cause cannot be found [5]. Recent studies suggest that social and psychological factors contribute to the development of acute LBP and its progression to chronic LBP [3]. The most frequently reported factors are smoking, obesity, stress, anxiety, depression, and hard work [6].

The number of studies investigating the effects of treatments in patients with LBP has increased in the past decade. Electrotherapy has a role in conservative management of acute LBP, but its effects are conflicting. This is the consequence of the predominance of low-powered and low-quality trials, the heterogeneity of disorder subtypes and varied clinical parameters [2, 7, 8].

Stimulating electrotherapy, like diadynamic current (DDC) and transcutaneous electrical nerve stimulation (TENS) are effective in the treatment of LBP by inhibiting pain-related potentials on the spinal and supraspinal level, known as "gate control" [9, 10, 32]. Analgesic effects of TENS can be observed in the whole segmental region, both ipsilateral and contralateral [11].

The mechanism of action of TENS is still poorly understood [10]. However, the clinical benefits of TENS remain controversial and there is lack of consensus regarding its efficacy [12, 13]. Some studies [14, 15] suggest a lack of evidence to support its use in the treatment of LBP, while others found evidence of benefit [13, 16, 17].

It is important to say that TENS has been used in a large number of patients for many indications over many years and it has been found to be remarkably safe and free from significant side-effects, when compared with other methods of analgesia [10].

There are a small number of studies on effects of TENS and DDC therapy on acute LBP.

The DDC is one of the most common electrotherapy treatments which use low currents with analgesic and spasmolytic effect. The DDCs are mixed currents, which use effects of the concurrent application of galvanic and faraday, or other impulse-like currents. This results in combined effects of both types of currents, especially induction of hyperemia and analgesia [18]. There are a limited number of studies investigating DDC effectiveness in the therapy of acute LBP and most of them are not in English language. The main objective of the study was to examine whether TENS is an effective treatment for acute LBP compared with the application of DDC.

Material and Methods

A prospective, single blind randomized controlled study included consecutive patients referred to a Physiotherapy Center with a diagnosis of nonspecific acute LBP. Inclusion criteria were patients aged 16 to 70 years, with a diagnosis of acute LBP lasting a maximum of 3 weeks. Exclusion criteria were patients with pacemakers, damaged or broken skin, malignancy, spinal infections, pregnancy, traumatic fractures, seriously impaired vision, and patients with contraindications to either treatment. The subjects with suspected above-mentioned exclusion factors underwent the following diagnostic methods: x-ray, magnetic resonance imaging, electromyography, and in case of need, laboratory tests were performed. In that way, serious pathology as a cause of acute lumbar pain was excluded.

Patients were randomly allocated to use either TENS or DDC. In the TENS group (30 patients) the stimulation was continuously applied for 15 minutes once a day at high frequency (150 Hz). Four graphic electrodes (4 cm x 4 cm) from a dual channel TENS unit were placed with aqueous gel. The electrodes were applied on the lumbosacral region, directly over the site of pain or adjusted to the painful area at a distance of 5 – 20 cm apart.

In the DDC group (30 patients) the stimulation was also given once a day, short period and long period modalities during 10 days. The electrodes were placed on the pain area in the paraspinal and lumbar region. Each application lasted for 6 minutes.

The assessment of treatment efficacy was done after each therapy on days 1, 5 and 10 during the treatment. The following parameters were evaluated by the physician: pain intensity, mobility of lumbosacral spine, paravertebral tonus, and hip range of motion.

The pain intensity level was recorded over 10 days using the 100 mm non-interval visual analogue scale (VAS). Lumbosacral flexibility was measured by Schober method. Paravertebral muscle tonus was evaluated by the physician, with palpation of affected paraspinal muscles using 5-point numerical rating scale graded from 1 to 5 as follows: 1. Hypotonia, 2. Eutonia, 3. Spasm, 4. Strong spasm, and 5. Extremely strong spasm. The hip range of motion was measured by straight leg raise test (SLRT) [2].

The data were evaluated using the Statistical package for the social sciences, version 17.0 for Windows. For the purpose of statistical analysis, measures of descriptive statistics - frequency, mean, and measures of variability were used. Parametric (t-test) and nonparametric (Mann Whitney test, chi-square test) tests were used to compare the distribution between the two groups. To compare three or more groups of respondents the analysis of variance and Kruskal-Wallis tests were used. Correlation of continuous variables was examined by Pearson correlation coefficient.

Ethical approval was given by the Ethics Committee of the School of Medicine, University of Belgrade, and informed consent to participate in the study was obtained from all the patients.

Results

Sixty patients were recruited and randomized into the study; 30 into the TENS group and 30 into the DDC group. All patients completed the trial.

The mean age of participants was 42 ± 11.5 years. In the TENS group, 53.3% of patients were males and 46.7% were females, while in the DDC group, 46.7% were males and 53.3% were females. In the TENS group, 18 (60%) patients had one or more earlier episodes of LBP and in the DDC group, 19 (63%) patients had earlier LBP episodes. Analysis of all demographic data demonstrated no significant difference between groups **(Table 1)**.

Pain intensity

The outcome measures between baseline and day 10 are summarized in **Table 2**. Compared with baseline values, the TENS group showed a significant ($p < 0.01$) decline (ranging from 44.00 ± 24.47 to 3.43 ± 4.57) in back pain severity (VAS score after ther-

Table 1. Basic characteristics of the participants
Tabela 1*. Osnovne karakteristike ispitanika*

Treatment *Tretman*	Age/*Starost* Years/*Godine*	Average pain intensity *Prosečan intenzitet bola (VAS 0 -100/VAS 0 - 100)*	Lumbosacral mobility, Schober *Lumbosakralna mobilnost, Šober*	Tonus of paravertebral muscles *Tonus paravertebralnih mišića*	SLRT (degrees) *TPEN (stepeni)*
TENS group *TENS grupa*	N = 30 (16 male and 14 female/*16 muškaraca i 14 žena* X ± SD 42.1	58.80 ± 24.55	18.13 ± 17.80	3.57 ± 0.68	61.3 ± 19.2
DDC group *DDS grupa*	N = 30 (14 male and 16 female)/*14 muškaraca i 16 žena* X ± SD 42.2	58.86 ± 23.96	18.20 ± 16.64	3.67 ± 0.66	60.5 ± 18.8

Legend/*Legenda*: X – mean value/*Prosečna vrednost*; SD – standard deviation/*Standardna devijacija*; VAS – visual analogue scale/*Vizuelna analogna skala*; TENS – transcutaneous electrical nerve stimulation/*Transkutana električna nervna stimulacija*; DDS – diadynamic current/*Dijadinamičke struje*; SLRT – straight leg raise test/TPEN – *Test podizanja ekstendirane noge*

Table 2. Change in outcome measures (mean ± standard deviation) prior to therapy (prior), immediately after first therapy (post 1) and at 10 days follow up (post 10)
Tabela 2. *Promena mera ishoda (srednja vrednost ± standardna devijacija) pre terapije (pre), neposredno nakon prve terapije (posle 1) i nakon 10 dana praćenja (posle 10)*

Outcome measures/*Mere ishoda*	TENS/*TENS* (n = 30) Mean ± SD/*Srednja vrednost ± SD*	DDC/*DDS* (n = 30) Mean ± *SD/Srednja vrednost ± SD*
Pain intensity (VAS)/*Intenzitet bola*		
Prior/*Pre*	58.80 ± 24.55	58.86 ± 23.96
Post 1/*Posle 1*	44.00 ± 24.47	51.66 ± 21.81
Post 5/*Posle 5*	18.17 ± 14.11[a]	34.30 ± 16.73
Post 10/*Posle 10*	3.43 ± 4.57[abc]	9.97 ± 6.78[bc]
Lumbosacral mobility (cm)/*Lumbosakralna pokretljivost (cm)*		
Post 1/*Posle 1*	18.13 ± 17.80	18.20 ± 24.55
Post 5/*Posle 5*	18.83 ± 13.47	18.76 ± 12.50
Post 10/*Posle 10*	20.13 ± 10.90[c]	20.00 ± 9.46[c]
Paravertebral tonus/*Paravertebralni tonus*		
Post 1/*Posle 1*	3.57 ± 0.68	3.67 ± 0.66
Post 10/*Posle 10*	2.43 ± 0.50[ac]	2.70 ± 0.47[c]
SLRT (degrees)/*TPEN (stepeni)*		
Post 1/*Posle 1*	61.3 ± 19.2	60.5 ± 18.8
Post 10/*Posle 10*	78.5 ± 11.3[c]	77.5 ± 10.8[c]

Legend/*Legenda*: SD – standard deviation/*Standardna devijacija*; TENS – transcutaneous electrical nerve stimulation/*Transkutana električna nervna stimulacija*; DDS – diadynamic current/*Dijadinamske struje*; SLRT – straight leg raise test/*TPEN – Test podizanja ekstendirane noge*
[a] Statistically significant difference from DDC/*Statistički značajna razlika u odnosu na DDS;* [b] Statistically significant difference from Prior/*Statistički značajna razlika u odnosu na pre;* [c] Statistically significant difference from Post 1/*Statistički značajna razlika u odnosu na posle 1*

apy). Also, the DDC group showed a significant ($p < 0.01$) decline in back pain intensity (from 51.66 ± 21.81 to 9.97 ± 6.78). In the TENS group, pain scores were significantly ($p < 0.01$) lower than in the DDC group after 10 days of therapy.

Lumbosacral flexibility

Compared with the baseline values, the TENS group showed a significant ($p < 0.01$) increase in the trunk range of motion after 5 and 10 days of therapy. The range of flexion increased at all follow-ups from 18.13 ± 17.80 cm to 20.13 ± 10.90 cm **(Table 2)**. The DDC group also showed a significant ($p < 0.01$) increase in the trunk motion at all follow-ups which extended from 18.20 ± 16.6 cm to 20.00 ± 9.46 cm. There were no significant differences between the TENS and DDC groups ($p > 0.5$) in the trunk range of motion after 5 and 10 days of therapy.

Tonus of the paravertebral muscles

The TENS and DDC groups showed a significant ($p < 0.01$) decrease in paravertebral muscle tonus after 10 days of therapy. Compared with the baseline values, the tenderness of paravertebral muscles in the TENS group decreased from 3.57 ± 0.68 to 2.43 ± 0.50. In the DDC group, the decline of paravertebral muscle tonus was from 3.76 ± 0.66 to 2.70 ± 0.47. The TENS group displayed significantly ($p < 0.05$) lower paravertebral muscle tonus compared with the DDC group after 10 days of therapy.

Straight leg raise test

Compared with the pretherapy values, patients in the TENS and DDC groups showed a significant ($p < 0.01$) improvement in the hamstring flexibility measured by SLRT after 10 days of therapy **(Table 2)**. Between the TENS and DDC groups there were no significant differences in extremity range of motion ($p > 0.05$).

Discussion

This study evaluated the effectiveness of the TENS and DDC therapy in patients with acute LBP, without neurological deficiency. We observed that subjects demonstrated significant improvement in all outcome measures following both therapeutic interventions. The main limitation of this study is the small sample size, potentially affecting the obtained treatment effects. Another issue is that we have considered short-term effects (immediate post-treatment) associated with electrotherapy.

The mean age of participants included in present study was 42 years. The age and gender range of subjects recruited to the study appear to reflect the clinical population most often affected by LBP [19]. In the TENS group, 60% of patients had one or more earlier attacks of LBP, and in the DDC group 63% of patients had earlier LBP episodes. The present results are in agreement with previous findings indicating a high level of LBP recurrences [3].

In our study, the TENS and DDC groups showed a significant ($p < 0.01$) decline in back pain severity by VAS score after the therapy compared with baseline values. Also the TENS group pain scores were significantly ($p < 0.01$) lower than the DDC group scores after therapy **(Table 2)**. This is comparable with the results of Can F. et al. [20] who compared the efficacy of TENS and DDC therapy in a group of patients with patellofemoral pain syndrome, showing that both therapies were effective in terms of pain management and activity level. But, they also demonstrated that there was no significant difference in analgesic effects between the two groups, which is in contrast with our results.

Reviewing the published literature on the treatment of painful conditions using electrotherapy, Rushton reported that TENS has proved to be remarkably safe and provides significant analgesia in about half of patients experiencing moderate predictable pain [10]. Also, Cheing et al. reported that TENS significantly reduced chronic pain [21]. A recent clinical trial compared the effectiveness of rhythmic stabilization exercises and TENS and their combination in treating women with chronic LBP. Their results suggested that combined treatment was superior to placebo [13].

The present results disagree with the recent findings of Keller et al. who reported small to moderate pooled effect size of TENS therapy for short-term pain relief in patients with chronic LBP [14]. A systematic review of acupuncture for LBP also found no difference in pain relief between TENS and acupuncture [12, 22]. Also, Chou et al. in a systemic review of the therapies for acute and chronic LBP reported that TENS has not been shown to be effective for chronic, subacute, or acute LBP and that the only therapy with good evidence of efficacy was superficial heat [12]. Analgesic effectives of DDC are showed in the study of Lisinski at al. who reported that DDC is very effective in managing pain in patients with knee osteoarthritis [23]. Beside the above mentioned results, the effectiveness of TENS and especially DDC therapy is difficult to assess because of limited quantity and quality of studies [2, 9, 20].

The differences between our results and other studies could be attributed to differences in physical as well as psychosocial factors between the patients with acute and chronic LBP [13, 24–26, 33]. Furthermore, differences among studies in the methodology and outcome measures used to test the effectiveness may also contribute to the above observation.

Compared with the baseline values, the TENS and DDC groups showed a significant ($p < 0.01$) increase in trunk range of flexion after 5 and 10 days of therapy. No significant differences were found between the TENS and DDC groups ($p > 0.5$) in the ability to flex the lumbar spine after 10 days of therapy. The range of flexion increased from 18 cm at baseline to 20 cm after therapy. From the clinical point of view, achievement of 20 cm in lumbosacral anteflexion after TENS and DDC therapy indicates that the goals of this particular therapy

have been met since lumbosacral anteflexion of 20 cm is considered as normal flexion measured by Schober **(Table 2)** [27, 30]. Such improvements indicate that subjects were able to perform daily activities comfortably and without pain.

Research on the effects of high-frequency TENS on trunk flexibility is scarce and no definite conclusions can be made regarding its effectiveness [9]. Kofotolis et al. showed that the rhythmic stabilization program resulted in significantly better improvement in functional disability and trunk flexion compared with TENS therapy in chronic LBP patients [13, 29].

Also, there is no evidence on DDC therapy effectiveness in the patients with acute LBP. Most studies of electrotherapy cover DDC therapy in a very superficial way, and a considerable proportion of the literature is not easily available in English. Because of that, the role of this therapy in functional disability of patients with acute LBP remains unclear.

Our study indicates that the pain relief following a 10-day therapy using TENS as well as DDC therapy program was sufficient to affect the trunk flexibility.

More high quality studies are needed to determine the role of DDC therapy in the management of functional disability in patients with acute LBP.

The TENS and DDC groups showed a significant ($p < 0.01$) decrease in paravertebral tonus after 10 days of therapy. A comparison between groups revealed that the TENS group displayed significantly ($p < 0.05$) lower paravertebral tonus compared with the DDC group. In our study, the mean paravertebral tonus dropped from baseline value of 3.57 to 2.43 during 10 days. The effectiveness of TENS on spasticity was studied by Hsueh et al. who reported on the effects of a single TENS treatment (60 Hz; 20 minutes) in 20 patients with chronic trigger points (trapezius muscle) [28, 31]. They found a significant decrease in trigger points tenderness and pain intensity in patients receiving TENS, compared with placebo treatment. In the Cochrane Review of Electrotherapy for Mechanical Neck Disorders, Kroeling et al. found limited evidence of benefit of the DDC therapy for the pain outcome and reduction of trigger point pain [9]. Besides that, we identified no results on DDC therapy effects on muscle spasticity in acute LBP.

Conclusion

Our findings showed that, in comparison with the pretreatment values, patients in the transcutaneous electrical nerve stimulation group and diadynamic current group showed a significant ($p < 0.01$) improvement in hamstring flexibility, as measured by straight leg raise test after 10 days of therapy. Between transcutaneous electrical nerve stimulation and diadynamic current groups there were no significant differences in extremity range of motion ($p > 0.05$). Since positive result has been defined as radiating pain observed at 30 to 70 degrees of hip flexion we can say that our patients achieved normal values in extremity range of motion.

In conclusion, the present results indicate that transcutaneous electrical nerve stimulation and diadynamic current therapy are effective in reducing back pain severity and paravertebral tonus as well as improving trunk and hamstring flexibility in patients with acute low back pain. Further studies examining these specific interventions are needed because the existing evidence is limited and conflicting.

References

1. Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. J Spinal Disord. 2000;13(3):205-17.

2. Gregory DS, Seto CK, Wortley GC, Shugart CM. Acute lumbar disk pain: navigating evaluation and treatment choices. Am Fam Physician. 2008;78(7):835-42.

3. Gurcay E, Bal A, Eksioglu E, Hasturk AE, Gurcay AG, Cakci A. Acute low back pain: clinical course and prognostic factors. Disabil Rehabil. 2009;31(10):840-5.

4. Patel AT, Ogle AA. Diagnosis and management of acute low back pain. Am Fam Physician. 2000;61(6):1779-86, 1789-90.

5. Atlas SJ, Deyo RA. Evaluating and managing acute low back pain in the primary care setting. J Gen Intern Med. 2001;16(2):120-31.

6. Nicholas MK, Linton SJ, Watson PJ, Main CJ. Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal. Phys Ther. 2011;91(5):737-53.

7. Bloodworth DM, Nguyen BN, Garver W, Moss F, Pedroza C, Tran T, et al. Comparison of stochastic vs. conventional transcutaneous electrical stimulation for pain modulation in patients with electromyographically documented radiculopathy. Am J Phys Med Rehabil. 2004;83(8):584-91.

8. Nwuga VC. Ultrasound in treatment of back pain resulting from prolapsed intervertebral disc. Arch Phys Med Rehabil. 1983;64(2):88-9.

9. Kroeling P, Gross AR, Goldsmith CH; Cervical Overview Group. A Cochrane review of electrotherapy for mechanical neck disorders. Spine (Phila Pa 1976). 2005;30(21):641-8.

10. Rushton DN. Electrical stimulation in the treatment of pain. Disabil Rehabil. 2002;24(8):407-15.

11. Stucki G, Kroeling P. Physical therapy and rehabilitation in the management of rheumatic disorders. Baillieres Best Prac Res Clin Rheumatol. 2000;14(4):751-71.

12. Chou R, Huffman LH; American Pain Society; American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007;147(7):492-504.

13. Kofotolis ND, Vlachopoulos SP, Kellis E. Sequentially allocated clinical trial of rhythmic stabilization exercises and TENS in women with chronic low back pain. Clin Rehabil. 2008;22(2):99-111.

14. Keller A, Hayden J, Bombardier C, van Tulder M. Effect sizes of non-surgical treatments of non-specific low-back pain. Eur Spine J. 2007;16(11):1776-88.

15. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Rumamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med. 1990;322(23):1627-34.

16. Melzack R, Vetere P, Finch L. Transcutaneous electrical nerve stimulation for low back pain. A comparison of TENS and massage for pain and range of motion. Phys Ther. 1983;63(4):489-93.

17. Bertalanffy A, Kober A, Bertalanffy P, Gustorff B, Gore O, Adel S, et al. Transcutaneous electrical nerve stimulation reduces acute low back pain during emergency transport. Acad Emerg Med. 2005;12(7):607-11.

18. Ratajczak B, Hawrylak A, Demidaś A, Kuciel-Lewandowska J, Boerner E. Effectiveness of diadynamic currents and transcutaneous electrical nerve stimulation in disc disease lumbar part of spine. J Back Musculoskelet Rehabil. 2011;24(3):155-9.

19. Loney PL, Stratford PW. The prevalence of low back pain in adults: a methodological review of the literature. Phys Ther. 1999;79(4):384-96.

20. Can F, Tandogan R, Yilmaz I, Dolunay E, Erden Z. Rehabilitation of patellofemoral pain syndrome: TENS versus diadynamic current therapy for pain relief. Pain Clinic. 2003;15(1):61-8.

21. Cheing GL, Hui-Chan CW. Transcutaneous electrical nerve simulation: nonparallel antinociceptive effects on chronic clinical pain and acute experimental pain. Arch Phys Med Rehabil. 1999;80(3):305-12.

22. Manheimer E, White A, Berman B, Forys K, Ernst E. Meta-analysis: acupuncture for low back pain. Ann Intern Med. 2005;142(8):651-63.

23. Lisinski P, Zapalski W, Stryla W. Physical agents for pain management in patients with gonarthrosis. Ortop Traumatol Rehabil. 2005;7(3):317-21.

24. Biering-Sorensen F. Physical measurements as risk indicators for low back trouble over a one-year period. Spine (Phila Pa 1976). 1984;9(2):106-19.

25. Loeser JD, Melzack R. Pain: an overview. Lancet. 1999;353(9164):1607-9.

26. Carragee EJ. Psychological and functional profiles in select subjects with low back pain. Spine J. 2001;1(3):198-204.

27. Hancock MJ, Maher CG, Latimer J, Spindler MF, McAuley JH, Laslett M, et al. Systematic review of tests to identify the disc, SIJ or facet joint as the source of low back pain. Eur Spine J. 2007;16(10):1539-50.

28. Hsueh TC, Cheng PT, Kuan TS, Hong CZ. The immediate effectiveness of electrical nerve stimulation and electrical muscle stimulation on myofascial trigger points. Am J Phys Med Rehabil. 1997;76(6):471-6.

29. Petrofsky J, Laymon M, Lee H. The effect of transcutaneous electrical nerve stimulation and low-level continuous heat on non-specific low back pain: a randomized controlled trial. Gazzetta Medica Italiana Archivio per le Scienze Mediche. 2020;179(‖6):419-27.

30. Resende L, Merriwether E, Rampazo ÉP, Dailey D, Embree J, Deberg J, et al. Meta-analysis of transcutaneous electrical nerve stimulation for relief of spinal pain. Eur J Pain. 2018;22(4):663-78.

31. Wu LC, Weng PW, Chen CH, Huang YY, Tsuang YH, Chiang CJ. Literature review and meta-analysis of transcutaneous electrical nerve stimulation in treating chronic back pain. Reg Anesth Pain Med. 2018;43(4):425-33.

32. Knežević A, Kovačević M, Klicov L, Pantić M, Vasin J, Spasojević T. Conditioned pain modulation assessment using contact heat as conditioning stimulus and two different test stimuli. Med Pregl. 2019;72(3-4):66-71.

33. Juković M, Koković T, Nikolić D, Ilić D, Till V. Lower back pain: silent symptom of chronic infrarenal abdominal aneurysm rupture. Med Pregl. 2016;69(3-4):115-7.

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VARIOUS TECHNIQUES OF ADAPTATION TO DENTAL TREATMENT OF CHILDREN WITH AUTISM SPECTRUM DISORDER

PRIMENA RAZLIČITIH TEHNIKA ADAPTACIJE NA STOMATOLOŠKE INTERVENCIJE KOD DECE SA POREMEĆAJEM IZ SPEKTRA AUTIZMA

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Summary

Introduction. Autism is a severe and lifelong developmental disorder characterized by impaired social interaction and interpersonal communication, as well as characteristic repetitive patterns of interest and behavior. The purpose of this study is to point to the possibility of applying various techniques of adaptation of children with autism to dental interventions in order to maintain oral health. **Material and Methods.** A multidisciplinary project was carried out by the Dental Clinic of Vojvodina, Special Education School "Dr. Milan Petrović" and the Autism Society of Novi Sad. The following education models were used in the project: behavior-oriented models, developmental strategies, therapy based interventions, and combined interventions. The success rate of applied education models and adaptation of children with autism spectrum disorders to dental interventions was examined. The success criteria included the ability to make contact, communicate, cooperate, and perform dental treatment. **Results.** The multidisciplinary project included 20 active members the Autism Society of Novi Sad and 20 members of the Special Education School "Dr. Milan Petrović" day care program. The results of the study showed a 95% success rate of the most commonly used applied behavior analysis. The success rate of the communication oriented interventions was 90%, while therapy based interventions showed an 85% success rate. The combined interventions showed a 100% success rate. **Conclusion.** Only integration of several methods, multidisciplinary cooperation and an individual approach to work with children with autism can lead to success in work and adaptation to dental interventions of persons with autism spectrum disorder.

Key words: Pediatric Dentistry; Oral Health; Autism Spectrum Disorder; Child; Adaptation, Psychological; Interdisciplinary Communication; Patient Compliance; Psychological Techniques

Sažetak

Uvod. Autizam ili autistični poremećaj je ozbiljan i doživotni razvojni poremećaj koji karakteriše pogoršanu međusobnu socijalnu interakciju, međusobnu komunikaciju i karakteristične ponavljajuće obrasce interesa i ponašanja. Svrha ove studije jeste da se prikaže mogućnost primene različitih tehnika i adaptacije dece sa poremećajima iz autističnog spektra na stomatološke intervencije u cilju očuvanja oralnog zdravlja. **Materijal i metode.** Ostvaren je multidisciplinarni projekat između Klinike za stomatologiju Vojvodine sa Školom za specijalno obrazovanje „Milan Petrović" i Društva za podršku osobama sa autizmom grada Novog Sada. Klasifikacija edukacijskih modela rada korišćenih u projektu: modeli usmereni na ponašanje – bihevioralni pristup, razvojne strategije, terapijski bazirane intervencije i kombinovane intervencije. Ispitivana je uspešnost primenjenih edukacijslih modela i adaptacije dece sa poremećajima iz autističnog spektra na stomatološke intervencije. Kriterijumi uspešnosti su mogućnost ostvarivanja kontakta, komunikacije, saradnje i vršenja stomatoloških intervencija. **Rezultati.** Multidisciplinarna saradnja je obuhvatila 20 aktivnih članova Društva za podršku osobama sa autizmom grada Novog Sada i 20 korisnika dnevnog boravka Škole za specijalno obrazovanje „Milan Petrović". Rezultat istraživanja pokazuje da je primenjena bihevioralna analiza ponašanja, kao najviše primjenjivani oblik rada, sa 95% uspešnosti. Uspešnost primene intervencija usmerenih na komunikaciju je 90%. Primenom terapijski baziranih intervencija, uspešnost je 85%. Primena kombinovanih intervencija dovela je do 100% uspešnosti. **Zaključak.** Samo integracijom više pojedinačnih metoda, multidisciplinarnom saradnjom i individualnim pristupom u radu sa osobama sa poremećajem iz autističnog spektra možemo doći do uspeha u radu i prilagođavanja na stomatološke intervencije.

Ključne reči: pedijatrijska stomatologija; oralno zdravlje; poremećaji autističnog spektra; dete; psihološka adaptacija; multidisciplinarna saradnja; saradljivost pacijenta; psihološke tehnike

Introduction

Autism or autism disorder (AD) is a severe lifelong developmental disorder characterized by impaired social interaction and communication, as well as characteristic repetitive patterns of interest and behavior [1]. Autism is considered to be a severe developmental disorder occurring in early child-

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Abbreviations

DSM-IV	– Diagnostic and Statistical Manual of Mental Disorders
PDD	– pervasive developmental disorder
ASD	– autism spectrum disorder
AD	– autism disorder
PDD-NOS	– pervasive developmental disorder not otherwise specified
ABA	– applied behavior analysis
DSPM	– developmental social-pragmatic model
PECS	– picture exchange communication system
AAC	– alternative and augmentative communication
LEAP	– learning experiences and alternative program

hood and for the most part it remains a lifelong condition [2]. The cause of autism is still unknown. Based on current research, it is believed that the disorder is multifactorial, including genetics, exposure to environmental toxins, and neuro-pshychopathy. The latest research suggests a current prevalence of 1 in 110 children [3]. The male to female ratio is 3.7 : 1.13, but females show a higher degree of mental disability. A higher degree of male prevalence suggests an X-chromosome linked inheritance. An American psychiatrist, Leo Kanner described 11 children who exhibited traits of severe loneliness, lack of affective contact, difficulty in adapting to changes in routines and increased sensitivity [4]. The AD has been categorized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) under the pervasive developmental disorder (PDD), also known as the autism spectrum disorder (ASD). According to the DSM-IV, PDD is an umbrella term that defines specific diagnoses, including AD, Asperger's syndrome, and rare disorders such as Rett syndrome, childhood disintegrative disorder and PDD-NOS (Not Otherwise Specified) or "atypical autism" [5]. During a dental examination, a number of issues may arise with ASD children, and research has shown that 50 – 72% of ASD children exhibit uncooperative behavior [6–8]. These are the main factors for barriers and issues during a dental examination of ASD children. The aforementioned uncooperative behavior may include hyperactivity, short attention span, rapid frustration, impulsiveness, anxiety, rage, self-harm, and repetitive aggressive behavior [9, 10]. The ASDs are diagnosed based on the presence of specific behavioral criteria, including social interaction disorder, social communication disorder, limited and repetitive behaviors, interests and activity patterns [11]. Dental issues, tooth decay, gingivitis and periodontitis represent some of the 10 most common associated conditions affecting persons with all types of disabilities, as well as those with ASDs. These conditions, in turn, limit everyday activities of these persons [12]. The purpose of this study is to show the possibility of applying various techniques of adaptation of children with ASDs to dental interventions.

Material and Methods

Dental Clinic of Vojvodina, Special Education School "Dr. Milan Petrović" and the Autism Society of Novi Sad participated in this project. The team consisted of dental practitioners, pediatric and preventive dental consultants of the Dental Clinic of Vojvodina, 3rd and 4th year dentistry students of the Faculty of Medicine of the University of Novi Sad, special educators and psychologists of the Special Education School "Dr. Milan Petrović" day care program, and volunteers of the Autism Society of Novi Sad.

This multidisciplinary project included the following education models:

1. Behavioral approach

Applied behavior analysis (ABA) is an approach with strong empirical foundations and represents the most empirically valued approach when treating autism [13]. It is based on exact interpretation of interaction between a previous variable (stimulus or order) and the consequence (reinforcement or reward), and the use of these pieces of information to systematically plan an object of desired learning and program of behavior change.

2. Developmental strategies

Developmental social-pragmatic model (DSPM) is focused on initiation and spontaneity in communication and monitoring the child's focus of attention and motivation. Developmental interventions are focused on the child's ability to create positive and meaningful relationships with other people even when being constrained by ASDs. The aim is to upgrade the child's current communication skills, even if it's deemed unconventional, as well as to use more natural activities and events that support the child's communication ability development [14].

3. Therapy based interventions

a) Communication-oriented interventions. Picture exchange communication system (PECS) is a unique complementary method for learning effective communication. The PECS was originally developed for the use with pre-school autistic children, in children with PDD, and children with other social communication disorders. The PECS has changed and developed over time and today it is used for individuals of all ages (including adults), but it is also effective among children with a wide spectrum of communication disorders [15].

b) Visual supports. Alternative and augmentative communication (AAC) is a term that encompasses communication methods that use supplementing or replacing speech or writing for those who have difficulties with producing and understanding spoken or written language. The AAC consists of unassisted communication that does not use tools but body language or assisted communication that uses external tools and consists of pictures and other aids. Children with autism have strong visual processing skills which make them excellent candidates for AAC [16]. The AAC system for this population actually started as PECS [17].

4. Combined interventions. Learning experiences and alternative program (LEAP) for preschoolers and parents is a model that involves children included in pre-school classrooms together with their typically developing peers from the very start. The program was designed to meet the education needs of both typical preschoolers and ASD

children in an integrated classroom environment. Peers are taught to aid the social and communicative behavior of ASD children. Families are also taught to apply behavioral strategies when interacting with the aforementioned children [14].

The first meeting with a dental practitioner, as an initial contact, took place at the Special Education School "Dr. Milan Petrović" day care program and the Autism Society of Novi Sad by applying a behavioral ABA approach. After a week of applying the development DSPM strategy, spontaneity in communication was initiated, while simultaneously monitoring the attention and motivation of ASD children. The next stage of adaptation included therapy based interventions, PECS and AAC, by communicating through pictures containing symbols of teeth and dental practices, oral hygiene tools, as well as photos of the Dental Clinic of Vojvodina. The following stage included the parental presence, and consisted of combined interventions - LEAP via an art workshop with a dental practitioner and teeth topics. After a gradual introduction, the next stage included the application of a behavioral approach - ABA, and consisted of tooth brushing at the day care program. After establishing contact and trust, the ASD children were examined at the Dental Clinic of Vojvodina. Since preventive prophylactic measures and diagnostics were conducted, an individual therapy was scheduled for each patient. The success criteria of the aforementioned methods were: success in establishing contact, initial communication, cooperation, workshop activities, and success in performing dental examination and intervention. Microsoft Excel 2010 was used to analyze the data on the success rate of applying various techniques for adaptation of ASD children to dental interventions.

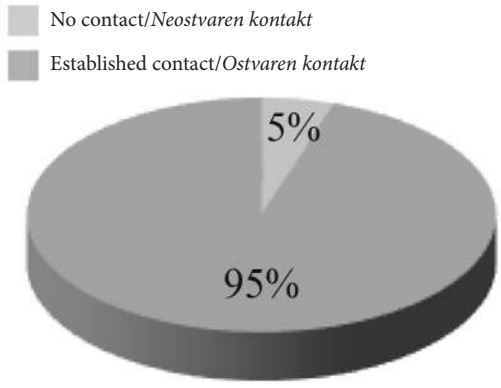
Results

A two-month project included 20 active members of the Autism Society of Novi Sad and 20 members of the Special Education School "Dr. Milan Petrović" day care program. There were a significantly higher number of male ASD children compared to female children, i.e. 38 and 2, respectively. The participants included 20 members of the Special Education School "Dr. Milan Petrović" day care program, of which 1 member was female, and 19 were male, aged 17 – 21 years. Twenty members of the Autism Society of Novi Sad included 18 males and 2 females, aged 6 – 21 years.

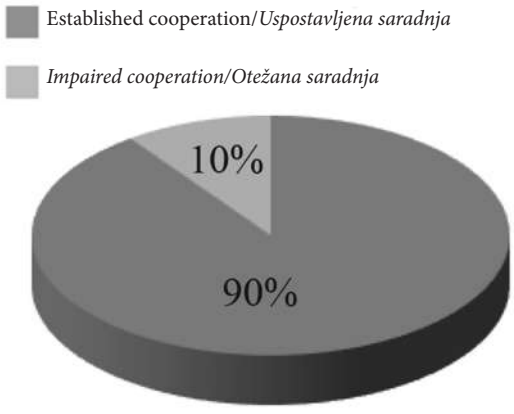
Graph 1. indicates the success rate of ABA method used in the Special Education School "Dr. Milan Petrović" day care program and the Autism Society of Novi Sad during the first meeting of the ASD children and a dental practitioner, in which the success rate was 95%.

Graph 2. shows the success rate of the DSPM model used in both institutions which yielded a success rate of 90%. Communication was successfully initiated with all male children, while no communication was established with the female children. **Graph 3.** indicates an 85% success rate when applying communication based intervention or PECS and the AAC method. The LEAP model also yielded a 100% success rate, i.e. the technique of working with the family in the Autism Society of Novi Sad. In both institutions the ABA method yielded a 100% success rate, which means that all members actively participated in their individual tooth brushing training.

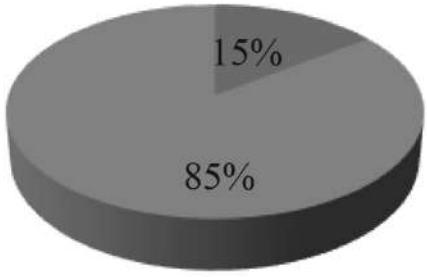
Graph 4. shows a 95% success rate during the first dental examination at the Dental Clinic of Vojvodina after the dental intervention adaptation techniques. **Graph 5**. indicates that 55% of children underwent successful preventive prophylactic measures including plaque removal, as well as supragingival and subgingival tooth decay treatment at the Dental Clinic of Vojvodina. In addition, 30% of children had a successful conservative treatment of their permanent teeth with decay after preventive prophylactic measures. As a result of inability to establish adequate cooperation and to perform dental interventions in outpatient conditions, 15% of children had dental treatment under general anesthesia.



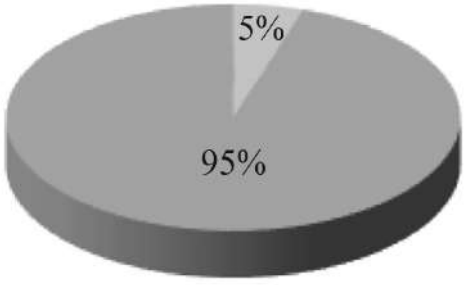
Graph 1. Success rate of applied behavior analysis
Grafikon 1. *Stopa uspešnosti primenjene analize ponašanja*



Graph 2. Success rate of applied DSPM model
Grafikon 2. *Stopa uspešnosti primenjenog razvojnog socijalno-pragmatičkog modela*



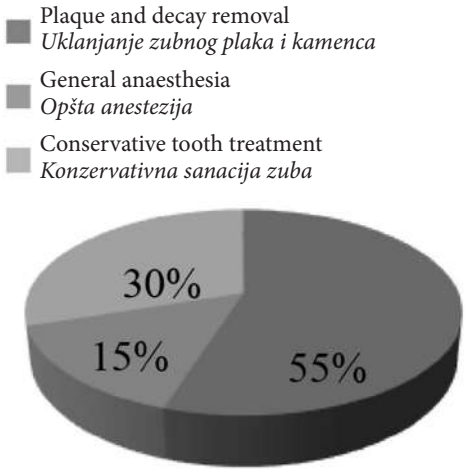
Graph 3. Success rate of applied PECS and AAC methods
Grafikon 3. *Stopa uspešnosti primene komunikacionog sistema razmene slika i alternativne i augmentativne metode*



Graph 4. Number of examined children
Grafikon 4. *Broj pregledane dece*

Discussion

The main challenge for the dental team is how to build trust and establish communication with ASD persons [13, 18]. A prerequisite of a successful dental treatment is the patient's consent and cooperation. Numerous behavioral methods of adaptation are used in pediatric dentistry. However, these types of methods alone are not enough when dealing with children with ASD. The success rate of greatly depends upon the cooperation with special educators, dental practitioners and parents of children with ASD. A bespoke prevention program offers appropriate education of family members of an ASD person, precise dental treatment and intervention schedule that ought to be proposed to the patient after evaluating the individual risk of tooth decay development, range of indicated dental treatment, as well as evaluation of the patient's ability to participate in the program [12]. The first visit to a dental practitioner can also represent the first meaningful experience outside the family environment. One should aim to have this experience as pleasant as possible, without stress and traumatic experiences. The best course of action is to schedule the child's first dental appointment when there is no need for an urgent dental intervention. Unfortunately, with ASD children this is rarely the case due to the child's basic condition and the fact that initial dental appointments usually never take place. Parents often avoid scheduling a dental appointment for their child because of fear of uncooperative behavior [6–8]. Many studies on tooth decay in mentally challenged persons have shown that there is a higher prevalence of untreated or inadequately treated tooth decay compared to the general population, as well as a higher prevalence of oral diseases [12]. As a result of the aforementioned and the specifics of providing dental treatments to ASD children, only integration of several methods and individual approach to work with children with autism can lead to success in work and adaptation to dental interventions in order to maintain oral health. As for the literature review and existing research results, it can be concluded that ABA is the most commonly used method of work and yields the best results for treatment and work with persons with ASD. The ABA model includes several models and therefore leads to success when working with ASD persons. It is based on adaptation of the ASD children to the environment, bearing in mind their development level, skills, degree of motivation and interests. The ABA model is a comprehensive approach that shows progress in three basic developmental areas affected by the ASD: social development, intellectual functioning and communication. Patients with autism have difficulties in accepting changes in their environment, require preparation for them, need gradual continuity in accepting changes [19], and they can react very strongly to unexpected changes in their environment [20]. As a result, by applying communication based interventions or PECS and AAC method, children can gradually be prepared to a change in their environment, as well as an upcoming intervention. The use of these methods has proved to be successful and has yielded excellent results. Swallow [21] recommends a slow and gradual approach to persons with ASD, with the possibility to learn every step in advance, letting them know what will happen in the following stages. Previous research indicates various factors that can



Graph 5. Success rate of preventive measures, conservative treatment, and inability to perform interventions
Grafikon 5. *Stopa uspešnosti sprovođenja preventivnih mera, konzervativnog tretmana i nemogućnosti vršenja indikovanih intervencija*

affect the degree of cooperation between a person with ASD and a dental practitioner, and these factors are the level of ASD, age and gender [22]. Our study showed that there are gender-related differences in cooperation as female children were not cooperative as male, so sometimes it was even impossible to establish communication. The two-month project was, therefore, based on the gradual adaptation of ASD persons by using ABA, DSPM, PECS, AAC, and finally LEAP offering a comprehensive education program for parents that can help in the real world and community [14].

Conclusion

The research results showed that due to the additional education, efforts of pediatric dental practitioners and a team of autism therapists, as well as the necessary and satisfactory cooperation with parents, a certain level of success was achieved. Success can be achieved only by integrating multiple methods, using multidisciplinary cooperation, and individual approach to work with children with autism spectrum disorder that can lead to adaptation to dental interventions.

References

1. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. Pediatrics. 2001;108(5):1155-61.

2. Gajić M, Stevanović R. Hendikepirano dete u stomatološkoj praksi [The disabled child in a dental practice]. Čačak: Svetlost; 2002.

3. Kopetz PB, Endowed DL. Autism worldwide: prevalence, perceptions, acceptance, action. Journal of Social Sciences. 2012;8(2):196-201.

4. Kanner L. Autistic disturbances of affective contact. Nerv Child. 1943;2:217-50

5. Chandrashekhar S, Bommangoudar JS. Management of autistic patients in dental office: a clinical update. Int J Clin Pediatr Dent. 2018;11(3):219-27.

6. Brickhouse TH, Farrington FH, Best AM, Ellsworth CW. Barriers to dental care for children in Virginia with autism spectrum disorders. J Dent Child (Chic). 2009;76(3):188-93.

7. Loo CY, Graham RM, Hughes CV. The caries experience and behavior of dental patients with autism spectrum disorder. J Am Dent Assoc. 2008;139(11):1518-24.

8. Marshall J, Sheller B, Williams BJ, Mancl L, Cowan C. Cooperation predictors for dental patients with autism. Pediatr Dent. 2007;29(5):369-76.

9. Friedlander AH, Yagiela JA, Paterno VI, Mahler ME. The neuropathology, medical management and dental implications of autism. J Am Dent Assoc. 2006;137(11):1517-27.

10. National Institute of Dental and Craniofacial Research. Practical oral care for people with autism (NIH publication No. 04-5190). Bethesda: National Institute of Dental and Craniofacial Research; 2004.

11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.

12. Petrović B. Dostupnost i kvalitet stomatološke nege mentalno nedovoljno razvijenih lica [Availability and quality of dental care of mentally challenged persons]. Dentallist. 2020;(13):13-6.

13. Kasahara H. Autistic children and their dental problems. Shiyo. 1985;33(10):843-4.

14. Roberts J, Prior MR. A review of the research to identify the most effective models of practice in early intervention for children with autism spectrum disorder. Canberra: Department of Health and Ageing; 2006.

15. Rajnović S. Encouraging communication in workig with autism children by applying pecs (the picture exchange communication system) [master paper]. Zagreb: University of Zagreb, Faculty of Education and Rehabilitation Sciences; 2001.

16. Cafiero JM. Meaningful exchanges for people with autism: an introduction to augmentative and alternative communication. Bethesda: Woodbine House; 2005.

17. Mirenda P. Autism, augmentative communication, and assistive technology. What do we really know? Focus Autism Other Dev Disabl. 2001;16(3):141-51.

18. Kamen S, Skier J. Dental management of the autistic child. Spec Care Dentist. 1985;5(1):20-3.

19. McDonald RE, Avery DR. Dentistry for the child and adolescent. 6th ed. St. Louis: Mosby; 1994. p. 601-5, 611.

20. Burkhart N. Understanding and managing the autistic child in the dental office. Dent Hyg (Chic). 1984;58(2):60-3.

21. Swallow JN. The dental management of autistic children. Br Dent J. 1969;126(3):128-31.

22. Nelson T, Chim A, Shelter BL, McKinney CM, Scott JM. Predicting successful dental examinations for children with autism spectrum disorder in the context of a dental desensitization program. J Am Dent Assoc. 2017;148(7):485-92.

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Erratum

Unfortunately, the article by Vesna PETROVIĆ, Vesna VUJIĆ ALEKSIĆ, Tanja ROŽEK MITROVIĆ and Aleksandra HRISTOV, published in the Medical Review, 73; 9–10, 2020, contained two errors: 1. On page 267, the title of the paper should read: PREVALENCE OF ASTHMA AND THE INFLUENCE OF NUTRITIONAL STATUS ON PRESCRIBED MEDICINES FOR ASTHMA IN CHILDREN, and 2. In Table 1, in the Section "Others", percents 57.9 and 8.9 are in the column for No/Br instead in the column for percentages. At the request of the authors, we hereby publish corrections.

Eratum

Nažalost, članak autora Vesne PETROVIĆ, Vesne VUJIĆ ALEKSIĆ, Tanje ROŽEK MITROVIĆ i Aleksandre HRISTOV objavljen u *Medicinskom pregledu*, 73; 9–10, 2020, sadržao je dve greške na stranici 267. 1. Naslov rada treba da glasi: PREVALENCIJA ASTME I UTICAJ NUTRICIONOG STATUSA NA PROPISANE LEKOVE ZA ASTMU KOD DECE. 2. U Tabeli 1, Odeljak *Ostalo*, procenti 57,5 i 8,9 stoje u koloni *No/Br* umesto u koloni za procente. Na zahtev autora, objavljujemo ispravke.

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

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

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

CASE REPORTS
PRIKAZI SLUČAJEVA

Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica

Case report
Prikaz slučaja
UDK 616-089.5-06:616-056.3]-07
https://doi.org/10.2298/MPNS2012381S

DIAGNOSIS AND MANAGEMENT OF ROCURONIUM-INDUCED PERIOPERATIVE ANAPHYLAXIS

DIJAGNOZA I TERAPIJA PERIOPERATIVNE ANAFILAKSE IZAZVANE ROKURONIJUMOM

Ivana STOJANOVIĆ, Jelena VUČKOVIĆ and Matej ŠUNTIĆ

Summary

Introduction. Perioperative anaphylaxis is a hypersensitivity reaction that occurs after exposure to drugs used for anesthesia during a surgical procedure. The most common triggers are neuromuscular blocking agents and antibiotics. **Case Report.** A 71-old man, with a history of anaphylaxis during previous anesthesia, was scheduled for elective coronary surgery. The clinical signs included skin rash, swelling of the upper part of the body with angioedema of the eyelids and lips, without bronchospasm. Based on the assumption that rocuronium was the most likely causative agent, percutaneous coronary intervention was performed during the same hospitalization. After recovery, he was sent for a prick skin test and intradermal test, where sensitivity to rocuronium and insensitivity to the anesthetics used were determined. Two months later, he developed an acute myocardial infarction. Chronic total occlusive percutaneous coronary intervention was attempted, but without optimal results, so the patient was prepared for elective surgery. Due to potential further complications during anesthesia, the medical team decided to send him for a skin allergy test for neuromuscular blocking agents. The only neuromuscular relaxant available was Cisatracurium, and it was tested for sensitivity by intradermal test. The intradermal test showed insensitivity to Cisatracurium and Suxamethonium chloride. **Conclusion.** Early recognition and management of anaphylaxis is based on clinical presentation. The diagnosis by in-vivo and in-vitro tests is useful to determine the cause of anaphylactic reaction and safe alternatives for future anesthesia.

Key words: Rocuronium; Anaphylaxis; Perioperative Period; Drug Hypersensitivity; Neuromuscular Nondepolarizing Agents; Anesthesia; Signs and Symptoms; Skin Tests; Atracurium; Neuromuscular Blockade

Sažetak

Uvod. Perioperativna anafilaksa predstavlja hipersenzitivnu reakciju koja se javlja nakon izlaganja lekovima koji se koriste u anesteziji i hirurgiji. Najčešći uzročnici su neuromišićni relaksanti i antibiotici. **Prikaz slučaja.** Muškarac star 71 godinu, sa istorijom anafilakse tokom prethodne anestezije, planiran je za elektivnu koronarnu hirurgiju. Od kliničkih znakova bili su prisutni osip po koži, otok gornjeg dela tela sa angioedemom očnih kapaka i usana, bez bronhospazma. Zbog sumnje da je uzročnik alergijske reakcije rokuronijum, učinjena je perkutana koronarna intervencija u istoj hospitalizaciji. Nakon oporavka, poslat je na kožni alergološki i intradermalni test gde je utvrđena senzitivnost na rokuronijum i nesenzitivnost na korištene anestetike. Dva meseca kasnije razvio je akutni infarkt miokarda. Pokušana je hronična totalna okluzivna perkutana koronarna intervencija, ali bez optimalnih rezultata, pa je bolesnik pripreman za elektivnu hirurgiju. Zbog mogućih komplikacija tokom anestezije, medicinski tim je odlučio da ga pošalje na kožni alergološki test na neuromišićne relaksante. Jedini dostupan neuromišićni relaksant bio je cisatrakurijum, čija senzitivnost je dokazivana intradermalnim testom. Intradermalnim testom pokazana je nesenzitivnost na cisatrakurijum i suksametonijum hlorid. **Zaključak**. Rano prepoznavanje i vođenje anafilakse vrši se na osnovu kliničke prezentacije. Dijagnoza in-vivo i in-vitro testovima korisna je u otkrivanju etiologije reakcije i sigurnih alternativa u budućoj anesteziji.

Ključne reči. rokuronijum; anafilaksa; perioperativni period; alergija na lekove; neuromišićni relaksanti; anestezija; znaci i simptomi; kožni test; atrakurijum; neuromišićna blokada

Introduction

Anaphylaxis is a severe, potentially fatal, systemic hypersensitivity reaction that occurs suddenly after exposure to a provoking agent [1]. Perioperative anaphylaxis is the result of drugs or substances used for anesthesia and surgery. Neuromuscular blocking agents and antibiotics are the most common triggers. Skin tests and in-vitro tests remain the gold standard for detection of suspected agent, pathophysiological mechanism, safe alternatives, and involve exposure of the skin mast cells of patients who experience anaphylaxis to the suspected allergen. The aim of this case report was to describe early diagnosis and management of perioperative anaphylaxis.

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Abbreviations
IgE – immunoglobulin E
SpO_2 – blood oxygen level

Case Report

A 71-old male (weight 70 kg and body mass index 22/36), American Society of Anesthesiologists physical status Class IV, was scheduled for elective coronary artery bypass graft surgery. He had a history of allergic reaction during anesthesia 11 months before in our hospital when he was scheduled for the same surgery. The patient's anesthesia record from the previous surgery showed that he received 5 mg Bisoprolol and 0.25 mg/kg Midazolam preoperatively. General anesthesia was induced with 80 mg Lidocaine, 50 mcg Sufentanil, 2 mg Midazolam, 60 mg Propofol and 70 mg Rocuronium. After the medications were given, he developed skin rash and edema on his head, neck and chest. With possible diagnosis of anaphylaxis, Methylprednisolone 1 mg/kg was given intravenously. Bronchospasm after tracheal intubation was not recorded and he remained hemodynamically stable. After tracheal intubation, angioedema of eyelids and mouth occurred, and another dose of Methylprednisolone 1 mg/kg was given together with Chloropyramine 40 mg intravenously with continuous infusion of diluted Adrenaline 0.1 mcg/kg/min. He responded to the treatment and the swelling of the face and body decreased gradually. The surgery was suspended and he remained orotracheally intubated and transferred to the Intensive Care Unit where he remained hemodynamically stable. He did not require any inotropes and after 3 hours he was extubated with satisfactory blood gas analysis. He was transferred to the ward the next morning. After 4 days, percutaneous coronary intervention was performed successfully and stents were placed in the ramus circumflex artery and ramus intermedius artery.

He was sent for prick skin test and intradermal test after 10 weeks to an Allergy and Immunology Clinic. It was found that he was not sensitive to Lidocaine, Bupivacaine, Atropine, Neostigmine, Fentanyl, Midazolam, Propofol, Midarine, Meropenem, and Metronidazole. The patient was a diabetic on combined therapy with Insulin and oral hypoglycemic drugs, but was also taking oral medications for hypertension (Bisoprolol, Ramipril, Trimetazidine, Furosemide, Spironolactone) and hyperlipoproteinemia (Rosuvastatine).

The medical history revealed that the patient underwent tonsillectomy and inguinal hernia repair on the right side, 30 and 20 years ago, respectively. However, there were no records on the type of anesthesia he had received. There was no history of any drug allergy, but he reported edema of the face after consuming products that contained propolis and edema of the mouth after a bee sting. One month after the skin test was performed the patient developed acute myocardial infarction of the anterior wall and was hospitalized. During that hospitalization, coronary angiography showed triple vessel coronary artery disease. Optimized results with chronic total occlusion percutaneous coronary intervention could not be achieved, so coronary bypass surgery was recommended. Because of persisting symptoms after myocardial infarction (chest pain, fatigue, dizziness, syncope) the patient was prepared for surgery. He was sent to Allergy and Immunology Clinic where examination on neuromuscular blocking agents was performed and confirmed immune reaction to Rocuronium (generalized urticaria). It was strongly recommended to avoid the triggering agent and other aminosteroid neuromuscular blocking agents (Pancuronium). There were no clinical signs of early or late allergic reactions to Suxamethonium chloride and Cisatracurium, so they could be used. The patient was hospitalized for a planned surgery. The only alternate neuromuscular blocking agent available to us was Cisatracurium. According to the allergist's recommendations, he was received intravenous Methylprednisolone 40 mg, a Levocetirizine and a Famotidine tablet the day before surgery. All precautionary measures were taken, drugs such as adrenaline, steroids and antihistamines were loaded in syringes and equipment required for resuscitation was kept ready. The premedication included intravenous Methylprednisolone 40 mg, 1 intramuscular Chloropyramine vial, and 1 intravenous Pantoprazole vial and the patient was transferred to the operating room. The electrocardiogram, blood pressure, pulse, SpO_2, and capnography were monitored and intravenous access was established. His preoperative blood pressure was 150/74, pulse 88/min and SpO_2 was 98% on room air. The patient was preoxygenated with 100% oxygen. General anesthesia was performed with 100 mcg Fentanyl, 2 mg Midazolam, and 60 mg Propofol. Muscle relaxation was achieved by infusion of Cisatracurium (0.2 mg/kg). After 3 minutes of ventilation, the patient was intubated and the position of orotracheal tube was checked. Anesthesia was maintained by sevoflurane 0.8 – 1.5% in 1: 2 mixture of oxygen and air. Muscle relaxation was maintained with 6 supplemental bolus doses of Cisatracurium (0.03 mg/kg). Intraoperatively, patient remained hemodynamically stabile. After Protamine administration, 100 mg Hydrocortisone was administered intravenously to slow down the patient's immune system and prevent allergic reaction. The surgery lasted 180 minutes and total anesthesia 205 minutes. The patient was moved into the Intensive Care Unit where he maintained hemodynamically stable. After 3 hours he was extubated with satisfactory blood gas analysis.

The patient was moved to the ward and discharged from hospital 7 days later. He received written information about all procedures and tests that were performed, safe and unsafe drugs and anesthesia procedures.

Discussion

Perioperative anaphylaxis is a life-threatening immediate hypersensitivity condition which may be a result of non-allergic (immunological mechanism excluded) or allergic (immunological mecha-

nism proved or highly suspected) reaction [2]. The incidence of perioperative anaphylaxis ranges from 1 in 18,600 to 1 in 353 with geographical variability [3]. Neuromuscular blocking agents and antibiotics are the most common cause of anaphylaxis and usually occur after induction of anesthesia. Rocuronium is associated with a higher rate of anaphylaxis compared to other neuromuscular blocking agents [4]. The other triggering agents that may cause perioperative anaphylaxis are hypnotics, opioids, local anesthetics, latex, nonsteroidal anti-inflammatory drugs, disinfectants, dyes, colloids, blood products, aprotinin, and protamine sulphate [5]. The diagnosis of perioperative anaphylaxis is based on a combination of clinical signs, their severity, and the time of reaction in relation to the drugs administration. Signs and symptoms may vary from mild symptoms to life-threatening anaphylaxis. Cutaneous signs, such as urticaria and generalized erythema are often present. Unexpected perioperative hypotension, bradycardia, isolated cardiovascular collapse, cardiac arrest and bronchospasm may also be the presenting features [6]. Ring and Messmer scale is the most widely used tool to describe clinical phenotypes. Grades I and II are not life-threatening and they include skin or mucosal signs and moderate signs from several organ systems. Grades III and IV are life-threatening and include sings from one or multiple organ systems and circulatory and/or respiratory arrest [7].

A patient with clinically suspected anaphylaxis should have an allergy test. The aim of investigation is to identify a culprit drug, find a safe alternative and ensure safe future anesthesia. Complete medical data, including relevant timelines and information about used drugs are essential. They include the anesthetic record, all drug charts including time of their administration, exposure to other agents (sprays, gels, disinfectants) and details of all procedures (catheters, stents). An ideal screening test is associated with optimal sensitivity and specificity and is safe to perform. Reliable in-vitro tests offer an opportunity to improve accurate diagnosis of perioperative anaphylaxis and identification of the triggering agent. When the culprit agent is identified and substance test is positive, cross-sensitivity should be investigated, due to risk that more than one culprit contributed to reaction. The performance of in-vitro tests in diagnostic algorithm should be done before or after the skin tests, but always before drug provocation testing [8].

In our patient, skin tests were carried out for all the drugs that were given before the anaphylactic reaction occurred. That helped identification of rocuronium as a triggering agent and provide safe alternatives. The skin tests for neuromuscular blocking agents have a sensitivity of 94–97% in patients with a history of anaphylaxis [9]. Negative predictive values are limited, and such studies require additional investigations such as controlled drug provocations test. Drug provocation tests should not be performed in high-risk patients (Steven-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms). In patients with life-threatening anaphylaxis, drug provocation tests after negative skin test should only be performed after balancing the risk-benefit ratio [10]. Because drug provocation tests are not frequently performed for ethical reasons, in many cases the clinical history and use of skin tests are considered the ”reference test”. The main goal of in-vitro tests performed in acute phase of the reaction is assessment of mast cell and/or basophil involvement and quantification of inflammatory mediators, such as tryptase, histamine, prostaglandins and leukotrienes. There are some limitations to these tests: it is difficult to perform testing at the right time, kinetics of peak tryptase and histamine has short half-life and comparison with basal levels is needed [11]. Identification of suspected drug or drugs in resolution phase of anaphylaxis can involve quantification of serum drug-specific IgE measurements and direct/indirect basophil activation tests. Serum drug-specific IgE detection is traditionally performed by using a solid-phase immunoassay. Because only a few drug-specific IgE assays are available, most of them have not been thoroughly validated.

In regard to neuromuscular blocking agents, it has been shown that the diagnosis should not rely on quantification and isolation of serum immunoglobulin E (IgE) [12]. Basophil activation tests are useful to study the involvement of basophils, irrespective of the activation pathway and display specificity (> 90%) and sensitivity rates up to 92% for neuromuscular blocking agents [13]. In-vitro approaches are cellular tests including determination of the cellular proliferative response in lymphocyte transformation tests, measurements of T-cell reactions, and production of cytokines and cytotoxicity. In these tests, cells are stimulated with suspected drug and cytokine release (IL-4, IL-5, INF-γ) or cytotoxic markers (granzyme B, granulysin) and can be detected by using ELIspot, ELISA or bead assay/flow cytometry. In patients with drug-suspected anaphylaxis, using different in-vitro approaches evaluating inflammatory mediators in effector cells increases the mean sensitivity and specificity [14]. In-vitro testing is usually not performed as a test in isolation, but rather as a component of a diagnostic strategy along with additional tests for evaluation of the association between a given drug and an observed clinical reaction. They can be complementary to in-vivo testing for the identification of cross-reactivity missed by skin test or in patients in whom the in-vivo test shows negative or equivocal results [15, 16].

Conclusion

Perioperative anaphylaxis is an unexpected and unpredictable critical event primarily associated with neuromuscular blocking agents and antibiotics. Our experience suggests that the rate of anaphy-

laxis to rocuronium is rising in proportion to the drug usage. In patients with neuromuscular blocking agents anaphylaxis, alternative anesthetic techniques that do not require the use of muscle relaxant medications should be considered. If the surgical procedure requires muscle relaxation, the anesthesiologist should determine the balance of risks. In patients who have experienced an allergic reaction to medication, it is necessary to perform in-vivo and in-vitro tests to determine the etiology of the reaction and their results must be correlated with the patient's medical history. When the responsible medication is identified, administration of the causative agent should be avoided and safe alternatives should be used. Early recognition of clinical signs of anaphylaxis and providing the proper treatment is essential. In our patient, with a history of neuromuscular blocking agent-induced anaphylaxis, an antihistamine and steroid were administered as a premedication prior to surgery to reduce any immune response to medications. The surgery was safely performed, after rocuronium was identified as the causative agent of anaphylaxis, using the intradermal skin test. Patients with anaphylaxis must be informed about its cause and causative agent, signs and symptoms, and about all diagnostic measures which were performed to confirm the diagnosis of anaphylaxis.

References

1. Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al. Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organ J. 2019;12(10):100066.

2. Harper NJN, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121(1):159-71.

3. Mertes PM, Ebo DG, Garcez T, Rose M, Sabato V, Takazawa T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. Br J Anaesth. 2019;123(1):e16-28.

4. Reitter M, Petitpain N, Latarche C, Cottin J, Massy N, Demoly P, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. Allergy. 2014;69(7):954-9.

5. Dewachter P, Savic L. Perioperative anaphylaxis: pathophysiology, clinical presentation, and management. BJA Educ. 2019;19(10)313-20.

6. Garvey LH. Perioperative hypersensitivity reactions: diagnosis, treatment and evaluation. Curr Treat Options Allergy. 2016;3:113-28.

7. Rose MA, Green SL, Crilly HM, Kolawole H. Perioperative anaphylaxis grading system: 'making the grade'. Br J Anaesth. 2016;117(5):551-3.

8. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2016;71(8):1103-34.

9. Mertes PM, Moneret-Vautrin DA, Leynadier F, Laxenaire MC. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. Anesthesiology. 2007;107(2):245-52.

10. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58(9):854-63.

11. Berroa F, Lafuente A, Javaloyes G, Ferrer M, Moncada R, Goikoetxea MJ, et al. The usefulness of plasma histamine and different tryptase cut-off points in the diagnosis of preanaesthetic hypersensitivity reactions. Clin Exp Allergy. 2014;44(2):270-7.

12. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. Clin Exp Allergy. 2014;44(8):1069-75.

13. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. Allergy. 2015;70(11):1393-405.

14. Porebski G, Gschwend-Zawodniak A, Pichler WJ. In vitro diagnosis of T cell-mediated drug allergy. Clin Exp Allergy. 2011;41(4):461-70.

15. Porebski G. In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? Int J Mol Sci. 2017;18(8):1737.

16. Mayorga C, Ebo DG, Lang DM, Pichler WJ, Sabato V, Park MA, et al. Controversis in drug allergy: in vitro testing. J Allergy Clin Immunol. 2018;143(1):56-65.

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Case report
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EARLY RECOGNITION OF POSTOPERATIVE PULMONARY THROMBOEMBOLISM AFTER ELECTIVE HIP REPLACEMENT SURGERY – A CASE REPORT

RANO PREPOZNAVANJE POSTOPERATIVNOG NASTANKA PLUĆNE TROMBOEMBOLIJE NAKON ELEKTIVNE ORTOPEDSKE OPERACIJE PROTEZE KUKA – PRIKAZ SLUČAJA

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Summary

Introduction. Surgical patients have an increased risk of developing pulmonary thromboembolism. Early diagnosis is difficult due to the presence of non-specific symptoms. **Case Report.** A case of a 72-year-old man admitted to the Intensive Care Unit after elective orthopedic hip replacement surgery is presented, due to a sudden worsening of the general condition accompanied by tachypnea, decreased oxygen saturation, neck cyanosis, hemodynamic instability, and heart rhythm disorders. Pulmonary thromboembolism was confirmed by computed tomography and echocardiography. **Conclusion.** The symptoms of pulmonary thromboembolism are usually nonspecific. Early recognition with confirmation by diagnostic procedures is important in order to reduce the mortality rate**.**

Key words: Pulmonary Embolism; Thromboembolism; Hip Prosthesis; Orthopedic Procedures; Early Diagnosis; Signs and Symptoms; Tomography, X-Ray Computed; Echocardiography; Risk Factors

Sažetak

Uvod. Hirurški bolesnici imaju povišen rizik od nastanka plućne tromboembolije. Rano postavljanje dijagnoze je otežano zbog prisustva nespecifične simptomatike. **Prikaz slučaja.** Prikazan je slučaj 72-godišnjeg muškarca primljenog u Jedinicu intezivnog lečenja nakon elektivne ortopedske operacije proteze kuka, zbog naglog pogoršanja opšteg stanja koje je bilo praćeno tahipneom, padom saturacije kiseonika, cijanozom vrata, hemodinamičkom nestabilnošću i poremećajima srčanog ritma. Kompjuterizovanom tomografijom i ehokardiografijom potvrđena je plućna tromboembolija **Zaključak.** Simptomatika plućne tromboembolije je najčešće nespecifična. Njeno rano prepoznavanje, uz dijagnostičku potvrdu, značajno je za smanjenje stope mortaliteta.

Ključne reči: pulmonarni embolizam; tromboembolija; proteza kuka; ortopedske procedure; rana dijagnoza; znaci i simptomi; CT; ehokardiografija; faktori rizika

Introduction

Pulmonary thromboembolism (PTE) is an obstruction of one or more branches of the pulmonary artery with thrombi originating from the venous system [1]. Patients with trauma, fractures of the long bones of lower extremities, patients after orthopedic, major abdominal, gynecological, oncology, chest, and cardiovascular surgeries are at increased risk of developing PTE [2].

Case Report

A72-year-old man was admitted to the General Hospital Vrbas for elective hip replacement surgery. Fifteen minutes after the surgery, performed in spinal anesthesia, in the post-anesthesia unit the patient presented with a sudden worsening of the general condition accompanied by tachypnea, decreased oxygen saturation, and neck cyanosis. Noninvasive monitoring revealed a hemodynamic instability followed by hypotension with periodic cardiac arrhythmia manifesting with ventricular extrasystoles. The intravascular volume compensation was done using vasoactive and antiarrhythmic drugs, but without the expected therapeutic response, so the patient was transferred to the Intensive Care Unit. After transfer to the Intensive Care Unit, the patient breathed spontaneously; a control chest X-ray and arterial blood gas analysis were performed, with satisfactory results. Even though oxygen therapy was used, a reduced oxygen saturation (77%) and cardiac rhythm disturbances, ventricular and supraventricular extrasystoles, persisted. All laboratory tests were performed and a significant increase of D-dimer (17,265) was observed. Contrast-enhanced computed tomography (CT) of the chest and echocardiography (EHO) were performed. The CT and EHO findings confirmed pulmonary thromboembolism **(Figure 1A and 1B).** After the diagnostic examinations, heparin was included in the therapeutic regimen, first in a bolus of 8000 international units, then in a continuous infusion of 42 milliliters per hour. After the check-up of coagula-

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Abbreviations
CT – computed tomography
ECHO – echocardiography
PTE – pulmonary thromboembolism

tion parameters every 3 to 4 hours, the heparin infusion rate was corrected and it was discontinued after 12 hours. On the first postoperative day, after stabilization of the general condition, the patient was transferred to the Institute of Pulmonary Diseases of Vojvodina in Sremska Kamenica for surgical treatment.

Pulmonary thrombectomy was performed successfully and 15 days after surgery the patient was discharged in a satisfactory general condition.

Discussion

The incidence of pulmonary thromboembolism after orthopedic surgical procedures is estimated to be 0.7–30% and 4.3% to 24% after hip fracture surgery [3]. Risk factors for venous thromboembolism are associated with comorbidities, perioperative course specificities, including acute inflammatory reaction caused by tissue trauma, coagulation cascade activation, immobilization and venous pathways. Males are at increased risk of PTE [4]. In most cases the symptomatology is nonspecific; symptoms in conscious patients may help establishing the diagnosis of PTE, while they are masked with the anaesthetized, mechanically ventilated patients.

The most common nonspecific symptoms are tachycardia and hypotension. Severe heart rhythm disorders are rare [4]. Atrial fibrillation/flutter, first, second and third degree blocks, as well as ventricular heart rhythm disorders, are present in less than 5–10% of cases [4, 5]. In patients who breathe spontaneously, the nonspecific indicators of inadequate gas exchange are hypoxemia, respiratory alkalosis and hypocapnia. D-dimer is a sensitive, but not a specific test; it may be positive in conditions unrelated to pulmonary embolism such as infection, malignancies, and trauma. Our patient presented with a significant increase in D-dimer, with initially satisfactory parameters of arterial gas analysis. A negative result is useful for excluding the diagnosis with low risk patients; however, it is of no benefit in establishing the diagnosis and estimating its severity. Chest radiography is not of great importance for diagnosis [6]. The presented patient had a satisfactory chest X-ray. The PTE was confirmed by CT and EHO.

According to Kearon, many patients may have a silent and clinically unrecognized PTE. As a proof, he states that not a single patient died of pulmonary embolism if he received anticoagulants, whereas 26% died since they did not receive anticoagulants [7]. In fact, 50% of surgical patients who develop pulmonary thromboembolism receive a perioperative thromboembolic prophylaxis [3]. Our patient also received preoperative thromboembolic prophylaxis.

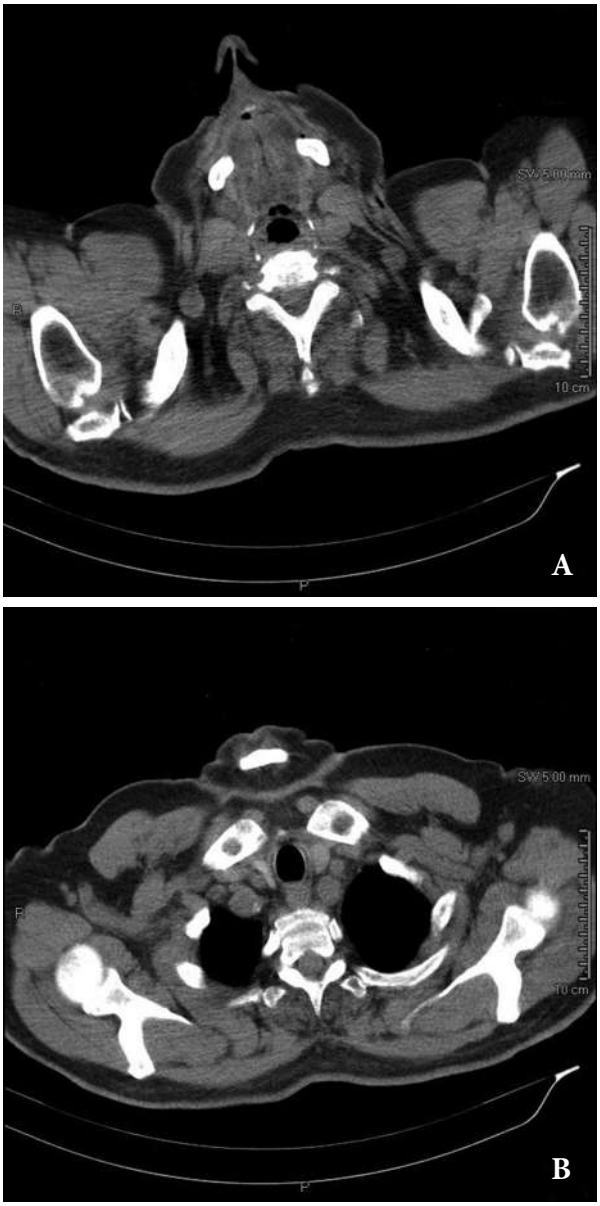

Figure 1A and 1B. Pulmonary thromboembolism on computed tomography
Slika 1 A i B. *Plućna tromboembolija prikazana kompjuterizovanom tomografijom*

The study of Charalambous C. et al. points to the importance of phlebography of the lower extremities in the diagnosis of deep venous thrombosis, because it can detect distal and proximal thrombosis, which is the most common cause of PTE. Phlebography of the lower extremities was not performed in our patient as part of the diagnostic procedures. In a prospective study of prophylactic anti-thrombotic therapy in orthopedic patients, color Doppler ultrasonography showed a low sensitivity in the detection of asymptomatic deep venous thrombosis in proximal leg veins of only 38% [8]. In his research, Charalambous C. et al. have shown that neither deep venous thrombosis nor pulmonary

embolism was found in 138 patients using knee compression pumps. Using a foot pump, Charalambous C. et al. proved that 29 patients who underwent arthroplasty of large joints, there was not a single case of deep venous thrombosis or PTE [8].

Geertsand et al. showed that thromboembolic prophylaxis reduces the incidence of PTE [9]. They have published a paper in which they showed that the high risk patients must preventively receive thromboembolic prophylaxis both pre- and postoperatively. After completion of surgical treatment, it is of utmost importance for patients at high risk to continue using thromboembolic prophylaxis as well as the recommended antiplatelet therapy [10].

In a review article, Unić-Stojanović D. showed that PTE may develop perioperatively in patients who have undergone drug and mechanical thromboembolic prophylaxis. She has also proven that the diagnosis is very difficult to make and it is accompanied by method of elimination. Intraoperative diagnosis is a major problem due to the similarity of clinical picture with other accompanying disorders such as bleeding and infection [11].

In their paper, Vučićević-Trobok J. et al. presented a patient with PTE that was associated with acute renal failure due to renal artery thrombosis. The patient was diagnosed with PTE and the therapeutic regime was initiated. On the third day of intensive treatment, hematuria appeared, followed by oliguria with a sharp elevation of nitrogenous substances in the blood, as a sign of acute renal failure. The patient died on the same day. The autopsy report revealed deep venous thrombosis of the left femoral vein, massive PTE, heart dilatation, and thrombosis of both renal arteries with numerous anemic infarcts which was the cause of acute renal failure [12].

Conclusion

There is an increased risk of pulmonary thromboembolism in orthopedic and trauma patients. The symptoms are most often nonspecific, so that early recognition with confirmation by diagnostic procedures is important in order to implement therapy and reduce the mortality rate**.**

References

1. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th edition). Chest. 2008;133(6 Suppl):381S-453.

2. Qadan M, Tyson M, McCafferty MH, Hohmann SF, Polk HC Jr. Venous thromboembolism in elective operations: balancing in choices. Surgery. 2008;144(4):654-60.

3. Arcelus JI, Kudrna JC, Caprini JA. Venous thromboembolism following major orthopedic surgery: what is the risk after discharge? Orthopedics. 2006;29(6):506-16.

4. Tapson VF. Acute pulmonary embolism. N Engl J Med. 2008;358(10):1037-52.

5. Desciak MC, Martin DE. Perioperative pulmonary embolism: diagnosis and anesthetic management. J Clin Anesth. 2011;23(2):153-65.

6. Indik JH, Alpert JS. Detection of pulmonary embolism by D dimer assay, spiral computed tomography and magnetic resonance imaging. Prog Cardiovasc Dis. 2000;42(4):261-72.

7. Kearon C, Kahn SR, Angelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence- Based Clinical Practice Guidelines (8th edition). Chest. 2008;133(6 Suppl):454S-545.

8. Charalambous C, Cleanthous S, Tryfonidis M, Goel A, Swindell R, Ellis D. Foot pump prophylaxis for deep venous thrombosis-rate of effective usage following knee and hip arthroplasty. Int Orthop. 2003;27(4):208-10.

9. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, et al. Prevention of venous thromboembolism. Chest. 2001;119(1 Suppl):132S-75.

10. Grubor P, Jakovljević A, Grubor G, Jakovljević B. The value of thromboembolic prophylaxis in the prevention of thromboembolic disease in the orthopedic and traumatological surgery. Acta Medica Medianae. 2006;45(39):34-9.

11. Unić-Stojanović D. Perioperative pulmonary embolism. Serbian Journal of Anesthesia and Intensive Therapy. 2016;38(1-2):33-8.

12. Vučićević-Trobok J, Trifković M, Bogdanov B, Klem I. Pulmonary thromboembolism and acute renal insufficiency caused by renal artery thrombosis. Med Pregl. 2002;55(1-2):44-6.

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MULTY-SYSTEM COMPLICATIONS OF ACCIDENTAL HYPOTHERMIA – A CASE REPORT

MULTISISTEMSKE KOMPLIKACIJE AKCIDENTALNE HIPOTERMIJE − PRIKAZ SLUČAJA

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Summary

Introduction. Accidental hypothermia is an unintentional fall in core temperature to less than 35°C and it occurs when the body's heat loss exceeds its heat production. The elderly population is particularly susceptible due to reduced adaptability to low temperatures and various comorbidities, which may be predisposing factors. **Case Report.** A 65-year-old Caucasian female was admitted to the hospital due to hypothermia (< 34°C), severe hypoglycemia (0.7 mmol/L), metabolic acidosis (6.970), elevated urea (42.4 mmol/L) and creatinine (686 μmol/L). The initial examination revealed shivering, dysarthria and general exhaustion. Hyperamylasemia (241 U/L) and hyperlipasemia (1920 U/L) were found on the second day after admission. Contrast enhanced computed tomography showed a focal asymmetric enlargement of the pancreatic head and body. Furthermore, a splenic infarction was also noticed. The complexity of human thermoregulatory mechanisms indicates the importance of precipitating factors in the development of hypothermia. Our patient presented with several precipitating factors such as age, sex, urinary tract infection, diabetes, and metformin-induced severe hypoglycemia. **Conclusion.** Based on the presented case and the relevant literature, it can be concluded that the clinical picture of hypothermia may be extremely complex. Knowledge of all the mechanisms involved in multi-organ failure due to hypothermia is of utmost importance, in order to conduct adequate and timely targeted diagnosis and apply appropriate treatment.

Key words: Hypothermia; Body Temperature Regulation; Pancreatitis; Multiple Organ Failure; Diabetes Mellitus; Risk Factors; Signs and Symptoms

Sažetak

Uvod. Slučajna pothlađenost predstavlja nenameran pad centralne telesne temperature ispod 35°C; nastaje kada odavanje toplote prevaziđe termogenezu. Često se javlja kod starije populacije usled smanjene adaptabilnosti i prisustva različitih komorbiditeta koji mogu da predstavljaju predisponirajuće faktore. **Prikaz slučaja.** Žena, stara 65 godina, hospitalizovana je zbog pothlađenosti (< 34° C), izražene hipoglikemije (0,7 mmol/L), metaboličke acidoze (6,970), povišenih vrednosti uree (42,4 mmol/L) i kreatinina (686 umol/L). Inicijalnim pregledom verifikovano je podrhtavanje bolesnice, disartrija, uz opštu sliku iscrpljenosti. Povišene vrednosti serumskih amilaza (241 U/L) i lipaza (1920 U/L) evidentirane su drugog dana hospitalnog lečenja. Pregledom kompjuterizovanom tomografijom trbuha viđeno je fokalno, asimetrično uvećanje glave i dela tela pankreasa. Takođe, opisana je istim pregledom promena koja odgovara infarkciji slezine. Kompleksnost termoregulatornih mehanizama čoveka ukazuje na značaj precipitirajućih faktora u razvoju pothlađenosti. Kod prikazane bolesnice bilo je prisutno više precipitirajućih faktora poput starosti, pola, urinarne infekcije, šećerne bolesti i metforminom indukovane teške hipoglikemije. **Zaključak.** Na osnovu prikazanog slučaja i relevantne literature, može se zaključiti da klinička slika pothlađenosti može biti veoma kompleksna. Izuzetno je važno poznavanje mehanizama preko kojih dolazi do multiorganskih oštećenja indukovanih pothlađivanjem, kako bi se sprovele adekvatna i pravovremena ciljana dijagnostika, te primenile odgovarajuće mere lečenja.

Ključne reči: hipotermija; regulacija telesne temperature; pankreatitis; sistemsko otkazivanje organa; dijabetes melitus; faktori rizika; znaci i simptomi

Introduction

Accidental hypothermia is defined as an unintentional fall in core (rectal, esophageal, tympanic) temperature below 35°C and it occurs when the body´s heat loss exceeds its heat production [1, 2]. Hypothermia may be primary, where the cold injury is the major pathology, or secondary, where patients develop hypothermia incidental to another illness. It is classified as mild (33 – 35°C), moderate (28 – 33°C), and severe (< 28°C), but the classification need not correlate with distinct clinical symptoms [3]. It is a serious condition, especially in patients with injuries and chronic diseases, since it can induce a vicious cycle of the synergistic effects of hypothermia, acidosis and coagulopathy, referred to as the trauma triad of death [4].

Humans need to maintain the body temperature close to 37°C, regardless of the environmental conditions [3]. It is well known that older people are particularly susceptible to accidental hypothermia, since the thermoregulatory ability progressively de-

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Abbreviations
CECT – contrast enhanced computed tomography
CNS – central nervous system

creases with age [1]. Experiments have shown that the elderly are more prone to hypothermia due to several factors: a decreased ability to increase the respiratory quotient and heat production when transferred from normal to a very cold environment; an inadequate vasoconstrictor response, causing the inability to feel cold, and therefore impaired behavioral responses of increasing heat or adding clothing. Also, the elderly population has decreased resting peripheral blood flow reflecting autonomic dysfunction [5]. In addition to this age-related impairment of adaptability to a fall in temperature, various pathological conditions and medications may be implicated in the development of hypothermia. For example, central thermoregulatory ability can be impaired in situations like stroke, central nervous system (CNS) trauma, tumors, or hemorrhage, uremia, Parkinson's disease, multiple sclerosis, and Wernicke's syndrome. Impaired control of peripheral vasculature through autonomic dysfunction can also play a role in diabetes mellitus and cardiac failure [1, 6].

Superimposed conditions, such as infections, can also be important [7]. Reduced heat production occurs in endocrinopathies such as hypothyroidism, hypocorticism, hypopituitarism, and hypoglycemia, which alone can predispose to hypothermia. Diabetes mellitus is an important factor to consider when assessing the risk of hypothermia, especially in elderly women [1, 8].

Hypothermia induces systemic effects, initially to maintain the inner balance, and if the unfavorable conditions exceed the compensatory mechanisms, multi-system complications occur, which may eventually lead to a lethal outcome.

In mild hypothermia, initial symptoms include profound vasoconstriction, acceleration of the heart and respiratory rates, increased oxygen consumption, with consequent increase in cardiac output and blood pressure. Further lowering of the temperature to moderate hypothermia leads to progressive bradycardia due to decreased spontaneous depolarization of the pacemaker cells [9]. The resultant reduction in cardiac output may be balanced by an increased systemic vascular resistance consequent on autonomic reflex response and catecholamine release. This elevated systemic resistance may be perpetuated by hemoconcentration, increased blood viscosity and local vasomotor responses [1, 9]. The hematological changes that are associated with hypothermia are important, particularly the increase in blood viscosity, fibrinogen and hematocrit.

The CNS manifestations are often clinically apparent, with initial confusion and, sometimes, dysarthria, impaired judgment and amnesia in mild stages. Shivering is initially increased in mild hypothermia, but later decreases as the body temperature falls further [1, 3].

Pancreatitis, as one of various morphological alterations of the pancreatic tissue, frequently occurs as a consequence of hypothermia, being found in 20–30% of cases at autopsy, possibly due to micro-thrombosis and consecutive infarctions. Other organs could be affected as well, such as the gut, brain, and liver [1, 10].

Case Report

A 65-year-old Caucasian female was admitted in February 2018 for hypothermia, severe hypoglycemia and high levels of serum urea and creatinine **(Table 1)**. Shivering was present, and the patient complained of having issues with articulation, and feeling exhausted during the previous 24 hours.

She had been diagnosed with diabetes mellitus type 2 at the age of 63, and had been treated with oral antihyperglycemic agents (metformin). At the same age, she was diagnosed with colon cancer, and later that year was surgically treated for the first time (resection of the rectosigmoid colon with transthoracic anastomosis), and two years later for the second time (total colectomy with ileorectal anastomosis), followed by adjuvant chemotherapy (5FU/LV No VI).

Around 24 hours prior to admission, the patient attended a funeral, and according to the available weather forecast information, the daily temperature reading in that region was reported to be in the range between -3 and -6 C° (26.6 – 21.2F) [11]. Upon admission, her body temperature was below 34.0°C (exceeding the measurement range of 34.0°C to 44.0°C of the thermometer, which had an error of measurement of ± 0.2°C). Her blood pressure, measured in the supine position, was 90/50 mmHg, and heart rate was 80 beats per minute.

The initial laboratory tests verified severe hypoglycemia, hyperkalemia, highly elevated blood urea nitrogen and serum creatinine levels. In addition, the renal failure index was 3.02. Arterial blood gas analysis indicated presence of metabolic acidosis. Serum amylase and lipase levels were also elevated (**Table 1**). The complete blood count showed the following results: white blood cells $10.32x10^9$/L (normal range 4.0 – 10.0), red blood cells 5.3 x 10^{12}/L (3.9 – 5.4), mean corpuscular volume (MCV) 89.0 fL (80 – 100), hemoglobin 138 g/L (120 – 160), hematocrit 0.467 L/L (0.370 – 0.470), thrombocytes 209 x 10^9/L (140 – 400).

Parameters of hemostasis: the activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT) of plasma and the level of fibrinogen, were within the normal range.

Semi quantitative urinalysis showed high levels of hemoglobinuria as well as pyuria, with no proteinuria, glycosuria or ketonuria. Urine microscopic analysis showed 79 red blood cells (0 – 5) per high-power field with 12 casts (0 – 0), 55 white blood cells (0 – 5) and 185 bacteria (0 – 20). Urine culture test was positive and showed more than 100000 bacteria (Escherichia coli)/ml, sensitive to empirically initiated antibiotics.

Figure 1. Abdominal contrast enhanced computed tomography image: focal asymmetric enlargement of the pancreatic head and body. A) transverse plane; B) coronal plane
Slika 1. *Prikaz kompjuterizovanog tomografskog pregleda abdomena sa kontrastom: fokalno asimetrično uvećanje glave i tela pankreasa. A) transverzalni presek B) koronalni presek*

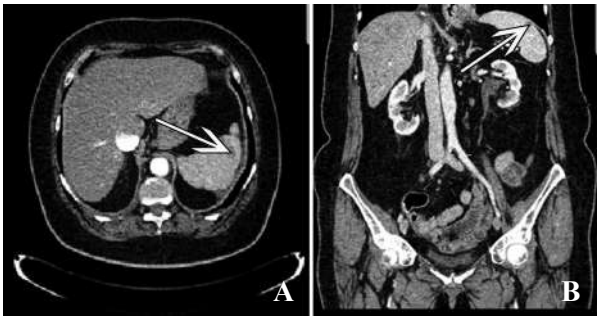

Figure 2. Abdominal contrast enhanced computed tomography image: hypodense lesion, present in the spleen, approximately 40 x 12 mm in size, indicating an infarction. A) transverse plane; B) coronal plane
Slika 2. *Prikaz kompjuterizovanog tomografskog pregleda abdomena sa kontrastom: hipodenzna lezija, prisutna u slezini, karakteristika infarkcije, aproksimativne veličine 40 x 12 mm A) transverzalni presek B) koronalni presek*

Table 1. Laboratory parameters at baseline and at final follow-up
Tabela 1*. Inicijalne i poslednje kontrolne laboratorijske vrednosti*

	Baseline value *Inicijalna vrednost*	Final follow up value *Poslednja kontrolna vrednost*	Normal range *Referentni opseg*
Glycemia/*Glikemija* (mmol/L)	0.7	5.5	3.9-6.1
Urea/*Urea* (mmol/L)	42.4	4.8	2.2-7.1
Creatinine/*Kreatinin* (μmol/L)	686	95	49-97
Amylase/*Amilaze* (U/L)	241	69	20-118
Lipase/*Lipaze* (U/L)	1920	230	73-393
Blood pH/*pH krvi*	6.970	7.378	7.350-7.50
Sodium/*Natrijum* (mmol/L)	135	141	135-148
Potassium/*Kalijum* (mmol/L)	7.2	4.6	3.5-5.5
Chlorine/*Hlor* (mmol/L)	113	109	98-112

Transabdominal ultrasonography showed normal echogenicity. Contrast enhanced computed tomography (CECT) scan performed on the third day of hospitalization showed a focal asymmetric enlargement of the pancreatic head and body **(Figure 1)**. Furthermore, a hypodense lesion was found in the spleen, approximately 40 x 12 mm in size, which indicated an infarction **(Figure 2)**. A CECT scan of kidneys showed normal density and intact corticomedullary differentiation without hydronephrosis. Esophagogastroduodenoscopy was performed and the finding revealed a chronic edematous and erythematous gastritis.

After supportive care, the serum creatinine and blood urea nitrogen, as well as serum amylase and lipase levels decreased gradually to normal range **(Table 1)**. During the entire hospitalization, glycemia was followed on daily basis, multiple times, and the findings were between 4.1 and 7.6 mmol/l. Serum potassium levels normalized promptly after the patient was admitted, on the second day, and the arterial blood gas analysis showed pH within the normal range on third day of hospitalization **(Table 1)**.

The control laboratory findings showed that the number of white blood cells decreased daily to 5.55 x 10^9/L, red blood cells to 3.54 x 10^{12}/L, hemoglobin dropped from 138 to 93 g/L, hematocrit to 0.316 L/L, and thrombocytes from 209 to 72x10^9/L.

Secondary semi quantitative urinalysis showed significant improvement: hemoglobinuria, proteinuria, glycosuria and ketonuria were negative, and pyuria reduced from ++ to +. Microscopic urine analysis showed improvements as well: the number of red blood cells decreased to 3 per high-power field with no casts, white blood cells to 6 and bacteria to 30. Also, the 24-hour urine volume reduced from the initial 3000 ml to 1500 ml within a couple of days.

The external body temperature normalized within the first 24 hours due to passive rewarming procedures.

Discussion

Here, we reported on a 65-year-old female with multi-system complications of accidental hypothermia.

The complexity of normal thermoregulation indicates that precipitating factors contributing to the

development of accidental hypothermia highly vary. The patient in this case had several, such as age, gender, urinary infection and other comorbidities, first of all diabetes mellitus, followed by drug-induced severe hypoglycemia.

The relationship between hypothermia and glucose metabolism can be complex. When developing rapidly, hypothermia often results in hyperglycemia through several mechanisms occurring simultaneously: inhibited insulin release by increased corticosteroid levels [12], impaired insulin uptake by peripheral tissues, and increased sympathetic activity with catecholamine-induced glycogenolysis and gluconeogenesis. On the other hand, when hypothermia develops more slowly or is long-lasting, glycogen levels may become depleted especially with intense shivering, thus frequently inducing hypoglycemia [13].

Metformin is a potent insulin-sensitizing agent that primarily targets the hepatic glucose production and has additional effects on peripheral insulin sensitivity. Even though it has an excellent safety profile and is effective as mono-therapy, metformin-related hypoglycemia, in patients not receiving insulin or sulfonylureas, is associated with heavy exercise, poor oral intake, other comorbidities and lactic acidosis [14]. Hypoglycemia can cause heat loss through peripheral vasodilation and sweating. Furthermore, shivering, a homeostatic mechanism through which skeletal muscles create heat is inhibited when glycemia falls in the range of 1.67 mmol/L to 2.5 mmol/L. In cases of hypoglycemic hypothermia, shivering reappears within 40 seconds of the administration of intravenous glucose [15].

Renal complications of hypothermia have received little attention in previous case reports. In this clinical case, the blood laboratory results upon admission showed highly elevated blood urea nitrogen and serum creatinine levels, followed by hyperkalemia and metabolic acidosis. A renal failure index higher than 1.0 (in this case it was 3.02) is consistent with oliguric acute renal failure [16]. This can be explained by the fact that kidneys have the highest oxygen consumption at normothermia, consuming 8% of the total body oxygen, while representing only 0.5% of the body weight. However, during hypothermia, the body perceives kidneys as the most dispensable organs for maintaining equilibrium, reducing the renal oxygen consumption rapidly compared to other organs, with a parallel decrease in blood flow during the same period of temperature reduction [9].

Mildly elevated serum amylase without clinical evidence of pancreatitis is common in the state of hypothermia, being present in 50 to 65% of patients [1, 17–19], and as the body temperature decreases, the serum amylase levels rise [18]. Due to the absence of epigastric abdominal pain in this patient, acute pancreatic inflammation has not been initially diagnosed. On the second day of hospitalization, the laboratory findings showed highly elevated serum lipase, and after CECT the diagnosis of acute edematous pancreatitis was made, since two of three main Atlanta diagnostic criteria [20] were present. The most common causes of acute pancreatitis, such as gallstone disease, alcohol abuse, pancreatic tumor, hyperlipidemia, trauma, hyperparathyroidism, and viral infection were excluded [21]. The mechanisms involved in acute pancreatitis and hypothermia have remained elusive. It is thought to result from thrombosis in the microcirculation, and resulting ischemia [1]. Several postmortem studies of accidental hypothermia showed thrombosis in the pancreatic micro-circulation, with evidence of acute pancreatitis in 20 – 30% of victims [22]. The underlying process may similarly cause micro-infarcts in the gut, liver, brain, myocardium, and many other organs, including the spleen, as verified by CECT scan in our case with the presence of a hypodense lesion, approximately 40 x 12 mm in size **(Figure 2)** [1].

The platelet count is commonly decreased due to splenic, hepatic, and intravascular sequestration in the state of hypothermia. Changes in vascular permeability result in the loss of plasma to extravascular compartments, leading to hemoconcentration, and the accompanying hypovolemia is compounded by a cold-induced diuresis. The hematocrit increases by about 2% for every 1°C decline in temperature, and a normal hematocrit in a moderately or severely hypothermic patients suggests blood loss or pre-existing anemia. This was the case in our patient according to her medical record [1, 7].

A severe metabolic acidosis that was present on admission can be well expected in the state of hypothermia, since shivering greatly increases the production and accumulation of lactic acid in the blood. The buffer capacity is seriously reduced in a state of hypothermia, and any disturbance in the circulatory, respiratory or renal function will seriously affect the acid-base homeostasis. In case of a circulatory insufficiency, severe tissue anoxia occurs. This stimulates the anaerobic metabolism, and excessive amounts of lactic acid are produced. Hypothermia affects the capability of the liver to metabolize this excess, and metabolic acidosis develops [23].

Conclusion

Based on the presented case and the relevant literature, it can be concluded that the clinical picture of hypothermia may be extremely complex. Knowledge of all the mechanisms involved in multi-organ failure due to hypothermia is of utmost importance, in order to conduct adequate and timely targeted diagnosis and apply appropriate treatment.

References

1. Mallet ML. Pathophysiology of accidental hypothermia. QJM. 2002;95(12):775-85.

2. Turk EE. Hypothermia. Forensic Sci Med Pathol. 2010;6(2):106-15.

3. Hanania NA, Zimmerman JL. Accidental hypothermia. Crit Care Clin. 1999;15(2):235-49.

4. Haverkamp FJC, Giesbrecht GG, Tan ECTH. The prehospital management of hypothermia - an up-to-date overview. Injury. 2018;49(2):149-64.

5. Reuler JB. Hypothermia: pathophysiology, clinical settings, and management. Ann Intern Med. 1978;89(4):519-27.

6. Zafren K. Accidental hypothermia in adults [Internet]. [cited 2020 May 4]. Available from: https://www.uptodate.com/contents/accidental-hypothermia-in-adults.

7. Manning B, Stollerman GH. Hypothermia in the elderly. Hosp Pract. 1993;28(5):53-70.

8. Neil HA, Dawson JA, Baker JE. Risk of hypothermia in elderly patients with diabetes. Br Med J (Clin Res Ed). 1986;293(6544):416-8.

9. Wong KC. Physiology and pharmacology of hypothermia. West J Med. 1983;138(2):227-32.

10. Preuss J, Lignitz E, Dettmeyer R, Madea B. Pancreatic changes in cases of death due to hypothermia. Forensic Sci Int. 2007;166(2-3):194-8.

11. AccuWeather Budisava, South Bačka [Internet]. 2018 [cited 2019 Dec 23]. Available from: https://www.accuweather.com/en/rs/budisava/1568576/month/1568576?monyr=2/01/.

12. Curry DL, Curry KP. Hypothermia and insulin secretion. Endocrinology. 1970;87(4):750-5.

13. Maclean D, Griffiths PD, Browning MC, Murison J. Metabolic aspects of spontaneous rewarming in accidental hypothermia and hypothermic myxoedema. Q J Med. 1974;43 (171):371-87.

14. Zitzmann S, Reimann IR, Schmechel H. Severe hypoglycemia in an elderly patient treated with metformin. Int J Clin Pharmacol Ther. 2002;40(3):108-10.

15. Gale EA, Bennett T, Green JH, MacDonald IA. Hypoglycaemia, hypothermia, and shivering in man. Clin Sci. 1981;61(4):463-9.

16. Doyle DJ. Renal Failure Index (RFI). In: Doyle DJ. Computer programs in clinical and laboratory medicine. New York: Springer; 1989. p. 90-2.

17. Foulis AK. Morphological study of the relation between accidental hypothermia and acute pancreatitis. J Clin Pathol. 1982;35(11):1244-8.

18. Inoue H, Uemura S, Harada K, Mizuno H, Bunya N, Nomura K, et al. Risk factors for acute pancreatitis in patients with accidental hypothermia. Am J Emerg Med. 2019;37(2):189-93.

19. Lin K, Ofori E, Lin AN, Lin S, Lin T, Rasheed A, et al. Hypothermia-related acute pancreatitis. Case Rep Gastroenterol. 2018;12(2):217-23.

20. Foster BR, Jensen KK, Bakis G, Shaaban AM. Revised Atlanta criteria for acute pancreatitis. RadioGraphics. 2016;36 (3):675-87.

21. da Silva S, Rocha M, Pinto-De-Sousa J. Acute pancreatitis etiology investigation: a workup algorithm proposal. GE Port J Gastroenterol. 2017;24(3):129-36.

22. Alty JE, Ford HL. Multi-system complications of hypothermia: a case of recurrent episodic hypothermia with a review of the pathophysiology of hypothermia. Postgrad Med J. 2008;84(992):282-6.

23. Rosenfeld JB. Acid-base and electrolyte disturbances in hypothermia. Am J Cardiol. 1963;12:678-82.

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COMPUTED TOMOGRAPHY ANGIOGRAPHY FINDINGS OF ABDOMINAL AORTIC DISEASE – A REVIEW OF EMERGENCIES

NALAZI KOMPJUTERIZOVANE ANGIOGRAFIJE KOD BOLESTI ABDOMINALNE AORTE – PREGLED HITNIH SLUČAJEVA

Mirela JUKOVIĆ[1, 2], Aleksandra MIJATOVIĆ[1], Ivana STOJIĆ[1], Ljiljana DRAŽETIN[1], Maja STANKOV[1] and Viktor TILL[1, 2]

Summary

Introduction. The aorta is a major blood vessel that supplies all segments of the human body. Acute aortic syndrome is a term that implies a life-threatening aortic disease. Due to the speed of examination and widespread availability, computed tomography angiography is a front-line diagnostic modality for emergencies and diseases of the abdominal aorta. The aim of this study was to provide a wide range of potentially life-threatening abnormalities of the abdominal aorta in daily clinical and radiological practice through a series of computed tomography angiography images and three-dimensional virtual reconstruction. **Abdominal aortic aneurysm** is defined as a 50% increase in diameter more than the normal arterial diameter. One of the most important complications of an aneurysm is a rupture that can be acute or chronic, presenting with various clinical manifestations. **Aortic dissections** are caused by abnormality of the tunica media layer, forming an intimal-medial flap and two types of lumen. **A penetrating aortic ulcer** may erode through the internal elastic lamina of the aortic wall and allow formation of hematoma within the tunica media. **Occlusive disease** of the abdominal aorta may refer to the late stage of chronic aortoiliac occlusive disease, whereas the acute and/or subacute form occurs due to sudden thrombosis or occlusion. **Conclusion.** The recognition of specific radiological signs of abdominal aortic disease using computed tomography angiography contributes to optimal treatment of patients and reduces mortality.

Key words: Computed Tomography Angiography; Aortic Diseases; Aorta, Abdominal; Emergencies; Aortic Aneurysm, Abdominal; Aneurysm, Dissecting; Ulcer; Aortic Rupture; Atherosclerosis

Sažetak

Uvod. Aorta je glavni krvni sud koji snabdeva sve segmente ljudskog tela. Akutni aortni sindrom termin je koji podrazumeva životno ugrožavajuću bolest aorte. Brzina pregleda i široka dostupnost postavljaju kompjuterizovanu tomografsku angiografiju u prvi plan dijagnostičkih modaliteta za urgentna stanja i bolesti trbušne aorte. Cilj ove studije je da pruži širok spektar potencijalno opasnih po život abnormalnosti trbušne aorte u svakodnevnoj kliničkoj i radiološkoj praksi kroz seriju kompjuterizovanih tomografskih angiografija i trodimenzionalnih slika virtuelne rekonstrukcije. **Aneurizma abdominalne aorte** se definiše kao vrednost povećanja dijametra za 50% više od normalnog prečnika, a jedna od najvažnijih komplikacija aneurizme je ruptura koja može biti akutna ili hronična i prezentuje se različitim kliničkim manifestacijama. **Disekcije aorte** uzrokovane su abnormalnošću sloja tunike medija, formirajući intimalno-medijalni flap i dve vrste lumena. **Penetrantni ulkus aorte** erodira kroz unutrašnju elastičnu laminu zida aorte i može formirati hematom unutar tunike medija. **Okluzivna bolest trbušne aorte** može se odnositi na kasni stadijum aortoilijačne okluzivne bolesti u hroničnim fazama, dok se akutni i/ili subakutni oblik javlja usled iznenadne tromboze ili okluzije. **Zaključak.** Prepoznavanje specifičnih radioloških znakova bolesti trbušne aorte primenom kompjuterizovane tomografske angiografije doprinosi optimalnom lečenju pacijenata i smanjuje smrtnost.

Ključne reči: kompjuterizovana tomografska angiografija; bolesti aorte; abdominalna aorta; urgentna stanja; aneurizma abdominalne aorte; disekcija aorte; ulkus; ruptura aorte; ateroskleroza

Introduction

The aorta is the largest blood vessel in the human body. It originates from the left ventricle of the heart and ends at the level of the L4 vertebral body, where it bifurcates into the common iliac arteries [1]. The first portion is the ascending aorta that continues as aortic arch and descending aorta [2]. From the level of T4 vertebral body, the descending aorta travels down to the diaphragmatic hiatus, where it leaves the thorax and becomes the abdominal aorta.

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Abbreviations

CTA – computed tomography angiography
AAS – acute aortic syndrome
AAP – acute aortic pathology
AAA – aortic abdominal aneurysm
rAAA – ruptured aortic abdominal aneurysm
AD – aortic dissection
MRA – magnetic resonance angiography
TEE – transesophageal echocardiography
PAU – penetrating aortic ulcer
AIOD – aortoiliac occlusive disease
AAO – acute aortic occlusion
PAT – primary aortic thrombosis
TA – Takayasu arteritis
GCA – giant cell arteritis

The aorta is composed of three layers. The tunica intima is the innermost layer made of endothelial cells, connective fibers and internal lamina [3]. The tunica media is the middle layer which consists of collagen, elastic fibers, fibroblasts, and smooth muscle cells. The adventitia is the most external layer consisting of connective tissue, nerves and the vasa vasorum. The causes of aortic wall damage may be traumatic or nontraumatic (inflammatory) [4, 5]. The severity of aortic wall injuries is classified as follows: grade 1 injury represents an intimal tear; grade 2 injury is an intramural hematoma or dissection caused by a broken media layer; grade 3 injury represents a pseudoaneurysm, and finally, grade 4 is a complete rupture of the aortic wall [4]. Inflammatory diseases of the aorta [5] may be divided into infectious (bacterial, fungal or mycobacterial) and non-infectious varieties (atherosclerosis, sarcoidosis, Wegener granulomatosis, Takayasu arteritis (TA), and giant cell arteritis).

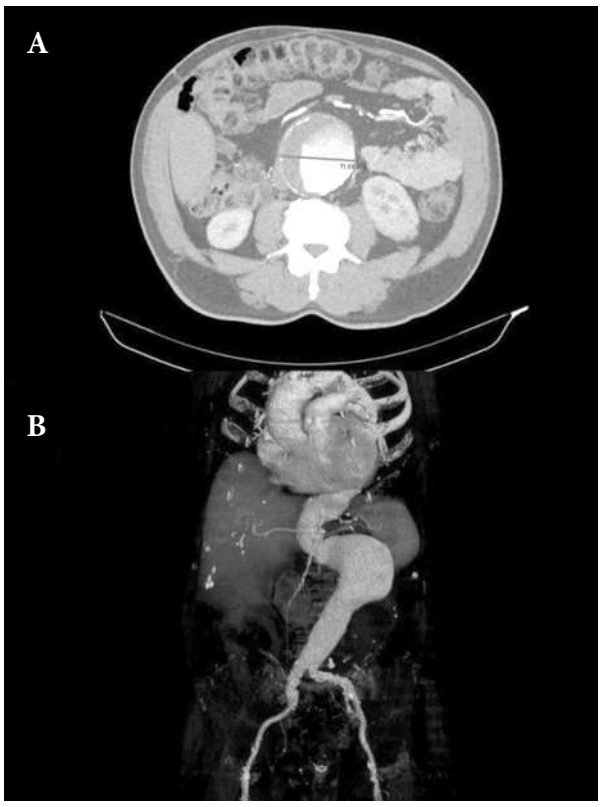


Figure 1A and 1B. A. Abdominal aortic aneurysm, axial CT scan; **B.** Abdominal aortic aneurysm, virtual reconstruction
***Slika 1A i 1B. A**. Aneurizma abdominalne aorte, aksijalna slika kompjuterizovane tomografske angiografije; **B.** Aneurizma abdominalne aorte, virtuelna rekonstrukcija*

Acute aortic syndrome (AAS) is a term that implies a spectrum of life-threatening aortic diseases. Diagnostic imaging of the abdominal aortic pathology (AAP) is the most important for prompt strategy planning and treatment, monitoring the state, preoperative planning or postoperative follow up [6]. One of the best modalities and the gold standard for the diagnosis of AAP, such as aortic aneurysms and rupture, dissections, thrombosis, endoleak after aneurysm repair, post-treatment complications, is computerized tomography angiography (CTA) that provides excellent anatomical visualization and evaluation of different blood vessels pathologies. Improved spatial resolution, extensive availability, fast scanning and accuracy make this diagnostic modality the method of choice in AAP [7].

Non-contrast computed tomography imaging is performed first, before the intravenous contrast application, with the purpose of detecting acute intramural hematoma, to measure single diameter of abdominal aneurysm sac and volume or to detect retroperitoneal hematoma in case of ruptured aneurysm. Image post-processing includes three-dimensional volume rendering technique (VRT) [8–10].

Abdominal aortic aneurysm and rupture

Aneurysms are focal permanent dilatations, at least 50% larger than the normal arterial diameter, while the term ectasia refers to arterial dilatation less than 50%. Abdominal aortic transverse diameter more than 30 mm is defined as aneurysm **(Figure 1A and 1B)** and contains all layers of the blood vessel [11]. Aortic aneurysms may occur at the root of the bifurcation. The infrarenal segment of the aorta is the most common location, accounting for more than 30% of aortic aneurysms and about nine times more common than in the thoracic part [12, 13]. Synchronous lesions of the thoracic aorta and peripheral arteries are also common [14, 15]. That highlights the importance of proper diagnostic evaluation in patients with aortic abdominal aneurysms (AAAs) that primarily affect the population older than 50 years and are two to three times more common in men than in women. In the Western Europe it is estimated that about 700.000 persons suffer from AAA [16]. Some countries reported a declining incidence of AAA in the 21st century, mostly due to strong public antismoking campaigns [17]. The perceived causes of AAAs include degenerative, inflammatory, dissection-associated, traumatic, infectious, developmental, and congenital [18]. Degenerative and atherosclerotic AAAs are the most common types of aneurysms.

Aneurysm formation has been associated with structural changes of the aortic wall, mostly by in-

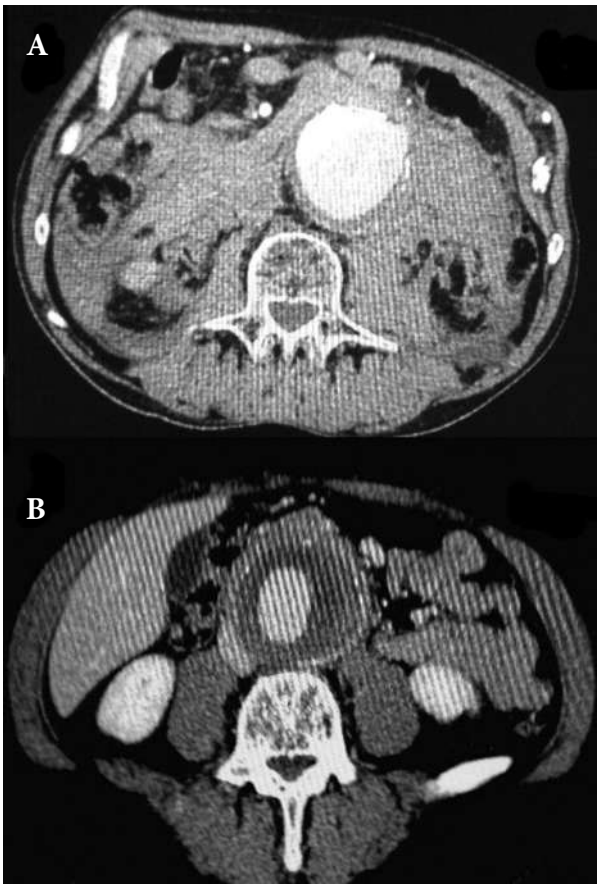


Figure 2A and 2B. A. Ruptured abdominal aortic aneurysm with retroperitoneal hematoma, axial CTA scan; **B.** Mycotic abdominal aortic aneurysm, axial CTA scan
***Slika 2A i B**. **A.** Rupturirana aneurizma abdominalne aorte sa retroperitonealnim hematomom, aksijalna slika kompjuterizovane tomografske angiografije; **B**. Mikotična aneurizma abdominalne aorte, aksijalna slika kompjuterizovane tomografske angiografije*

flammatory degeneration of the connective tissue matrix and smooth muscle cells of the aortic media, mediated through a cascade leading to oxidative stress and proteolytic injury. Activation of matrix metalloproteinases (MMPs) directly participates in matrix protein degeneration. The presence of an intraluminal thrombus, which acts like a biologically active neo-tissue, is associated with aneurysm progression, but also with aortic wall hypoxia, medial loss of smooth muscle cells, elastin degradation and adventitial inflammation [19].

Most aneurysms are asymptomatic. Aneurysms may rupture, lead to thrombosis, embolization, and compression of adjacent structures [20]. Rupture is the most common and devastating complication of AAA. Patients with ruptured AAA (rAAA) usually present with sudden back or abdominal pain, hypotension or collapse and pulsating abdominal mass. A symptom of rAAA may appear as retroperitoneal hematoma **(Figure 2A)**. Other types of rAAA are intraperitoneal hemorrhage, aortocaval and aortoduodenal fistula and chronic "sealed" rupture. Patients with aortoduodenal fistula often present with melena and hematemesis, patients with aortocaval fistula with pelvic congestion syndrome and right heart failure. Patients with "sealed" rupture have the best prognosis and usually present with chronic back pain.

Patients with symptomatic AAA are hemodynamically stable and have non-specific abdominal and back pain. The CTA signs, crescent and draped aorta, show an unstable aneurysm wall and predict impending rupture. Such patients need urgent treatment to prevent rupture. The AAA diameter is the basis for calculating the rupture risk; the larger the diameter, the higher the risk of rupture [21].

Evaluation of a patient with ruptured AAA depends on the state of the patient. If the patient is extremely hemodynamically unstable and does not respond to initial resuscitation, focused assessment with sonography for trauma (FAST) is used to confirm the diagnosis and the patient is immediately transferred to the operating room. Patients who respond to initial resuscitation and are hemodynamically stable, undergo CTA which is the modality of choice.

All patients with rAAA need active treatment. Most patients undergo open treatment with aneurysmectomy and graft interposition. Some health centers can treat these patients with Endovascular aneurysm repair (EVAR) technique. Every patient considered for endovascular treatment needs CTA evaluation for selecting the best stent choice.

Infection of AAA is a form of mycotic aneurysm **(Figure 2B)** that occurs as a complication in 0.7 – 2.6% of patients, especially in patients with comorbidities such as diabetes mellitus, collagen vascular diseases, acquired immunodeficiency syndrome, all immunocompromising conditions, and trauma [22].

Aortic dissection

Aortic dissection (AD) is associated with high morbidity and mortality (lethality rate of 1 – 2%) [23]. The annual incidence of AD is 5 to 30 cases per one million people, affecting men three times more often than women. One of the most important risk factors is age, occurring in patients between 50 and 65 years [24]. Contributing factors for non-traumatic AD include hypertension, sudden increase in blood pressure, connective tissue disease, aortic valvular disease, aortitis, Marfan syndrome, Ehlers-Danlos and Turner syndrome, coarctation of the aorta, Loeys-Dietz syndrome [25]; atherosclerosis, pre-existing aortic aneurysm or family history can also be the cause [22, 26]. The AD **(Figure 3A and 3B)** is caused by abnormality of the tunica media layer which is made of layers of collagen, smooth muscle cell, elastin, and fibrillin fibers [25]. Continuous susceptibility to high blood pressure leads to weakening of the aortic wall and intimal tear. A right lateral wall of the aorta is most commonly affected [26]. The intimal flap divides the true from the false lumen. The other cause of dissection is bleeding inside the aortic wall, which then extends the intimal flap in both ante- and a retrograde way. The common loca-

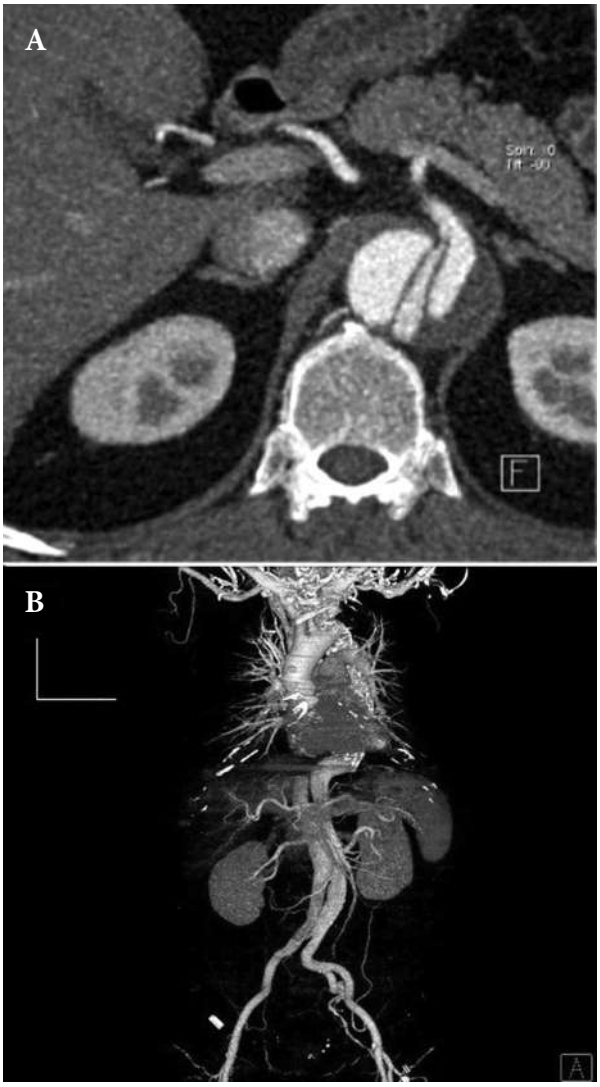
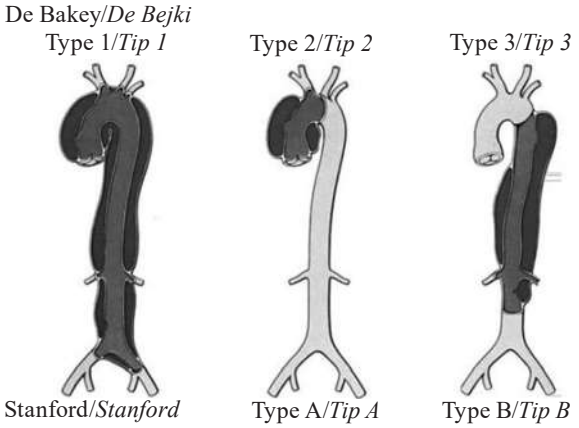


Figure 3A and 3B. A. Abdominal aortic dissection, axial CTA scan; **B.** Abdominal aortic dissection, virtual reconstruction
Slika 3A i 3B. A. *Disekcija abdominalne aorte, aksijalna slika kompjuterizovane tomografske angiografije;* ***B.*** *Disekcija abdominale aorte, virtuelna rekonstrukcija*

tion for the aortic dissection is 2 – 2.5 cm above the aortic root distal to the origin of the left subclavian artery, and in the aortic arch [26, 27]. There are three stages of aortic dissection: the first two weeks are considered as acute stage or AAS. It is a life-threatening condition in which patients present as acutely ill [7]. Subacute stage is considered to be three months since the onset, and then comes the chronic stage. Patients with a chronic AD have slightly better outcomes than those with acute stage. This classification is not so helpful. Nowadays, the decision and classification are being made according to the location of the dissection of aorta and its extension. The AD usually begins in the region of the thoracic aorta and continues to the descending and abdominal aorta. There are two classification systems: Stanford and DeBakey. They are used to separate ADs into those that need surgical treatment and those with medical treatment only. Stanford type A (or DeBakey type I and type II) ADs affect the ascending aorta only and account for about 60% of all ADs [28]. They require an open surgical treatment and one of the most dangerous complications is a cardiac tamponade, which happens if the dissection aneurysmal sac ruptures into the pericardial sac. Stanford type B (or DeBakey type IIIa and type IIIb) dissections begin beyond the brachiocephalic vessels and account for 40% of all dissections. They are treated medically or by endovascular repair [27]. The schematic diagram shows two types of classifications [29] **(Figure 4)**.

Sudden severe "tearing" chest pain, or delicate chest pain are some of the clinical symptoms. In Marfan syndrome, in 10% of the cases, patients do not feel any pain [26]. Physical findings like discrepancy of blood pressures in the upper extremities (difference of more than 20 mmHg), combination of chest pain and limb weakness, and pulse deficit should raise suspicion of an AD. Due to hypovolemia, syncope can also be one of the symptoms. Correct diagnosis is made in as few as 15% to 43%



De Bakey
Type I Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II Originates in and is confined to the ascending aorta
Type III Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch and ascending aorta
Stanford
Type A All dissections involving the ascending aorta, regardless of the site of origin
Type B All dissections not involving the ascending aorta

De Bejki klasifikacija
Tip I. Nastaje na ascedentnoj aorti, propagira najmanje do aortnog luka šireći se distalno
Tip II. Nastaje i ograničava se na ascedentnoj aorti
Tip III. Nastaje na descedentnoj aorti i širi se distalno, a retko retrogradno u aortni luk i ascedentu aortu
Stanford klasifikacija
Tip A. Sve disekcije koje obuhvataju ascedentnu aortu, bez obzira na mesto porekla
Tip B. Sve diskecije koje ne obuhvataju ascedentnu aortu

Figure 4. Two types of classification of aortic dissections
Slika 4. *Dva tipa klasifikacije aortne disekcije*

Figure 5A and 5B. A. Penetrating aortic ulcer, axial CTA scan; **B**. Penetrating aortic ulcer, sagittal CTA scan
Slika 5A i 5B. A. *Penetrantni aortni ulkus, aksijalna slika kompjuterizovane tomografske angiografije;* ***B.*** *Penetrantni aortni ulkus, sagitalna slika kompjuterizovane tomografske angiografije*

of cases. If incorrectly treated or unrecognized, mortality approaches 50% in the first 48h after the onset [30]. Laboratory finding, such as elevation of serum smooth muscle myosin heavy chain assay, is specific for this disease. Cell blood count (CBC), electrolytes, D-dimer and troponin also need to be examined. Diagnostic methods used to rule out the AD and reveal another cause of chest pain are chest x-ray and electrocardiography. However, they can be misleading. The method of choice to detect an AD is CTA, transesophageal echocardiography (TEE) and magnetic resonance imaging angiography (MRA). The CTA can show an intimal flap, a double lumen, aortic dilatation and hematoma or contrast leak. If the patient is unstable, TEE is the method of choice. It can show true and false lumen in the ascending aorta, pericardial effusion, dissection flap or thrombosis in the false lumen [31]. Its sensitivity is between 83% and 100% and specificity is 100% [32].

In type A AD, surgical treatment is necessary, including a placement of a synthetic vascular graft, whereas in type B AD, a surgical approach is advised for patients with a more complex course. A less invasive and a relatively new procedure, compared to open surgery, is endovascular stent-grafting (TEVAR) [33]. The most dangerous dissections are those involving the aortic arch. Differential diagnosis for this condition includes cardiac tamponade, myocardial infarction, pulmonary embolism, aortic aneurysm, stroke [34]. For the best patient's clinical outcome a multidisciplinary specialist team is mandatory, including a cardiologist, radiologist and interventional radiologist, intensivist, pulmonologist, cardiac surgeon and all the other clinicians.

Penetrating aortic ulcer

The aortic aneurysm, rupture and dissection, and penetrating aortic ulcer (PAU) make up a spectrum of diseases in which one entity may evolve into or coexist with another. The PAU is an ulcer-like lesion that erodes through the internal elastic lamina of the aortic wall and may allow hematoma formation within the media [35]. The PAUs are located in the descending aorta in 60–70% of cases and account for 5% to 7.5% of all cases of AAS [36]. The most common symptoms are abrupt onset of severe chest or back pain. Because many patients with PAU are asymptomatic, the diagnosis is often made incidentally on imaging tests. The CTA, MRA and TEE are imaging modalities for the diagnosis of AAS. Each has a sensitivity and specificity approaching 90–100% [37], but CTA is the first choice, owing to minimal invasiveness, short time of acquisition, wide availability and high resolution. The CTA is also helpful for visualization of the entire aorta and extraluminal structures. The disadvantages of CTA are exposure to radiation and use of contrast agents.

The typical PAU **(Figure 5A and 5B)** is a contrast-filled, pouch-like protrusion of the aorta in the thickened aortic wall in the atherosclerotic process, penetrating intima into the media or over the media to the adventitia layer. The ruptured media layer can lead to intramural hematoma formation with possible complications, such as AD. Involvement of the adventitia contributes to the formation of pseudoaneurysms [36, 38]. Amin et al. showed that the largest number of lesions was in the region of the distal descending aorta, the mean ulcer diameter was 1.6 cm and the mean diameter of aorta at the level of ulcer was 3.7 cm [38]. In the acute phase, PAU is often associated with a locoregional hematoma. Other complications associated with PAU are pleural effusion, contrast extravasation, pseudoaneurysm, and saccular aortic aneurysm. The PAU usually occurs in the elderly, predominantly in patients with hypertension and

Figure 6. Thrombosis of the infrarenal segments of the abdominal aorta, sagittal CTA scan
Slika 6. *Tromboza infrarenalnog segmenta abdominalne aorte, sagitalna slika kompjuterizovane tomografske angiografije*

atherosclerotic disease. Conservative therapy, endovascular or open surgery, are management strategies for PAU. Conservative treatment is applied in asymptomatic patients and includes radiological surveillance or follow-up, using antihypertensive therapy with beta blockers. Indications for radical PAU treatment (endovascular or open surgery) depend on the position and manifestations of the PAU [39].

Aortoiliac occlusive disease

Aortoiliac occlusive disease **(**AIOD) is a chronic condition associated with older age, presenting with stenosis and/or occlusion due to the deposition of atherosclerotic plaque below the renal arteries. Leriche syndrome is characterized by complete obliteration of the aortic bifurcation [40, 41]. Infrarenal aorta is predisposed for forming plaque due to the bifurcation angle and oscillating stress on the wall [42].

Symptoms associated with AOID include calf claudication, weak femoral pulses as well as impotence, but it can also remain asymptomatic due to development of abundant collateral networks. The CTA is effective for evaluation of location, level of stenosis, involvement of vital arteries and distribution of collateral channels [41].

Acute abdominal aortic occlusion

Acute abdominal aortic occlusion **(**AAO) is a rare, life treating condition. It can be connected with late stage of AIOD in chronic phases **(Figure 6)**, whereas acute and/or subacute form occurs due to sudden thrombosis or occlusion (e.g. thrombosis of aortic aneurysm, spread of dissection, trauma) [43].

Primary aortic thrombosis (PAT) is described as aortic thrombosis without evidence of underlying atheromatous lesions. The PAT may occur in patients on chemotherapy, with essential thrombocythemia or hypercoagulable states, inflammatory bowel disease, or during acute pancreatitis [44]. Clinical symptoms depend on the level of thrombosis, but they usually involve painful paraparesis and cyanotic lower extremities.

The CTA characteristics of AAO include absence of blood flow on postcontrast image distal to the level of occlusion, and no visualization of collateral vessels [45]. Treatment includes anticoagulant therapy, bypass surgery, and endovascular interventions [46].

Chronic vasculitis

Vasculitis presents a wide spectrum of disorders, which include infectious and noninfectious inflammation of the vasculature. Arteries and veins of any size can be affected and inflammation can be focal or diffuse [41, 47].

Takayasu arteritis is a systemic disease associated with segmental inflammation of all the layers of a vessel. It affects large vessels and pathological findings in aorta, most often the abdominal part; it can be found in 53% of all cases with predominance in young females and its peak incidence is the 3rd decade [40]. Pathological and radiological features are divided into two stages: acute and chronic/occlusive. Early findings present with murals thickness and if not treated it leads to fibrosis and wall calcification [41, 47].

The CTA presents a modality of choice for diagnosis and follow up patients with TA. Findings include concentric thickening of the vessel wall, thrombosis, stenosis, and occlusion. The CTA detects the disease in the early phase, which often presents with a "double ring" sign, where an insufficiently or non-enhancing inner circle of swollen intima is surrounded by delayed enhancement of inflamed media. Prompt diagnosis of TA is important for early treatment and consequently better prognosis [47].

Digital subtraction angiography, with its invasive nature, higher radiation dose and inaccuracy for precise wall architectural changes, is no longer a procedure of preference. A high dose of corticosteroids is the therapy of choice. Complications like stenosis and occlusion are treated by surgery or endovascular intervention [48].

Giant cell arteritis (GCA) is a systemic granulomatous usually diffuse vasculitis which affects large and medium-sized vessels, commonly subclavian, axillary and femoral arteries [49]. The GCA usually affects patients over 50 years of age, with incidence peaking in the 8th decade. Pathological changes in the acute stage are associated with inflammatory cellular infiltrate with multinucleated giant cells and lymphocytes, leading to progressive fibrosis in the chronic stage [48]. Radiological findings are similar to those in TA and include stenosis, occlusion, aneurysm formation, and mural thrombi [47]. The CTA and MRA angiography can detect blood vessel wall edema, indicator of the disease activity [48]. Although stenotic lesions may occur, aortic aneurysms are more common. Steroid therapy provides improvement, but relapses are common. Revascularization is the modality of choice in symptomatic patients [47].

Behcet's disease is a chronic, multisystem and relapsing inflammatory disease, associated with oral ulcerations, genital ulcers, recurrent eye and skin lesions. It usually affects young males. Although venous involvement such as deep and superficial thrombosis is more common, the most commonly affected artery is the aorta, where inflammation of the wall leads to occlusion, thrombosis and aneurysms. In Behcet's disease aneurysms are more common than occlusions [47].

Steroid and cytotoxic agents are used for patients with arteritis. Anticoagulant therapy is reserved for patients with venous thrombosis.

Conclusion

The recognition of specific radiological signs of abdominal aortic disease using computed tomography angiography contributes to optimal treatment of patients and reduces mortality.

References

1. Tran CT, Wu CY, Bordes S, Lui F. Anatomy, abdomen and pelvis, abdominal aorta. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020 [updated 2020 Jul 31; cited 2021 Jan 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525964/.

2. Shahoud JS, Miao JH, Bolla SR. Anatomy, thorax, heart aorta. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020 [updated 2020 Aug 15; cited 2021 Jan 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538140/.

3. Rosen RD, Bordoni B. Embryology, aortic arch. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021 [cited 2021 Feb 15]. Available from: https://pubmed.ncbi.nlm.nih.gov/31985966/.

4. Harper C, Slesinger TL. Aortic transection. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020 [updated 2021 Jan 20; cited 2021 Feb 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555980/.

5. Maleszewski JJ. Inflammatory ascending aortic disease: perspectives from pathology. J Thorac Cardiovasc Surg. 2015;149(2 Suppl):S176-83.

6. Kumar Y, Hooda K, Li S, Goyal P, Gupta N, Adeb M. Abdominal aortic aneurysm: pictorial review of common appearances and complications. Ann Transl Med. 2017;5(12):256.

7. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. J Am Coll Cardiol. 2015;66(4):350-8.

8. Gutschow SE, Walker CM, Martínez-Jiménez S, Rosado-de-Christenson ML, Stowell J, Kunin JR. Emerging concepts in intramural hematoma imaging. Radiographics. 2016;36(3):660-74.

9. Spasić A, Til V, Basta-Nikolić M, Milošević Đ, Hadnađev-Šimonji D, Ilić D. Imaging techniques in the assessment of endovascular infrarenal abdominal aortic repair. Med Pregl. 2020;73(1-2):29-35.

10. Rakita D, Newatia A, Hines JJ, Siegel DN, Friedman B. Spectrum of CT findings in rupture and impending rupture of abdominal aortic aneurysms. Radiographics. 2007;27(2):497-507.

11. Johnston KW, Rutherford RB, Tilson MD, Shah DM, Hollier L, Stanley JC, et al. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg. 1991;13(3):452-8.

12. Isselbacher EM. Thoracic and abdominal aortic aneurysms. Circulation. 2005;111(6):816-28.

13. Pál D, Szilágyi B, Berczeli M, Szalay CI, Sárdy B, Oláh Z. Ruptured aortic aneurysm and dissection related death: an autopsy database analysis. Pathol Oncol Res. 2020;26(4):2391-9.

14. Ruddy JM, Jones JA, Spinale FG, Ikonomidis JS. Regional heterogeneity within the aorta: relevance to aneurysm disease. J Thorac Cardiovasc Surg. 2008;136(5):1123-30.

15. Wallinder J, Georgiou A, Wanhainen A, Björck M. Prevalence of synchronous and metachronous aneurysms in women with abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2018;56(3):435-40.

16. Lindholt JS, Juul S, Fasting H, Henneberg EW. Hospital costs and benefits of screening for abdominal aortic aneurysms. Results from a randomised population screening trial. Eur J Vasc Endovasc Surg. 2002;23(1):55-60.

17. Anjum A, Powell JT. Is the incidence of abdominal aortic aneurysm declining in the 21st century? Mortality and hospital admissions for England & Wales and Scotland. Eur J Vasc Endovasc Surg. 2012;43(2):161-6.

18. Cronenwett JL, Krupski WC. Arterial aneurysms. In: Rutherford RB, Cronenwett JL, Wayne JK. Rutherford's vascular surgery. 7th ed. Philadelphia: W.B. Saunders Company; 2010. p. 1241.

19. Engellau L, Albrechtsson U, Dahlström N, Norgren L, Persson A, Larsson EM. Measurements before endovascular repair of abdominal aortic aneurysms. MR imaging with MRA vs. angiography and CT. Acta Radiol. 2003;44(2):177-84.

20. Juković M, Koković T, Nikolić D, Ilić D, Till V. Lower back pain - silent symptom of chronic infrarenal abdominal aneurysm rupture. Med Pregl. 2016;69(3-4):115-7.

21. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-58.

22. Yu T, Zhu X, Tang L, Wang D, Saad N. Review of CT angiography of aorta. Radiol Clin North Am. 2007;45(3):461-83.

23. Nienaber CA. Pathophysiology of acute aortic syndromes. In: Eagle KA, Baliga RR, Isselbacher EM, Nienaber CA, editors. Aortic dissection and related diseases. 1st ed. Boston: Springer; 2007. p. 26.

24. Baliyan V, Parakh A, Prabhakar AM, Hedgire S. Acute aortic syndromes and aortic emergencies. Cardiovasc Diagn Ther. 2018;8(Suppl 1):S82-96.

25. Chin AS, Fleischmann D. State-of-the-art computed tomography angiography of acute aortic syndrome. Semin Ultrasound CT MR. 2012;33(3):222-34.

26. Levy D, Goyal A, Grigorova Y, Farci F, Le JK. Aortic dissection. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020 [updated 2020 Dec 17; citing 2021 Jan 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441963/.

27. Nienaber CA, Clough RE, Sakalihasan N, Suzuki T, Gibbs R, Mussa F, et al. Aortic dissection. Nat Rev Dis Primers. 2016;2(1):1-18.

28. Lempel JK, Frazier AA, Jeudy J, Kligerman SJ, Schultz R, Ninalowo HA, et al. Aortic arch dissection: a controversy of classification. Radiology. 2014;271(3):848-55.

29. Nienaber CA, Ince H. Classification of aortic dissection. In: Elefteriades JA, editor. Acute aortic disease. 1st ed. New York: Informa Healthcare; 2007. p. 1-28.

30. Lau C, Leonard JR, Iannacone E, Gaudino M, Girardi LN. Surgery for acute presentation of thoracoabdominal aortic disease. Semin Thorac Cardiovasc Surg. 2019;31(1):11-6.

31. Erbel R. Aortic diseases: modern diagnostic and therapeutic strategies. Herz. 2018;43(3):275-90.

32. Gu G, Wan F, Xue Y, Cheng W, Zheng H, Zhao Y, et al. Lumican as a novel potential clinical indicator for acute aortic dissection: a comparative study, based on multislice computed tomography angiography. Exp Ther Med. 2016;11(3):923-8.

33. Mkalaluh S, Szczechowicz M, Dib B, Weymann A, Szabo G, Karck M. Open surgical thoracoabdominal aortic aneurysm repair: the Heidelberg experience. J Thorac Cardiovasc Surg. 2018;156(6):2067-73.

34. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol. 2010;55(14):e27-129.

35. Corvera JS. Acute aortic syndrome. Ann Cardiothorac Surg. 2016;5(3):188-93.

36. Evangelista A, Maldonado G, Moral S, Teixido-Tura G, Lopez A, Cuellar H, et al. Intramural hematoma and penetrating ulcer in the descending aorta: differences and similarities. Ann Cardiothorac Surg. 2019;8(4):456-70.

37. Koop A, Melendez-Rosado JM, Farres H, Mergo PJ, Shapiro BP. Penetrating aortic ulcer manifesting as atypical chest pain. Journal of Radiology and Imaging. 2016;1(3):18-9.

38. Amin MF, Abd El Gawad EA. Diagnostic performance of MDCT angiography in penetrating atherosclerotic aortic ulcer and its complications compared with digital subtraction angiography. The Egyptian Journal of Radiology and Nuclear Medicine. 2016;47(3):909-17.

39. Liu J, Liu Y, Yang W, Gu J, Xue S. Five-year outcomes after thoracic endovascular aortic repair of symptomatic type B penetrating aortic ulcer with intramural hematoma in Chinese patients. J Thorac Dis. 2019;11(1):206-13.

40. Hardman RL, Lopera JE, Cardan RA, Trimmer CK, Josephs SC. Common and rare collateral pathways in aortoiliac occlusive disease: a pictorial essay. AJR Am J Roentgenol. 2011;197(3):W519-24.

41. Sebastià C, Quiroga S, Boyé R, Perez-Lafuente M, Castellà E, Alvarez-Castells A. Aortic stenosis: spectrum of diseases depicted at multisection CT. Radiographics. 2003;23(Spec No):S79-91.

42. Shaaban AM, Duerinckx AJ. Wall shear stress and early atherosclerosis. AJR Am J Roentgenol. 2000;174(6):1657-65.

43. Maddu KK, Telleria J, Shuaib W, Johnson JO, Khosa F. Nontraumatic acute aortic emergencies: Part 2, Pre- and postsurgical complications related to aortic aneurysm in the emergency clinical setting. AJR Am J Roentgenol. 2014;202(3):666-74.

44. Verbeeck N, Cavez N, Plawny L, Weber J, Lens V. Primary aortic thrombosis: role of enhanced multislice CT demonstrated in three exceptional cases. JBR-BTR. 2014;97(2):76-80.

45. Roxas R, Gallegos L, Bailitz J. Rapid detection of aortic occlusion with emergency ultrasonography. Ann Emerg Med. 2011;58(1):21-3.

46. Grip O, Wanhainen A, Björck M. Temporal trends and management of acute aortic occlusion: a 21 year experience. Eur J Vasc Endovasc Surg. 2019;58(5):690-6.

47. Litmanovich DE, Yıldırım A, Bankier AA. Insights into imaging of aortitis. Insights Imaging. 2012;3(6):545-60.

48. Gotway MB, Araoz PA, Macedo TA, Stanson AW, Higgins CB, Ring EJ, et al. Imaging findings in Takayasu's arteritis. AJR Am J Roentgenol. 2005;184(6):1945-50.

49. Jang JJ, Gorevic PD, Olin JW. Images in vascular medicine. Giant cell arteritis presenting with acute myocardial infarction. Vasc Med. 2007;12(4):379.

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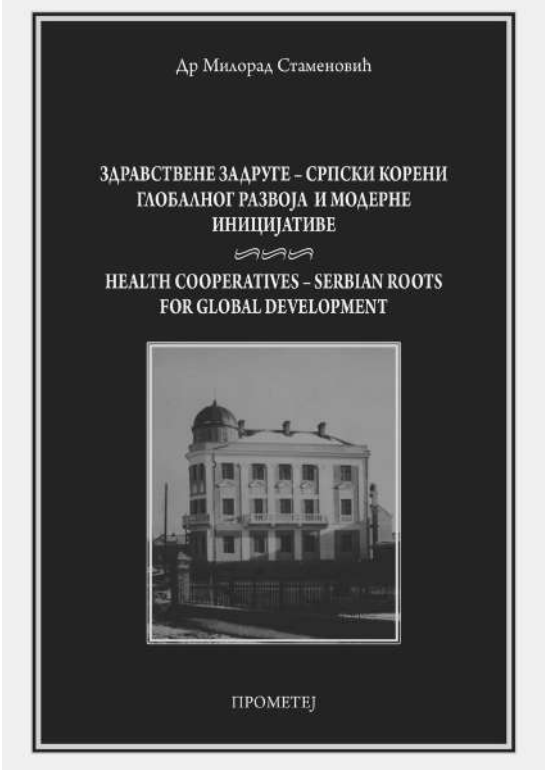
BOOK REVIEWS
PRIKAZI KNJIGA

Stamenović M. *Zdravstvene zadruge – srpski koreni globalnog razvoja i moderne inicijative.* Novi Sad: Prometej; 2020. 173 str.

Naučna monografija *Zdravstvene zadruge – srpski koreni globalnog razvoja i moderne inicijative* autora dr Milorada Stamenovića pojavila se u vreme pojačanog interesovanja najšire javnosti za zbivanja u zdravstvenom sistemu. Covid-19 pandemija koja je zahvatila svet na kraju druge decenije 21. veka samo je zaoštrila pitanja o kojima pokretači reformi u zdravstvu debatuju već duže od pola veka u mnogim zemljama u svetu. U prvom planu nenadano su se našla pitanja koja se odnose na bolničke kapacitete, raspoloživost opreme i zaposlene u zdravstvu. Tokom poslednjih decenija činjeni su brojni pokušaji da se problem insuficijentnog finansiranja zdravstvene zaštite i hroničan nedostatak resursa u zdravstvu reši uvođenjem raznih dopunskih mehanizama za njihovu mobilizaciju. Jedna od takvih mogućnosti jeste i zdravstveno zadrugarstvo na koje autor monografije skreće pažnju naučne i stručne javnosti. Kao što je već u naslovu navedeno u monografiji se razmatra širi skup pitanja koja se odnose na period postojanja zdravstvenih zadruga u Srbiji tokom prve polovine 20. veka. Bogat dokumentacioni materijal koji autor koristi omogućuje uvid u način funkcionisanja i rezultate koji su ostvarivani primenom zdravstvenog zadrugarstva u srpskom zdravstvu tokom perioda između dva svetska rata. Autor takođe obrazlaže inicijativu kojom predlaže ponovno implementiranje zdravstvenog zadrugarstva u zdravstveni sistem Srbije.

U širem istorijskom osvrtu autor je na osnovu većeg broja izvora izložio *srpski model zdravstvenih zadruga* koji je u vreme njihovog uvođenja predstavljao inovaciju i koji je pomogao rešavanju javnozdravstvenih, prosvetnih, demografskih i drugih problema tog vremena. Monografija se, pored predgovora na sprskom i engleskom jeziku i zaključnih razmatranja, sastoji iz 11 poglavlja. U prvoj i drugoj glavi definisan je koncept zdravstvenog zadrugarstva i dat osvrt na istorijski razvoj ovog modela finansiranja zdravstvene zaštite. U trećoj glavi predstavljen je zakonsko-pravni okvir koji je regulisao način osnivanja i funkcionisanja zdravstvenih zadruga. U četvrtoj glavi objašnjen je način organizacije i finansiranja zdravstvenih zadruga. U ovom delu navode se statistički podaci o razvoju zdravstvenih zadruga, broju zadrugara i zadružnih lekara. Godine 1923. u Srbiji je postojalo 12 zadružnih zdravstvenih stanica i 12 zadružnih apoteka, u kojima je medicinske usluge pružalo 12 zadružnih lekara. Broj zadrugara iste godine iznosio je 6.432. Zdravstvene zadruge su 1929. godine već obuhvatile 420 sela i oko 300.000 stanovnika. Do 1935. godine broj zadružnih



zdravstvenih stanica porastao je na 69, a broj zadružnih apoteka na 61. Medicinske usluge pružalo je 75 zadružnih lekara. Iste godine broj članova zdravstvenih zadruga iznosio je 61.064.

U okviru pete i šeste glave analizirani su javnozdravstveni problemi tog vremena i aktivnosti koje su preduzete u vezi sa zaštitom zdravlja dece i zdravstvenog prosvećivanja naroda. Autor se u sedmoj glavi osvrnuo na aktivnosti zdravstvenih zadruga usmerenih na zaštitu i unapređenje zdravlja stoke i borbe protiv biljnih štetočina. Izazovi sa kojima su se u svom radu susretale zdravstvene zadruge tema su naredne, osme glave. Među njima najznačajniji su demografski problemi, visoka smrtnost odojčadi, epidemije. Postojale su teškoće da se ostvare ciljevi kao što su unapređenje zdravstvenog stanja stanovništva i produženje očekivanog trajanja života. One su se ogledale pre svega u nedovoljnoj razvijenosti zdravstvenog sistema, niskom obrazovnom nivou stanovništva i skromnoj zdravstvenoj prosvećenosti. Poseban problem je predstavljao hronični nedostatak medicinskog osoblja. U devetoj i desetoj glavi ukazano je na međunarodni značaj zdravstvenih zadruga i podršku koju je razvoju zdravstvenih zadruga pružio kralj Aleksandar Prvi Karađorđević. U poslednjoj glavi predstavljena je *Inicijativa za osnivanje zdravstvenih*

zadruga u Republici Srbiji u kojoj je ukazano na zakonsko-pravni okvir koji reguliše rad zdravstvenih zadruga i značaj razvoja ovog oblika udruživanja.

Autor monografije posvetio je dosta pažnje odabiru dokumenata i podataka na osnovu kojih je moguće u istorijskom pristupu sagledati razvoj zdravstvenih zadruga u Srbiji tokom vremena njihovog postojanja. Nakon Prvog svetskog rata opšte zdravstveno stanje stanovništva bilo je loše što je uticalo na osnivanje prvih zdravstvenih zadruga. Prva zdravstvena zadruga nakon Prvog svetskog rata osnovana je krajem 1921. godine u Bajinoj Bašti, nakon čega su osnovane zadruge u Užičkoj Požegi, Kosjeriću, Velikom Šiljegevcu, Blacu, Krupnju, Lazarevcu i Mačvanskom Prnjavoru i drugim mestima. Kako su se razvijale zdravstvene zadruge, širio se i broj programa koji su pružani korisnicima. Posebna pažnja posvećena je radu na zaštiti materinstva, odojčadi i male dece, zaštite zdravlja školske dece, trudnica, suzbijanju masovnih oboljenja i zdravstvenom prosvećivanju.

Autor monografije ističe da se prednost zdravstvenih zadruga u odnosu na druge oblike organizovanja zdravstvene zaštite ogledala u tome što zadruge nisu ostvarivale profit, već je cilj bio pružanje adekvatne usluge (ili robe) po što nižoj ceni kako bi se postigla šira dostupnost. Prema iznetim podacima 1936. godine od 102 zadruge, 38 je poslovalo sa suficitom, 17 sa deficitom, dok je kod 47 zadruga bilansni račun bio u ravnoteži. Kako bi zadruge uspešno obavljale svoju aktivnost, bilo je važno da se obezbede redovne uplate zadrugara. Finansijska disciplina članova zadruga bila je na viskom nivou. Pored redovnih uplata, za dobre finansijske rezultate zdravstvenih zadruga bilo je važno i dobro planiranje i racionalno trošenje sredstava zadrugara.

U monografiji je sagledana aktivnost zdravstvenih zadruga u prosvećivanju naroda, a posebno su prikazane aktivnosti odeljaka (kako su se tada zvali) *Zadrugarke* i *Zadružna omladina*. Funkcionisanje odeljaka u okviru zdravstvenih zadruga imalo je važnu ulogu u prosvetno-propagandnom radu. Zadatak odeljka *Zadrugarke* ogledao se u prosvećivanju žena o higijenskim propisima, adekvatnoj nezi i podizanju dece, pripremi hrane, davanju instrukcija u slučaju bolesti i sl. U okviru odeljka *Zadružna omladina* postojali su tečajevi i kursevi i zimske škole gde su priređivane zabave i aktivnosti za razonodu. Poseban značaj prosvećivanju naroda imao je časopis *Zdravstveni pokret – Zdravlje* koji je štampan od 1921. godine do početka Drugog svetskog rata i koji je u pisanju monografije korišćen kao izvor istorijskih podataka i fotografija.

U monografiji su navedeni ljudi i organizacije koji su dali poseban značaj razvoju zdravstvenih zadruga. Među njima posebno se ističe doprinos dr Gorana Kojića, dr Milana Jovanovića Batuta, prof. dr Andrije Štampara i drugih. Američka misija za pomoć srpskoj deci pružila je značajnu pomoć prilikom osnivanja zadruga i kasnije prilikom rešavanja brojnih problema koji su se javljali u prvim godinama njihovog postojanja. Podršku razvoju zdravstvenih zadruga pružili su takođe i mnogi uticajni ljudi toga vremena, među njima i Mihajlo Pupin.

Monografija *Zdravstvene zadruge – srpski koreni globalnog razvoja i moderne inicijative* predstavlja istorijski osvrt na zdravstvene zadruge kao jedan od modela finansiranja zdravstvene zaštite. Posebnu vrednost monografije predstavljaju prilozi, fotografije i arhivski tekstovi koji su korišćeni kako bi se čitaocima približila obrađena tema. Potvrda uspešnog funkcionisanja zdravstvenih zadruga vidi se i u interesovanju stranih stručnjaka za jugoslovensko zdravstveno zadrugarstvo. Tokom poseta oni su nastojali da se upoznaju sa načinom funkcionisanja i postignutim rezultatima.

Doktor Stamenović je naučnoj javnosti poznat kao pokretač i promoter inicijative za osnivanje zdravstvenih zadruga u Republici Srbiji. Prema podacima Međunarodne organizacije zdravstvenih zadruga navedenim u monografiji, zdravstvene zadruge uspešno funkcionišu u više od 15 zemalja. Iz literature je moguće sagledati iskustva drugih zemalja u primeni zdravstvenog zadrugarstva, a ovim navodima se pridružuje Stamenovićeva monografija kao izvor o zdravstvenim zadrugama u Srbiji i domaćih iskustava stečenih u periodu između dva svetska rata.

Zdravstveno-zadružni pokret u Srbiji pokazao se tokom godina svog postojanja u Srbiji kao izuzetno vitalan sa očiglednom sklonošću ka razvoju. Dobri rezultati iz ovog perioda i iskustva zemalja u kojima danas uspešno funkcionišu zdravstvene zadruge predstavljali su polaznu osnovu za izradu *Inicijative za osnivanje zdravstvenih zadruga u Republici Srbiji*. U poglavlju kojim se monografija završava autor obrazlaže cilj inicijative i ukazuje na značaj uvođenja i zdravstvenog zadrugarstva u srpski zdravstveni sistem. Razvoj zdravstvenih zadruga omogućio bi kvalitetniju i dostupniju zdravstvenu zaštitu na teritoriji cele zemlje s poželjnim uticajem na geografsku pravičnost. Autor takođe ističe korektivnu ulogu zadruga kada je u pitanju alokacija resursa u zdravstvu, jer zadruge predstavljaju fleksibilne entitete koji se mogu baviti aktivnostima za koje se pokazalo da ostaju zapostavljene ne samo od privatnog već često i od javnog sektora. Inicijativa predstavlja metodološki dobro utemeljen predlog koji zaslužuje pažnju ne samo naučne i stručne, već i šire javnosti, pre svega udruženja korisnika zdravstvenih usluga.

Pojava monografije *Zdravstvene zadruge – srpski koreni globalnog razvoja i moderne inicijative* doktora Stamenovića skreće pažnju na jednu dopunsku mogućnost mobilizacije zdravstvenih resursa koja svakako zaslužuje da bude razmotrena. Ova monografija predstavlja značajan doprinos literaturi koja se bavi zdravstvom, zdravstvenim sistemom i zdravstvenom politikom, objedinjujući istovremeno kako istorijski osvrt na jedan dopunski mehanizam finansiranja zdravstvene zaštite koji je pre mnogo godina postojao u Srbiji tako i pogled na savremena zbivanja.

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Visoka poslovna škola strukovnih studija, Novi Sad

REGISTAR ZA 2020. GODINU

INDEKS AUTORA

INDEX KEY WORDS

INDEKS KLJUČNIH REČI

UPUTSTVO ZA AUTORE

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

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

Korisnici časopisa treba da se registruju na adresi:
http://aseestant.ceon.rs/index.php/medpreg/user/register

Prijava rada treba da se učini na adresi:
http://aseestant.ceon.rs/index.php/medpreg/

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

Elektronsko uređivanje časopisa obezbeđuje korišćenje sistema *CrossCheck*, koji prijavljene radove automatski proverava na plagijarizam i autoplagijarizam. Autori ne bi smeli da pošalju isti rad u više časopisa istovremeno. Ukoliko se to desi, glavni urednik časopisa *Medicinski pregled* ima pravo da rad vrati autorima bez prethodnog slanja rada na recenziju; da odbije štampanje rada; da se obrati urednicima drugih časopisa u koje je rad poslat ili da se obrati direktoru ustanove u kojoj su autori rada zaposleni.

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

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

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

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

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

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

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

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

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

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

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

Priprema rukopisa

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

Propratno pismo:

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

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

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

Rukopis

Opšta uputstva

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

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

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

2. Sažetak

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

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

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

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

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

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

3. Tekst članka

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

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

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

Uvod

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

Materijal i metode

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

Rezultati

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

Diskusija

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

Zaključak

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

4. Literatura

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

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

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

∗ Organizacija kao autor

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

∗ Bez autora

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

∗ Volumen sa suplementom

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

∗ Sveska sa suplementom

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

∗ Sažetak u časopisu

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

Knjige i druge monografije

∗ Jedan ili više autora

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

∗ Urednik (urednici) kao autor (autori)

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

∗ Poglavlje u knjizi

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

∗ Zbornik radova sa kongresa

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

∗ Disertacija

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

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

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

∗ Monografija u elektronskom formatu

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

∗ Kompjuterska datoteka

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

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

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

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

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

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

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

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

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

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

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

6. Dodatne obaveze

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

INFORMATION FOR AUTHORS

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

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

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

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

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

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

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

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

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

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

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

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

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

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

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

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

Preparation of the manuscript

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

The covering letter:

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

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

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

The manuscript:

General instructions.

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

The manuscript should contain the following elements:

1. The title page.

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

2. Summary.

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

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

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

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

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

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

3. The text of the paper.

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

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

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

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

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

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

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

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

Articles in journals

∗ *A standard article*

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

∗ *An organization as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *A computer file*

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

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

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

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

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

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

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

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

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

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

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

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.