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ORIGINAL SCIENTIFIC PAPER

PREVALENCE OF DEPRESSION SYPTOMS IN THE STUDENT POPULATION AND THE POSSIBILITY OF PREVENTION

Snezana Stojanovic - Ristic[1] Branka Toljić[1] Milica Buhovac[1] Marina Fiseković - Kremić[1]

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Introduction: Mental illness is the most common cause of disability and a major public health issue worldwide due to its increasing prevalence, the difficulty of therapeutic treatment and the possible progression of the disease.
Objectives: To determine the prevalence of depressive symptoms in the student population over a 5-year period and the connection between sociodemographic characteristics and lifestyle habits of students and the occurrence of depressive symptoms.
Methods: A retrospective study was conducted in the period 2018-2022 at the Institute for Health Protection of Students in Belgrade. Data was obtained by analyzing the questionnaire completed by student including the PHQ-9 questionnaire. The difference between students' socio-demographic characteristics and lifestyle habits and the presence of depression was examined using the X2 test. Variables that were significant in the X2 test were included in a binary logistic regression. The data were analyzed with SPSS 20.
Results: 34047 students participated, 17.53% of whom were identified as individuals with high risk for depression. In the study first graders showed more symptoms of depression than third graders. The students who showed symptoms of depression were typically female, lived with their parents, did not consume alcohol or smoke and exercised 2-3 times per week. In the logistical regression model, alcohol consumption was positively and significantly associated with the presence of depressive symptoms.
Conclusion: The preventive measures should focus on lower alcohol consumption and frequent physical activity. Regular systematic examinations and referral to a specialist for the individuals identified as high-risk for depression should be mandatory.
Keywords: students, symptoms of depression, prevention

PREVALENCE OF DEPRESSION SYPTOMS IN THE STUDENT POPULATION AND THE POSSIBILITY OF PREVENTION

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Uvod: Mentalna bolest je najčešći uzrok invaliditeta i veliki javnozdravstveni problem širom sveta zbog svoje sve veće prevalencije, teškoće terapijskog lečenja i moguće progresije bolesti.
Ciljevi: Utvrditi prevalenciju depresivnih simptoma u studentskoj populaciji tokom perioda od 5 godina i vezu između sociodemografskih karakteristika i životnih navika studenata i pojave depresivnih simptoma.
Metode: Retrospektivna studija je sprovedena u periodu 2018-2022. u Zavodu za zdravstvenu zaštitu studenata u Beogradu. Podaci su dobijeni analizom upitnika koji su popunili studenti, uključujući i upitnik PHQ-9. Razlika između sociodemografskih karakteristika i životnih navika studenata i prisustva depresije ispitana je pomoću X2 testa. Promenljive koje su bile značajne u X2 testu uključene su u binarnu logističku regresiju. Podaci su analizirani pomoću SPSS 20.
Rezultati: Učestvovalo je 34047 studenata, od kojih je 17,53% identifikovano kao osobe sa visokim rizikom od depresije. U studiji su studenti prve godine pokazali više simptoma depresije nego studenti treće. Studenti koji su pokazivali simptome depresije bili su tipično ženskog pola, živeli su sa roditeljima, nisu konzumirali alkohol niti pušili i vežbali su 2-3 puta nedeljno. U modelu logističke regresije, konzumiranje alkohola je bilo pozitivno i značajno povezano sa prisustvom depresivnih simptoma.
Zaključak: Preventivne mere treba da se fokusiraju na manju konzumaciju alkohola i čestu fizičku aktivnost. Redovni sistematski pregledi i upućivanje kod specijaliste za osobe identifikovane kao osobe sa visokim rizikom od depresije trebalo bi da budu obavezni.
Ključne reči: studenti, simptomi depresije, prevencija

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INTRODUCTION

According to the World Health Organization (WHO), mental health is "a state of well-being in which a person recognizes their own abilities, is able to cope with normal life stresses, work productively and fulfillingly and contribute to themselves and their community". [1]
Mental illness is the most common cause of disability and is a major public health problem worldwide due to its increasing prevalence, the difficulty of therapeutic treatment and the possible progression of the illness. [2,3] Stress, anxiety and depression are considered important indicators of mental health which, if left untreated, can have a negative impact on the individual. [4] Depression is characterized by a range of symptoms, including lack of interest in daily activities, lack of energy, poor concentration, feelings of worthlessness or guilt, altered sleep patterns, significant weight loss or gain, and even recurrent thoughts of death or suicide. [5]
Most mental health problems occur in early adulthood (college years) but often go unrecognized. [6] Mental health problems in this population group are associated with a higher frequency of physical and emotional problems, poorer sleep quality, dysfunctional relationships with the environment and marginalization in the labor market in the medium and long term. [7-10] Students are at risk of stress, anxiety and depression, which can affect their academic performance. Globally, it is estimated that 12–50% of students have at least one diagnostic criterion for one or more mental disorders. [11] Differently organized educational processes, alienation and impersonal relationships with teachers, competition, more time available and the ability to plan and organize it, relaxation or complete absence of parental control and often physical distance from them, encountering a new environment ... these are all challenges which are easier for some people to adapt to and more difficult for others. The health of young people during this period depends on the health potential they have brought with them from their school years, such as the accommodation and conditions they find after graduation, diet, physical activity, sexual behavior, smoking, alcohol consumption, psychoactive substances and leisure activities. Biological factors such as age and gender, especially female gender and socioeconomic status, also play a role. [12] Studies conducted on various samples of students have found a moderate to high prevalence of stress, anxiety and depression in this population. [13-15] Early diagnosis and treatment of mental health problems leads to better outcomes for patients. Therefore, it is necessary to identify those students who are at higher risk of developing mental health problems during their studies.

To determine the prevalence of depressive symptoms in the student population over a 5-year period and to determine the relationship between sociodemographic characteristics and lifestyle habits of students and the occurrence of depressive symptoms.

Methods

Study Design and Participants

A retrospective study was conducted in the period 2018-2022. in the Institute for Health Protection of Students in Belgrade. The data were obtained by analyzing the "Preventive Health Records", which are completed as part of the regular systematic examinations.

Data Collection

Regular systematic examinations of students at the University of Belgrade are conducted in the first and third year of study. Before the medical examination, students complete a questionnaire containing basic demographic and socioeconomic data, data on lifestyle habits, the presence of chronic diseases and previous significant illnesses, and the PHQ-9 questionnaire, which was also a research instrument. [16] A score of less than 5 indicates no depression, 5 to 9 indicates mild depression, 10 to 14 indicates moderate depression, 15 to 19 indicates moderate depression, and 20 or more indicates severe depression. The relationship between socio-demographic characteristics (gender, place of residence, diet and finances), the students' lifestyle habits (alcohol and tobacco consumption and physical activity) and their mental health was investigated. Lifestyle habits, do you use alcohol: no (does not drink alcoholic beverages), sometimes (involves consumption of two alcoholic beverages per day), regularly (daily drinks alcoholic beverages). Smoking (no and yes), and for physical activity three variables: no, 2-3 times a week, every day means train some sport. Follow-up meant that the student was sent for additional examinations based on the opinion of the physician who was conducting a systematic examination at the time.

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Data Analysis

Data are presented as absolute values (N) and frequencies (%) for categorical variables. The difference between students' sociodemographic characteristics and lifestyle habits and the presence of depression in the first and third years of study were examined using the X2 test. Variables that were significant in the X2 test in all five calendar years of student follow-up were included in a binary logistic regression performed to assess the association with the presence of depression as a dependent variable.

Data were analyzed using SPSS 20, results were considered statistically significant if $p<0.05$.

Results

In the study took part 34047 students of whom 17.53% stated that they were suffering from depression. The majority of respondents were female, 67.4%. The representation of different levels of depression symptoms in first and third year students is shown in Table 1.

Year of study	2018		2019		2020		2021		2022	
Level of depression N(%)	first	third	first	third	first	third	first	Third	first	third
Minimal depression	4860 (80.8)	3356 (84.7)	5554 (79.2)	3321 (85.6)	2946 (81.2)	1597 (84.5)	630 (81.4)	604 (90.0)	1849 (81.7)	3362 (84.6)
Mild depression	934 (15.5)	485 (12.2)	1107 (15.8)	462 (11.9)	521 (14.4)	236 (12.5)	116 (15.0)	57 (8.5)	303 (13.4)	488 (12.3)
Moderate depression	165 (2.7)	89 (2.2)	249 (3.6)	73 (1.9)	121 (3.3)	41 (2.2)	20 (2.6)	6 (0.9)	72 (3.2)	89 (2.2)
Moderately severe depression	44 (0.7)	25 (0.6)	72 (1.0)	17 (0.4)	29 (0.8)	5 (0.3)	6 (0.8)	0 (0)	26 (1.1)	26 (0.7)
Severe depression	15 (0.2)	5 (0.1)	27 (0.4)	4 (0.1)	8 (0.2)	9 (0.5)	2 (0.3)	1 (0.1)	7 (0.3)	5 (0.1)

In all school years studied, first-graders show more symptoms of depression than third-graders.

The investigation of the relationship between socio-demographic characteristics and the lifestyle habits of first graders and the presence of depressive symptoms is shown in Table 2.

	2018		2019		2020		2021		2022	
	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression
Gendre										
Male	1912 (39.4)	336 (29.0)	1975(35.6)	321(22.1)	1107(37.6)	165(24.4)	80 (27.1)	73(21.9)	481(26.0)	62(15.2)
Female	2944(60.6)	**822(71.0)****	3571(64.4)	**1132(77.9)****	1836(62.4)	**512(75.6)****	215(72.9)	261(78.1)	1366(74.0)	**346(84.8)****
Living arrangement										
At parent's house	2465 (51.6)	**657(57.3)****	2770(50.4)	**745(51.6)****	1531(53.0)	**364(54.3)****	150 (52.4)	158(49.7)	867(49.4)	189(50.9)
Rented flat	484 (10.1)	66 (5.8)	664(12.1)	131(9.1)	351(12.1)	54(8.1)	38(13.8)	25(7.9)	180(10.3)	31(8.4)
Student,s dorm	1831 (38.3)	423 (36.9)	2065(37.6)	568(39.3)	1008(34.9)	252(37.6)	98(34.3)	135(42.5)	708(40.3)	151(40.7)
Do you use alcohol ?										
No	3827 (79.2)	**794(68.9)****	4587(82.8)	**1079(74.5)****	2428(83.4)	**470(70.1)****	262(90.3)	**266(82.1)****	1580(88.8)	**309(82.4)****
Sometimes	997 (20.6)	355 (30.8)	932(16.8)	359(24.8)	477(16.4)	197(29.4)	27(9.3)	58(17.9)	195(11.0)	65(17.3)
Regularly	7 (0.1)	4 (0.3)	20(0.4)	11(0.8)	6(0.2)	3(0.4)	1(0.3)	0(0)	4(0.2)	1(0.3)
Do you smoke?										
No	4253 (87.9)	**965(83.8)****	4905(88.5)	**1217(83.9)****	2571(88.2)	**541(80.5)****	262(90.3)	280(86.4)	1607(90.3)	**317(84.3)****
Yes	587 (12.1)	187 (16.2)	637(11.5)	234(16.1)	344(11.8)	131(19.5)	28(9.7)	44(13.6)	173(9.7)	59(15.7)
Do you excersise?										
No	1255 (25.9)	414 (36.0)	1317(23.8)	466(32.1)	517(17.7)	182(27.1)	22(7.6)	46(14.2)	200(11.2)	65(17.3)
2-3 times a week	3119 (64.5)	**653(56.7)****	3656(66.0)	**894(61.6)****	2022(69.4)	**445(66.3)****	241(83.1)	**242(74.7)***	1412(79.3)	**290(77.1)****
Every day	464 (9.6)	84 (7.3)	567(10.2)	91(6.3)	376(12.9)	44(6.6)	27(9.3)	36(11.1)	168(9.4)	21(5.6)
Referred to specialist										
No	4552 (93.7)	**844(72.9)****	5239(94.3)	**1033(71.0)****	2850(96.7)	**498(73.3)****	289(98.0)	329(98.2)	1808(98.0)	**292(71.7)****
Yes	308 (6.3)	314 (27.1)	315 (5.7)	422(29.0)	96(3.3)	181(26.7)	6(2.0)	6(1.8)	37(2.0)	115(28.3)
Where do you eat ?										
At home	4027 (78.6)	1098(21.4)	2783(50.4)	**748(51.6)****	1530(53.0)	**364(54.3)****	493(80.0)	109(79.0)	663(47.1)	**102(56.0)****
In student' s restaurant	1348(81.3)	310 (18.7)	665(12.1)	131(9.0)	351(12.1)	54(8.1)	94(15.3)	19(13.8)	182(12.9)	9(4.9)
Other	178 (78.4)	**49 (21.6) ***	2069(37.5)	571(39.4)	1008(34.9)	252(37.6)	29(4.7)	10(7.2)	563(40.0)	71(39.0)
Source of income										
Parents	5326 (79.3)	1393 (20.7)	5326(95.8)	1393(95.7)	2878(95.7)	636(94.6)	557(90.4)	128(92.8)	1945(80.4)	155(84.2)
Student loan/scolarship	96 (78.0)	27 (22.0)	96(1.7)	27(1.9)	51(1.8)	16(2.4)	7(1.1)	1(0.7)	107(7.5)	9(4.9)
I work	85 (81.7)	19 (18.3)	85(1.5)	19(1.3)	43(1.5)	12(1.8)	41(6.7)	7(5.1)	136(9.5)	13(7.1)
Other	51 (75.0)	17 (25.0)	51(0.9)	17(1.2)	31(1.1)	8(1.2)	11(1.8)	2(1.4)	37(2.6)	7(3.8)

The variables that were statistically significant in all five years were the students' alcohol consumption and physical activity. The students who showed symptoms of depression were female, lived with their parents, did not consume alcohol, did not smoke, were not referred for follow-up and exercised 2-3 times per week.

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The study of the relationship between third-year students' lifestyle habits and the presence of depressive symptoms is shown in Table 3.

	2018		2019		2020		2021		2022	
	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression	No signs of depression	Shows signs of depression
Gendre										
Male	1146 (34.2)	150 (24.8)	1138(34.3)	120(21.6)	484(30.4)	61(21.0)	141 (23.4)	12(18.8)	1149(34.2)	151(24.8)
Female	2209(65.8)	**454(75.2)****	2181(65.7)	**436(78.4)****	1110(69.6)	**230(79.0)***	462(76.6)	52(81.2)	2212(65.8)	**457(75.2)****
Living arrangement										
At parent's house	1526 (46.0)	**309(51.8)****	1568(47.9)	**283(51.5)****	763(48.6)	**158(54.5)***	275(47.5)	**37(58.7)***	1527(46.0)	**310(51.6)****
Rented flat	658 (19.8)	55 (9.2)	581(17.7)	59(10.7)	219(13.9)	23(7.9)	71(12.3)	0(0)	659(19.8)	55(9.2)
Student,s dorm	1132 (34.1)	233 (39.0)	1126(34.4)	207(37.7)	588(37.5)	109(37.6)	233(40.2)	26(41.3)	1134(34.2)	236(39.3)
Do you use alcohol?										
No	2576 (77.1)	**391(64.8)****	2734(82.7)	**388(70.2)****	1249(78.6)	**195(67.0)***	504(85.1)	49(76.6)	2578(77.1)	**394(64.9)****
Sometimes	756 (22.6)	208 (34.5)	569(17.2)	161(29.1)	336(21.1)	92(31.6)	88(14.9)	15(23.4)	758(22.7)	209(34.4)
Regularly	9 (0.3)	4 (0.7)	4(0.1)	4(0.7)	4(0.3)	4(1.4)	0(0)	0(0)	9(0.3)	4(0.7)
Do you smoke?					1388(87.4)					
No	2883 (86.3)	**477(79.1)****	2917(88.1)	**454(82.1)****	201(12.6)	**238(81.8)***	509(86.3)	54(84.4)	2886(86.3)	**481(79.2)****
Yes	456 (13.7)	126 (20.9)	393(11.9)	99(17.9)		53(18.2)	81(13.7)	10(15.6)	457(13.7)	126(20.8)
Do you excersise?										
No	808 (24.2)	225 (37.4)	626(18.9)	154(27.8)	275(17.3)	84(28.9)	90(15.2)	7(11.1)	808(24.2)	226(37.3)
2-3 times a week	2238 (67.0)	**345(57.3)****	2450(74.1)	**377(68.2)****	1192(74.9)	**201(69.1)***	459(77.5)	53(84.1)	2242(67.0)	**348(57.4)****
Every day	294 (8.8)	32 (5.3)	231(7.0)	22(4.0)	125(7.9)	6(2.1)	43(7.3)	3(4.8)	294(8.8)	32(5.3)
Referred to specialist										
No	3069 (91.4)	**445(73.7)****	3097(93.3)	**436(78.4)****	1533(96.0)	**234(80.4)***	596(98.8)	**56(87.5)****	3122(92.9)	**492(80.9)****
Yes	287 (8.6)	159 (26.3)	224 (6.7)	120(21.6)	64(4.0)	57(19.6)	7(1.2)	8(12.5)	240(7.1)	116(19.1)
Where do you eat?					1199(75.6)					
At home	2369 (70.8)	**396(65.6)****	2361(71.3)	**426(77.0)****		223(76.6)	447(75.5)	**59(92.2)***	1419(79.2)	**295(79.1)***
In student's restaurant	852(25.5)	172 (28.5)	818(24.7)	98(17.7)	326(20.5) 62(3.9)	53(18.2)	95(16.0)	1(1.6)	300(16.8)	52(13.9)
Other	126 (3.8)	36 (6.0)	132(4.0)	29(5.2)		15(5.2)	50(8.4)	4(6.2)	72(4.0)	26(7.0)
Source of income										
Parents	3040 (90.7)	553 (91.6)	2970(89.7)	491(88.8)	1381(87.0)	257(88.3)	471(79.4)	55(85.9)	1646(91.9)	344(92.2)
Student loan/scolarship	204 (6.1)	34 (5.6)	239(7.2)	40(7.2)	114(7.2) 63(3.8)	21(7.2)	48(8.1)	1(1.6)	22(1.2)	5(1.3)
I work	52 (1.6)	6 (1.0)	62(1.9)	17(3.1)	31(2.0)	6(2.1)	61(10.3)	6(9.4)	95(5.3)	20(5.4)
Other	56 (1.7)	11 (1.8)	40(1.2)	5(0.9)		7(2.4)	13(2.2)	2(3.1)	28(1.6)	4(1.1)

*p<0.05 **p<0.001

For third-year students, place of residence and referral for reexamination are the most important variables. Those who showed symptoms of depression were female, lived and were fed by their parents, did not consume alcohol, did not smoke, were not referred to the specialist, and exercised 2-3 times per week.

Table 4 shows the relationship between the sociodemographic characteristics and lifestyle habits of the students and the presence of depressive symptoms

Independent variables	B	OR (95% CI)	P value
Do you use alcohol	0.49	1.63 (1.21-2.19)	P<0.001
Do you excersise	-0.46	0.63 (0.50-0.80)	P<0.001
Where do you live	0.003	1.00 (0.91-1.11)	0.959
Referred to the specialist	1.12	3.08 (2.42-3.92)	P<0.001

In the logistic regression model, the variables positively and significantly associated with the presence of depressive symptoms were alcohol consumption (OR: 1.63, 95% CI: 1.21-2.19) and referred to the specialist (OR: 3.08, 95% CI: 2.42-3.92). We found an inverse association between the occurrence of depression and physical activity (OR: 0.63, 95% CI: 0.50-0.80).

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DISCUSSION

Adolescents are an extremely heterogeneous group whose upbringing can be peaceful and without major problems, but also stressful, with numerous frustrations, fears, insecurities and suffering that lead to extreme vulnerability. It is a phase of leaving childhood, in which one learns new boundaries and discovers one's self-image, in which one paradoxically wants to become independent from one's parents, but at the same time wants to belong to a group of peers. Therefore, communication with them should be open, intimate and with a lot of appreciation, respect and empathy.

Mental illness can have a negative impact on overall physical health, quality of life and engagement in important life domains and activities, including school, work and social relationships. [17-19] Experience shows that chronic and persistent symptoms of mental illness can contribute to suicide risk. Identification of factors that contribute to mental health recovery in transition-age youth and early intervention are therefore recognized as priority areas within national and global mental health strategies and guidelines. [20,21]

Young people aged 16–29 years are the most at-risk age group for the onset of mental illness, as this is a significant period of psychosocial development, identity formation and many other life changes. [17,18]

This study covered a five-year period (2018-2022), including the first three years of the Covid-19 virus pandemic (2020-2022).

In the study conducted, it was shown that women are more prone to symptoms of depression, which is consistent with numerous studies by other researchers in which the female gender is mentioned as a risk factor for mental disorders. [22]

Students are a group that was already at high risk of mental disorders before the pandemic. It is estimated that up to 20% of students suffer from a mental disorder, which mainly includes anxiety, mood swings, and psychoactive substance use. [23] As young adults, they may have genetic factors that interact with environmental factors during their studies, such as academic workload and demands, financial support, social interaction with peers and faculty (impersonal relationships), and even traumatic experiences and stresses of various kinds. [24] In our study, the prevalence of depressive symptoms was 17.53%.

Undergraduate students have different socioeconomic statuses, which may entail a number of risk factors for mental health. [25]
In their study, Eisenberg et al. demonstrated a positive correlation between depression and financial instability in the student population; the same correlation was also found in the study by Lerman et al. [26]

In our study, we found a correlation between depression symptoms and students' lifestyle habits, which included alcohol consumption, cigarettes and physical activity. The results showed that the incidence of depression symptoms was highest in first-year students who lived and ate with their parents, did not consume alcohol, did not smoke, were not referred for follow-up, and exercised 2-3 times per week. Some studies show a correlation between the occurrence of depression and male gender and smoking. [27] In addition, the socio-demographic characteristics of the population studied were analysed (place of residence, diet and livelihood) and it was found that third-year students were significantly more likely to be depressed if they lived with their parents, which can be explained by the fact that they were under more pressure from their parents in terms of their university commitments, lack of privacy and independence.
The study also showed that students with a higher level of depression were not sent for reexamination. The reasons for this could be the following: that the doctors do not spend enough time and recognize the problem due to the lack of time in their daily work in primary health care; that there are currently no free appointments for specialist examinations or that the offered appointments do not suit the students due to private commitments; that the students reject the doctor's suggestion or are offered to think for a while and come back later; that they do not have health insurance. Studies show that symptoms of depression would be recognized up to three times more often if patients were referred for rehabilitative examinations. [28]
In their work, Keum et al. point to a positive correlation between depression and alcohol consumption. [29] Our results showed that the higher the level of depression symptoms, the more regularly the students consumed 1.63 times more alcohol.
Jiang and Rudenstine showed in their studies the

association between depression and reduced physical activity, first years of study and the impact of the Covid-19 virus pandemic on the mental health of university students. [30] The impact of the Covid-19 pandemic on students' mental health was also noted. This can be explained by the fact that the pandemic itself led to changes in living habits, isolation, a low number of social contacts, online courses and insecurity, that certain strains caused more severe clinical forms, a higher number of hospitalizations and a higher mortality rate, so that people feared for their own health and the health of their roommates... These are all factors that could affect the mental health of students at the time and cause the onset of depressive symptoms.

Our study showed that students' physical activity decreased 0.63-fold the more severe their depression was. People with depression often experience reduced motivation, a lack of energy, and little interest in everyday activities — especially in engaging in additional physical activity. On the other hand, physical activity can be beneficial for students in regulating and reducing depressive symptoms. However, these effects may vary depending on gender. [31] Some studies have found no statistically significant correlation between physical activity and the presence of depression. However, others have shown that more intense physical activity is associated with better mental health status. [32] Further research is needed to better understand the relationship between a sedentary lifestyle, physical activity, and depression in this population.

Cross-sectional study design, facilitates the simultaneous assessment of outcomes and exposures among study participants. The efficiency and cost-effectiveness of cross-sectional strategies make them appealing for preliminary data collection, but hinders establishing causal relationships. This is a cross-sectional study designed to provide information on the prevalence of depression and odds ratios. A questionnaire and retrospective self-reporting by respondents were used in the data collection, so there is a possibility of bias and unrealistic assessment. Secondly, there could be a lack of willingness on the part of respondents to disclose information about their private lives and this could have negative consequences.

CONCLUSION

Students were identified as a risk group for developing symptoms of depression, which is 17.53% in the Serbian student population. The students who showed symptoms of depression were female, lived and were fed by their parents, did not consume alcohol, did not smoke, exercised 2-3 times a week and were not referred for examination after systematic examinations. The importance of preventive measures by physicians should focus on promoting lower alcohol consumption, reducing and quitting smoking, more frequent physical activity and regular systematic examinations, as well as mandatory referral to the specialist to reduce the progression and occurrence of severe forms of depression.

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PRAXISMEDICA

REVIEW PAPER

INDIVIDUALIZED SULCAL AND GYRAL CORTICAL ANATOMY: A NEGLECTED CONCEPT?

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Future unavoidable development of individualized brain anatomy as a part of personalized medicine requires large databases from a vast number of individual brains. The simple descriptions, important in the clinic, demonstrated the wide morphological and morphometric variability of the sulci and gyri. Today, it is no longer enough, like in traditional anatomy, to simply describe one single, several, or even "all" sulcal/gyral variations in one region of the brain. Potential problems in the comprehensive analysis of their patterns with attempts to suggest further research are briefly reviewed. The medial hemispheric surface is suitable for a morphological pilot study of complete sulcal and gyral variability. Sulcal patterns should be presented in simplified linear form rather than as detailed images, and one useful simplification for analyzing gyral patterns, the essential gyral line, is described. Simultaneous investigation of gyri and sulci is recommended, but the problem is combinations of specific patterns in different percentages. Sophisticated algorithms could recognize cortical patterns and calculate their possible combinations. Anatomical terminology is an unavoidable component of these studies. Big data about variations of sulci and gyri would be useful in personalized medicine but also in genetic studies of potential laws and inheritance of their associations.
Key words: Human brain, sulci, gyri, shapes, variability, analysis

INDIVIDUALIZOVANA ANATOMIJA KORTIKALNIH ŽLEBOVA I VIJUGA: ZANEMAREN KONCEPT?

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Predstojeći neizbežan razvoj individualizovane anatomije mozga, kao dela personalizovane medicine, zahteva velike baze podataka sa ogromnog broja pojedinačnih mozgova. Jednostavni opisi, važni za kliniku, pokazali su široku morfološku i morfometrijsku varijabilnost žlebova i vijuga kore mozga. Međutim, danas više nije dovoljno, kao u tradicionalnoj anatomiji, da se samo jednostavno opiše jedna, nekoliko ili čak „sve" varijacije žlebova i vijuga u jednom regionu mozga. Zato su ovde su ukratko prikazani mogući problemi u sveobuhvatnoj analizi njihovih oblika, uz pokušaje ukazivanja na dalja istraživanja. Medijalna površina hemisfere je pogodna za pilot studiju sveobuhvatne varijabilnosti žlebova i vijuga. Žlebovi bi trebalo da se prikazuju u pojednostavljenom linearnom obliku pre nego kao detaljne slike, a opisana je i korisna pojednostavljena metoda analize šara vijuga, „the essential gyral line". Preporučuje se istovremeno istraživanje žlebova i vijuga, pri čemu problem predstavljaju kombinacije specifičnih obrazaca koji su prisutni u različitim procentima. Sofisticirani algoritmi bi mogli da prepoznaju kortikalne obrasce i da izračunaju njihove moguće kombinacije. Anatomska terminologija je neizbežna komponenta ovakvih istraživanja. „Veliki podaci" (big data) o varijacijama žlebova i vijuga bili bi korisni u personalizovanoj medicini, ali takođe i u genetskim studijama potencijalnih pravila i mogućih zakona nasleđivanja njihovih udruženosti.
Ključne reči: Mozak čoveka, žlebovi, vijuge, oblici, varijabilnost, analiza

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INTRODUCTION

It is now widely believed that the underlying heterogeneity of many disease processes suggests that strategies for treating an individual with a disease, and possibly monitoring or preventing that disease, must be tailored or 'personalized' to that individual's unique biochemical, physiological, environmental exposure, and behavioral profile [1]. Each human brain imagined or studied by different methods is by itself individualized. This short review uses the term "individualized anatomy," understanding that it can only be a part of personalized medicine.

Numerous descriptions of the human brain's sulcal and gyral variability are available [2] and are constantly being renewed. Although brain structure and brain function are not strictly dependent on each other, studies show that they are closely related, and the knowledge of this relationship allows the surgeon to plan procedures [3]. It is enough to mention here only two illustrative examples of the excellent and detailed traditional anatomical studies, describing a large number of variations of the occipital [4], subparietal, and parietooccipital sulci [5], as well as a monograph about anatomical variability and terminology of sulci [6]. Analysis of sulcal and gyral morphology and quantitative data is necessary also for studies of cortical development, cortical plasticity, pathological changes, comparative neuroanatomy, and the evolution of the cortex [2].

Despite the vast amount of information about the cerebral sulci, and particularly their variability [7], it is not entirely clear, apart from simple descriptions and morphometry, how to additionally treat and exploit obtained data. One of the goals could be to achieve the optimal use of these qualitative and quantitative data in different research and to explore possible genetic backgrounds or regularities of brain variability. In the available literature there is no data on whether or how often comprehensive morphological studies of all sulci and/or gyri in large samples of human brains have been reported. When sex, age, or brain side data are included, an enormous number of possible combinations of variations appear in the analysis of the individualized whole brain cortical patterns. The consequent increase in the scope of detailed research of the very large number of samples required makes work difficult, but it may be solved using artificial intelligence.

How to assess whether two sulcal/gyral shapes are similar or not, and what is the confidence limit for determining similarity? The recognition, definition, manual labeling, and typification of the sulcal/gyral shapes require training of a human observer to be able to identify sulci and gyri in individual brains. Since it is often based on the personal judgment of one or several investigators and is obviously up to the researcher (subjective error), the results of such studies are only roughly comparable. If, in order to facilitate work, the pre-labeled templates for identifying anatomical variations are used, this does not lead to an improvement of the study. The "standardization", such as the use of the intercommissural line system, also limits the accuracy of findings and can provide an illusory feeling of excessive confidence. On the other hand, these can be considered primitive, but the widely available methods still have their purpose.

During the studies of the human corpus callosum, authors more than thirty years ago encountered the problem of variable shape analysis, even if callosal shape is simpler and well delineated compared with sulcal and gyral patterns [8]. It seemed impossible to determine which callosal shapes are identical or are only similar, especially if analysis required further parcellation into callosal parts, which are without defined boundaries. Compared to this, the analysis of gyral and sulcal patterns appears several times more complex. The traditional partial descriptions with percentages reported of the morphological variations of the certain sulci and gyri, although adequate for the clinical purposes (see refs. [4, 5]), are no longer sufficient. Recently anatomical data preparation requires different new approaches for the analysis of a lot of brains to acquire actual "big data" about variable cortical morphology. Sophisticated programs or algorithms, such as artificial intelligence (the details of which are beyond the knowledge of anatomists), are needed to recognize morphological patterns and their similarities and, in some research, to apply the analysis of the fractal structure. Namely, the brain science will become more reliant on big data to provide a wealth of knowledge and can also be used to build computational models, and a model of the human brain as a "reference brain" provides important biological details [9].

This paper reviews briefly some challenging issues based in large part on the experience of the author's morphological research of the human brain cortical folding patterns, that is, sulcal/gyral shapes. To illustrate common issues in morphological studies of the cortical sulci and gyri, first are presented comparative views of photos and simplified linear presentations of sulci as examples for

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their potential use in complex analysis, which is much more than simple description. Thereafter are presented two examples of gyral variability, all based on the author's own research and experience.

Sulci

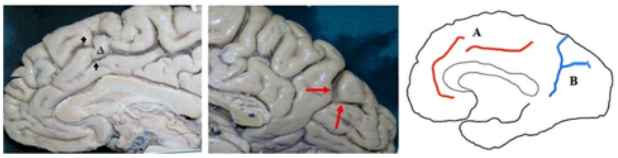

Figure 1. Left: Photo of Sulcus cinguli (17.9%) with a gyrus interposed (A). From [10]. Middle: Photo of Y-shaped sulcus parietooccipitalis - arrows (38.1%). From [11]. Right are their simplified linear presentations: A - Sulcus cinguli (red); B - Y-shaped sulcus parietooccipitalis (blue)

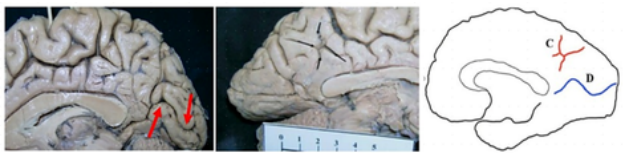

Figure 2. Left: Photo of Sulcus calcarinus - continuous, with two or more waves (36.9%) (arrows). From [11]. Middle: Sulcus subparietalis of H shape (arrows) (57.1%); from [10]. Right are their simplified linear presentations: C - Sulcus subparietalis of H shape, D - Sulcus calcarinus, with two or more waves.

There is a dilemma whether in pattern analysis the simplified linear presentations of sulci, the whole sulcal pattern of the related brain, or the whole brain imaging should be used, with a lot of details confusing or blurring the results. The answer to this dilemma of comparing “reality” or linear presentations could be the statement that the term “sulcus” is typically described qualitatively rather than as a concept or notion as a quantitative anatomical object [7]. Technically, inclusion of secondary and tertiary sulci in the linear presentations of sulcal patterns can be realized easily using different line thicknesses for showing them.

Gyri

Similar issues, as for morphological studies of sulci, can be considered for most of the brain gyri.

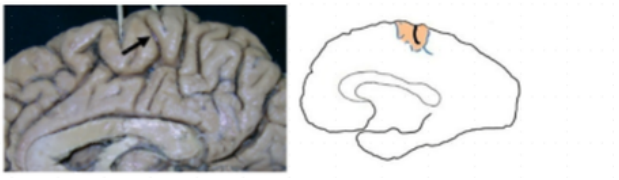

Figure 3. Left: Very rare segmented type of lobulus paracentralis, black arrow (4.8%). From [12]. Right: simplified presentation of segmented lobulus paracentralis (thick black line - the rare sulcus dividing lobulus paracentralis).

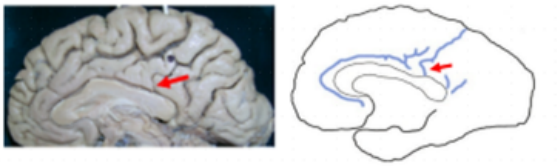

Figure 4. Left: Segmented gyrus cinguli (35.7%) divided by deep sulcus (red arrow). From [13]. Right: simplified presentation of segmented gyrus cinguli (red arrow).

Quantitative sulcal/gyral shape analysis

We do not know for sure whether the differences in the sizes of the corresponding cortical sulci/gyri really play any, perhaps even essential, role in this determination of shape similarities. When comparing the large and small structures, both of identical shapes, could these be characterized as „similar“, as the same, or not? Are these functionally absolutely "analogous" in some way, or are they functionally different either with or without certain adjustments or corrections? Related to this, for estimation of some anatomical variability and sizes, the morphometry should be used, considering it is complex. One must be careful with ambition to define everything or to measure whatever can be easily measured because it is necessary to avoid the generation of fictional numbers, which are in the realm of guesswork and are surrounded by controversy [14]. In the quantitative morphological investigations that are comparative, all material must be treated in an identical fashion, or if not, the application of corrective factors, such as for brain volume, body weight, body height, sex, age, etc., is necessary. When measuring formalin-fixed parts of the brain, the obtained sizes are not the same as on living (imaging) or fresh cadaveric brains. For example, the average volume of the orbitofrontal region after fixation by 10% formalin (3.7% formaldehyde) was increased by 5.7%, which was a highly significant change ($p < 0.01$), but the linear change of the same

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region was only 1.7% [15].
Morphometry, as almost unavoidable in sulcal/gyral research, is important for the solution of scientific problems concerning function, development, comparison, and pathological changes. It mainly includes measurements of volume, surfaces, and length of lines [16]. One systematic review [7] concluded that surface-based morphometry techniques have been shown to be particularly useful, as they allowed the description of parameters that characterize specific aspects of the cortex, such as its thickness, gyrification index, and sulcal width and depth [17]. New approaches to sulcus quantification, besides these parameters, include new ones, namely, sulcal volume, wall skewness, and the number of white matter basins [7]. However, there is a need for much more information to get out of the realm of fictional numbers we may be left in [14]. One difficulty in quantitative sulcal/gyral shape analysis, including asymmetries, is precisely establishing and defining reference points and lines with the often-unclear boundaries of the sulci/gyri being measured. Generally, main sulci are always defined, but in some studies it was necessary to use lines extending in the direction of certain sulci as the approximate boundaries of some gyri [12, 13, 18]. The problem of using inadequate methods can be potentially overcome since track tracing, imaging, and dissection are based on different biological or physical principles, and it is natural for their results to sometimes be different, but they are often complementary [19].

In the quantitative studies of the gyrencephalic cortex, additional difficulty is morphological complexity, related to its convoluted structure. One of the ways to solve this was the use of fractals. Fractal dimension has been widely used to provide a quantitative description of structural cortical complexity; it summarizes the morphological detail of an object in a range of spatial scales and was positively associated with the folding area in both hemispheres [17, 20]. Namely, one of the most salient properties of the brain's macroscale geometry is gyrification, the fractal-like folding of the cerebral cortex [21]. The fractional dimensionality of gray matter (cortical complexity) can be more sensitive to age-related differences than other metrics of cortical integrity, and fractal analysis has been applied to anatomic/histological images and neuroimaging for quantifying the developmental complexity of the human cerebral cortex [22, 23].

The essential gyral line (EGL)

The increase of the cortical volume in larger species is almost entirely due to a disproportionate expansion of the cortical surface area, and the brains change their shape by becoming folded as they increase in size [24, 25]. The human cortex develops a complex structure by increasing the frequency of folds and the convolution of gyral shape, rather than by deepening sulcal regions [20]. The length of the interconnected fibers reduced by folding the cortical surface shortens the radial and tangential distances between brain regions [25]. Recognition of gyral patterns does not have the same meaning as recognition of sulcal shapes. One reason for this is gyro-sulcal functional difference in cognitive performances, because gyral regions as well as intergyral connections consistently participate more as functional information exchange hubs than sulcal ones, contributing to accurate mapping between brain anatomy and function [26]. An additional reason is the well-known sulcal-gyral difference, where the thickness is larger at ridges (gyri) than at valleys (sulci) [27].
In spite of the specific architecture of the cerebral gyrus inner core [19], generally an increase in the relative number of gyri can only be achieved by reducing the gyral width, which predicts an upper limit to cortical folding [28]. Related to this, the concept of the "gyral window" represents the region through which fibers must pass when leaving or entering the gyrus [28]. To this gyral window corresponds "the essential gyral line" (EGL) as its projection on the crown of the gyrus, which showed as suitable for indicating the basic direction of the gyrus (Fig. 5) [29, 30, 31].

Figure 5. The essential gyral line (EGL—interrupted line) indicates (projects) the longitudinal direction of the gyral window (part of it indicated by square). According to [28, 29, 30, 31].

Several following facts support the use of the EGL. The inner cortical surfaces presenting gyral white matter for observing folding patterns [20] correspond both to the

gyral window and to the EGL. After removing the cortex, the exposed gyral subcortical white matter takes the form of ridges that reproduce the gyral anatomy [19]. The EGL also corresponds to the definition of the gyral white matter crest line on the cortical surface, which, used in sulcus construction, also defines the gyrus [7]. Crest lines, as a powerful tool in medical imaging, follow the convolutions of the cerebral sulci and gyri. These lines should satisfy the criteria of position, continuity, and uniqueness, have a nice mathematical background, and be feasible to identify automatically [32]. The calculation of the projection of the gyrus midline can be performed by imaging, and some sulcal and gyral constructions can be automated by existing methods and public tools [7]. More gray matter is present on the surface (gyri) than in the depth (sulci) of the cortex, because the gyri are universally thicker than the sulci [27], which also favors the applicability of EGL.

The findings of more frequent sulcal than gyral asymmetries, with the differences in the frequency of asymmetries depending on the method (simple observation vs. the EGL), could be of importance for research of cortical asymmetries [29, 30]. This finding that morphological asymmetries of gyri were significantly "reduced" by use of EGL suggests that in such analyses the shape of gyri, rather than sulci, may be fundamental.

Adult human brain and sulcal/gyral invariability

While the morphology of human primary and secondary sulci/gyri is practically unchanging during healthy adult life, this is not yet entirely certain for so-called tertiary sulci/gyri. Related to this could be the findings of more pronounced sulcal asymmetries on the level of tertiary sulci and that the individual sulcal variability may be related to very large coefficients of variation of total length of tertiary sulci [31]. It opens the question: are tertiary sulci somehow related to specific cytoarchitectonic subfields ("campuli"), or do they represent their boundaries? The extremely nonuniform aging of the brain among the various brain regions [33] can also be related to specific cytoarchitectonic subfields. Could there be a possible role of adult brain plasticity at the meso- or microscale levels since it was shown [34] that an environment's features strongly shape the quality and nature of the functional representations formed? Recently it is impossible to exclude that some long-term functional processes, by long-lasting dynamics, affect not only adult brain functioning but also its morphology on micro- or mesoscales. In spite of the very limited capacity of the adult brain to form new connections after stroke, studies indicate that post-stroke axonal sprouting occurs in mice, rats, primates, and humans (see [35]). The changes in neuronal sizes and collateral axonal sprouting, as well as in non-neuronal components (glia, capillaries, vasculature, and even the liquor bulk flow), will also impact MRI signals and must all be accounted for [36, 37]. The brain, once considered to be a fixed and stable organ, is now viewed as dynamic, flexible, and adaptive, with documented neuroplastic structural changes in healthy human brains as a result of normal processes that occur with learning (see [36, 37]). Given the microscopic nature of training-dependent structural changes in animals and the relatively low spatial resolution of MRI, it is unclear that in the human adult brain these changes can be reliably detected [38]. The current neuroimaging techniques cannot directly inform us about the underlying cellular events mediating the observed effects, and phenomena visible via MRI are likely never the result of a single process happening independently [36].

Broader aspects of individualized brain anatomy

Imaging can also be some kind of „identification method" of distinct patterns for each individual brain, like fingerprints. The research of brain sulcal/gyral variability is of clinical significance, because anatomical knowledge of their shapes is important for neurosurgical procedures and diagnostics, but this knowledge is not sufficient: brain function should be studied at the individual level to optimize the results of cerebral surgery [3]. Recently, nothing is known about potential associations of variable sulci on a single brain, especially if they occur in different percentages. Generally, we don't know if there is a need to establish rules for predicting and identifying potential combinations of associated different variable sulci/gyri on an individual brain in a large population (e.g., associations of sulci A, B, C, and D from Figs. 2 and 3) based on the data obtained. The occurrence of the very different sulcal percentages excludes simple mathematical combinatorics, correlations, and predictions, but its determination is possible with the help of imaging methods and of artificial intelligence. So obtained results could be useful in other research for easier and more accurate identification of cortical regions on each individual brain.

However, each of the numerous anatomical variations of the human brain surface should be accounted for in many other studies, complicating the generalizations of other anatomical data (e.g., about vascularization, receptorarchitectonics, cytoarchitectonics, connectomics, and neuropsychology), as well as for analysis of potential genetic influences. If connectome analysis is applied to the gyri, an additional problem due to their variability is defining the location of origin and/or end of the tracts. Variation in the brain's gyrification pattern must be considered as a factor that may impact the understanding of short-range connections and which prevents conclusions from being drawn from isolated cases and imposes the study of many subjects [19]. Besides limitations related to the methods or to morphological variability, new data about frontal lobe short association fibers obtained by various imaging methods generally complement the anatomical data [39].

The brain morphology in the sagittal plane is significant because it is the only definitive and inherently uniform, whatever the morphological type of the brain [40], and the mediosagittal plane is one of the key anatomical landmarks in the human brain [41]. Therefore, it could be of interest to start the wide individualized brain research with a detailed but completed anatomical sulcal/gyral analysis of the medial hemispheric side, which is practically in the mediosagittal plane along the falx cerebri.

The application of modern data-intensive methods, including imaging protocols, has revealed a great deal of inter-individual variation. Much of the personalized medicine is related to the findings of genetic studies, because each individual possesses subsets of literally many millions of genetic variants [1]. Studies by different magnetic imaging to investigate genetic associations in defining intermediate phenotypes and the effects of common genetic variants have broad implications for the advancement of both anatomical and functional knowledge (see in [42]). The interindividual variation in human brain size is almost entirely determined by genes, but overall cortical gyral patterns, though significantly affected by genetic factors, are determined primarily by nongenetic (random environmental) factors [43]. Finally, some results suggest that genetic, geometric, and physical factors during brain development are closely interrelated [27]. Individual variation in anatomy affects perceptual and cognitive abilities, but it is not known whether anatomical differences existed prior to the training or environmental event [36]. Today it is generally clear that now there is a need to overcome traditional anatomy and to fully describe each individual brain, or in other words, the need for individualized brain anatomy.

Terminology issues

All considered issues have an impact on the use of adequate terminology. The corresponding terminology with the use of correct unified terms is needed, not only for the common but also for at least the more frequent variable sulci and gyri. For numerous relatively minor or rare variants, there are no suitable anatomical terms, and these variations would be difficult to name. Therefore, one should try to establish certain regularities, such as the limit up to which the frequency of the rare anatomical forms found would be used in the creation of specific terminology. However, when such terms are applied to different individual brains, it would practically make systematic descriptive classification impossible. In spite of a consensus that the inclusion of names for trivial or variably present structures should be avoided and not be included in Terminologia Anatomica, they may find their place in alternative or specific versions of anatomical terminology [44]. However, certain numerical systems of codes can be created and used, such as in Terminologia Anatomica or in Terminologia Neuroanatomica [45, 46].

Also, with the development of advanced translator programs, practically all world languages could be officially included in order to avoid any errors in medical communication [47].

CONCLUSION

Individualized human anatomy as a specific item can only exist as a part of the development of personalized medicine, which is the practice of characterizing an individual on different levels and scales (macro- and mesoscales) and where inter-individual variation will continue to be identified [1]. This short review considers potential possibilities and problems in the analysis of cortical sulcal/gyral morphology and tries to indicate some ways for further studies of its variability. It is no longer enough, like in traditional anatomy, to simply describe one single, several, or even "all" sulcal/gyral variations in only one region of the brain. Now, the variable sulcal/gyral patterns of entire individual brains in wide populations should be described. This is very complex research if, in

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data processing, combined associations of variable sulcal/gyral patterns are present in very different percentages. Simplified linear presentations of sulci can be convenient for in-depth analysis of their variability. Into one comprehensive morphological analysis, sulcal pattern should be included equally as a gyral one, in spite of the possibility that gyral morphology can be more important than morphology of sulci. The medial hemispheric surface is a suitable region for the pilot study of its complete sulcal and gyral variability. The EGL described here can be considered as suitable for the research of gyral patterns in wider use. Cortical anatomical variability overlaps with problems in research on connectomes, cytoarchitectonics, and receptorarchitectonics, where there may not be a match with variable sulci and gyri, and they themselves may be variable. It is also inevitable to resolve terminological problems during these investigations.

Consequently, in the deep research of sulcal/gyral shapes and patterns of the human brain, the enormous need arises for and justifies integrated study centered on education in the disciplines of science, technology, engineering, and mathematics (STEM) referring to integrated knowledge and skills from those fields as is defined [48]. The unavoidable approach to individualized brain anatomy may have justification only as a part of personalized medicine. The breakthroughs in all considered directions could be widely used both in the clinic and in neuroscience research.

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PRAXISMEDICA

REVIEW ARTICLE

SECONDARY HYPERTENSION AND CONTINUUM OF RISING CASES

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Arterial hypertension is well-known strong risk factor that can lead to the development of coronary artery disease, heart attacks, heart failure, stroke, and other heart-related issues. Arterial hypertension has increased exponentially in the last few decades in adult men and women. Traditionally arterial hypertension is classified as primary, when no specific cause has been identified and is usually associated with multiple genetic polymorphisms and various environmental factor interactions, and secondary when there are conditions with biological plausibility to cause hypertension. Traditional data in medical textbooks indicate that in 90-95% of cases, arterial hypertension is primary, while only a small percentage of cases have secondary hypertension. European guidelines for elevated blood pressure and hypertension from 2024 indicate a higher prevalence of secondary hypertension, ranging from 10-35% of cases. Secondary hypertension is still not fully understood and often remains undiagnosed. Identifying the underlying cause of secondary hypertension is crucial, as treating the root condition can significantly reduce the risk of heart disease, stroke, and improve overall quality of life. Obesity is a major global health problem and the prevalence of obesity is constantly increasing and simultaneously leads to an increase in the prevalence of both primary and secondary arterial hypertension. Some forms of secondary hypertension cause more severe cardiac damage than primary hypertension and are associated with a higher cardiovascular risk. Secondary hypertension is more often resistant hypertension, which means that it is difficult to achieve target blood pressure values. It is important to timely conduct appropriate examinations and begin treatment promptly.
Keywords: secondary hypertension, blood pressure, cardiac damage, myocardial hypertrophy, obesity

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Arterijska hipertenzija je dobro poznat i glavni faktor rizika koji može dovesti do razvoja koronarne arterijske bolesti, infarkta miokarda, srčane insuficijencije, moždanog udara i drugih kardiovaskularnih komplikacija. U poslednjih nekoliko decenija prevalenca arterijske hipertenzije eksponencijalno raste kod odraslih muškaraca i žena. Tradicionalno se arterijska hipertenzija klasifikuje na primarnu, kada se ne može identifikovati specifičan uzrok i kada je obično povezana sa brojnim genetskim polimorfizmima i interakcijama različitih faktora sredine, i sekundarnu, kada postoje stanja sa jasnom biološkom osnovom koja mogu izazvati hipertenziju. Tradicionalni podaci iz medicinskih udžbenika pokazuju da je primarna arterijska hipertenzija zastupljena u 90–95% slučajeva, dok samo manji procenat obolelih ima sekundarnu hipertenziju. Evropske preporuke za povišen krvni pritisak i hipertenziju iz 2024. godine ukazuju na višu prevalencu sekundarne hipertenzije, koja se kreće od 10 do 35% slučajeva. Sekundarna hipertenzija i dalje nije u potpunosti razjašnjena i često ostaje nedijagnostikovana. Identifikovanje osnovnog uzroka sekundarne hipertenzije od suštinskog je značaja, jer lečenje osnovnog stanja može značajno smanjiti rizik od kardiovaskularnih oboljenja, moždanog udara, čime se poboljšava ukupni kvalitet života. Gojaznost predstavlja veliki globalni zdravstveni problem, a njena prevalenca je u stalnom porastu, što istovremeno dovodi i do porasta prevalence kako primarne, tako i sekundarne arterijske hipertenzije. Određeni oblici sekundarne hipertenzije dovode do izraženijeg oštećenja srca u odnosu na primarnu hipertenziju i povezani su sa većim kardiovaskularnim rizikom. Sekundarna hipertenzija je češće rezistentna hipertenzija, što znači da je teško postići ciljne vrednosti krvnog pritiska. Važno je blagovremeno sprovesti odgovarajuće dijagnostičke pretrage i započeti lečenje na vreme.
Ključne reči: sekundarna hipertenzija, krvni pritisak, oštećenje miokarda, hipertrofija miokarda, gojaznost

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INTRODUCTION

Arterial hypertension is the leading cause of cardiovascular disease, stroke and premature death worldwide. According to the World Health Organisation (WHO) globaly report, only 54% of adults with hypertension are diagnosed, 42% receive treatment, and 21% have their hypertension controlled. These data underscore the necessity for improved awareness and management of hypertension. The region of South-East Asia and the Western Pacific region experienced a significant increase of hypertension since 1990 (1).

Arterial hypertension is traditionally classified as primary or essential when no specific cause has been identified and is usually associated with multiple genetic polymorphisms and various environmental factor interactions, and as secondary when there are conditions with biological plausibility to cause hypertension regardless of other factors. Traditional data in medical textbooks indicate that in 90-95% of cases, arterial hypertension is primary, while only a small percentage of cases have secondary hypertension (1).

The prevalence of primary hypertension is rising globally owing to ageing of the population and increases in exposure to risk factors, such as high sodium intake, low potassium intake, obesity, alcohol consumption, smoking cigarettes, physical inactivity and unhealthy diet (2).

According to the 2003 European guidelines for the managment of arterial hypertension, the prevalence of secondary hypertension is 5-10% of cases, while the 2024 European guidelines for elevated blood pressure and hypertension indicate a higher prevalence of secondary hypertension, ranging from 10-35% of cases (2,3).

Secondary hypertension is still not fully understood and often remains undiagnosed. It has long been known that secondary hypertension is more likely to affect younger individuals and those whose high blood pressure is difficult to control with standard treatments. Identifying the underlying cause of secondary hypertension is crucial, as treating the root condition can significantly reduce the risk of heart disease, stroke, and other serious health issues, improving overall quality of life (4).

The importance of identifying secondary hypertension cannot be exaggerated. Chronic hypertension, regardless of the cause, can lead to serious damage to vital organs, including the heart, blood vessels, kidneys, brain, and eyes. While most patients with hypertension have primary hypertension (with no known cause), identifying secondary causes is essential because, with proper treatment, secondary hypertension can often be cured. Therefore, recognizing and addressing secondary hypertension is a key step in the effective management and prevention of long-term health complications (4).

The common suggestive clinical signs that require investigation into the cause of secondary hypertension are listed in (Table 1) (5,6).

Table 1. Patient characteristics that should raise the suspicion of secondary hypertension

- An acute and significant increase in blood pressure in patients who previously had stable blood pressure
- Age of onset of hypertension before puberty
- Age of onset of hypertension in individuals younger than 30 years who are not obese and have no family history of hypertension
- Severe hypertension with blood pressure higher than 180/110 mmHg, accompanied by target organ damage
- Resistant hypertension, which represents persistent elevation of blood pressure above 140/90 mmHg despite the use of optimal doses of at least three or four antihypertensive medications from different classes, including a diuretic
- Refractory hypertension, which refers to persistent elevation of blood pressure despite the use of five or more antihypertensive medications

Causes of secondary hypertension

Secondary hypertension is categorized based on its underlying causes into various subgroups. As is well known, more common causes of secondary hypertension include: renal parenchymal disease, chronic kidney disease, renovascular hypertension (atherosclerotic renovascular disease, fibromuscular dysplasia), primary hyperaldosteronism, obstructive sleep apnea, the effects of alcohol and certain medications (non-steroidal antiinflammatory drugs, corticosteroids, mineralocorticoids, sympathomimetics, oral contraceptives, antineoplastic drugs, immunosuppressants, erhytropoetin) etc. Less common causes of secondary hypertension include: pheochromocytoma, paraganglioma, acromegaly, Cushing's syndrome, hyperthyroidism, hypothyroidism, hyperparathyroidism, pregnancy-induced hypertension, coarctation of the aorta, etc. (7-9).

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Common causes of secondary hypertension

Kidney and renal artery disease

The kidneys play a central role in blood pressure regulation. Arterial hypertension can lead to kidney damage, while renal and renal artery diseases can contribute to an increase in blood pressure. Possible secondary forms of renal hypertension include glomerular kidney disease (e.g. glomerulonephritis) and tubulointerstitial processes (e.g. polycystic kidney disease) or microvascular kidney damage and renovascular hypertension (10).

Renal artery stenosis may be suspected as a cause of hypertension in younger individuals, mainly females with fibromuscular dysplasia, without a family history of arterial hypertension or in elderly patients presenting with hypertensive crises, flash pulmonary edoema (commonly in the context of bilateral renal artery stenoses, or of unclear progressive deterioration of renal function. The prevalence of the different aetiology of renal artery stenosis varies according to age and cardiovascular risk factor but it is reported that atherosclerotic renal artery stenosis account for 60–90% and fibromuscular dysplasia for 10-30% of the cases. Aetiologically, fibromuscular dysplasia, which typically affects young women needs to be distinguished from atherosclerotic artery stenosis, which is more common in older patients. Renal artery disease can lead to the narrowing of the renal vessel lumen, which reduces the pressure in the afferent arteriole and impairs renal perfusion. This triggers the kidneys to release renin, resulting in elevated levels of angiotensin II and aldosterone. These hormones raise blood volume by increasing the reabsorption of sodium and water in the kidneys, which in turn boosts cardiac output via the Frank-Starling mechanism. Elevated angiotensin II also causes systemic vasoconstriction, increasing systemic vascular resistance, and stimulates sympathetic activity. Chronic angiotensin II elevation further promotes cardiac and vascular hypertrophy. As a result, hypertension associated with renal artery stenosis is driven by both an increase in systemic vascular resistance and a rise in cardiac output (10).

Chronic kidney disease is a global health problem, with its prevalence on the rise. It is well known that primary arterial hypertension and chronic kidney disease are intrinsically related, with hypertension being a strong determinant of worsening kidney function. On the other hand, chronic kidney disease has a high prevalence of secondary hypertension (11-13).

Primary hyperaldosteronism

Primary hyperaldosteronism is the leading cause of secondary hypertension in middle-aged adults (ages 40–64 years). Elevated aldosterone levels cause heart damage and increase cardiovascular morbidity and mortality. It is actually a collection of conditions, including aldosterone-producing adenomas and bilateral idiopathic hyperaldosteronism. An adrenal adenoma or adrenal hyperplasia can lead to excessive aldosterone secretion. The elevated levels of aldosterone cause the kidneys to retain sodium and water, which results in increased blood volume and higher arterial blood pressure. As the body tries to suppress the renin-angiotensin system, plasma renin levels are typically low. Additionally, high aldosterone levels are often associated with hypokalemia. It is believed that the prevalence of primary hyperaldosteronism is also on the rise, and in a certain number of cases, it remains unrecognized as a cause of secondary hypertension (14-16).

Sleep apnea

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep, resulting in apnea or hypopnea, and it is an independent risk factor for cardiovascular disease such as arterial hypertension, heart failure, arrhythmias, and coronary heart disease. The mechanism underlying the development of arterial hypertension in sleep apnea involves multiple factors, including increased sympathetic tone and decrease in parasympathetic tone, inflammation through mechanisms such as obesity, decreased intrathoracic pressure, pulmonary stretch receptor stimulation, chemoreceptor stimulation, hypoxemia, and hypercapnia. Consequently, renin-angiotensin-aldosterone system is activated, the endothelin-1 level is increased, and the nitric oxide level is decreased, all of which contribute to the increase in vascular resistance and the development of hypertension. The presence of OSA has been related to an increase in the prevalence and incidence of hypertension, regardless of other factors. In fact, approximately 50% of patients with OSA present hypertension. Recent studies show that the rise in obesity continues, and the prevalence of sleep apnea is also increasing, but in Asia there are many non-obese sleep apnea patients. Furthermore, many mild

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cases of sleep apnea with minimal symptoms are difficult to detect (17-19).

Drug-induced hypertension

Due to their widespread use, nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid and acetaminophen, represent the most common medications associated with worsening blood pressure control. Both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors can elevate blood pressure. NSAIDs increase blood pressure primarily by altering prostaglandin synthesis, which leads to adverse renal effects. In addition, NSAIDs raise systemic vascular resistance through enhanced endothelin-1 production and disturbances in arachidonic acid metabolism. Systemic corticosteroids such as dexamethasone, fludrocortisone, methylprednisolone, prednisone, and prednisolone may cause an elevated blood pressure. Corticosteroids can cause sodium and fluid retention, and can lead to an increase in blood pressure. The increase in blood pressure is dose dependent. Sympathomimetics such as the decongestants containing phenylephrine or pseudoephedrine may cause an elevated blood pressure. Estrogens, androgens, and oral contraceptives may cause an increase in blood pressure.
Antidepressants such as monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants may cause an elevated blood pressure. Some immunosuppressants like cyclosporine and tacrolimus can affect kidney function, which can lead to the retention of sodium and water, ultimately causing blood pressure to rise. Several classes of antineoplastic drugs, including mainly vascular endothelial growth factor (VEGF) inhibitors, proteasome inhibitors, and cisplatin derivatives, can cause an increase in blood pressure due to their anti-tumor effects (20,21).

Less common causes of secondary hypertension

Phaeochromocytoma

Phaeochromocytomas or paragangliomas are tumors that secrete excessive amounts of catecholamines. These lesions may occur in the adrenal glands (phaeochromocytomas) or in sympathetic ganglia found along the sympathetic chain (paragangliomas or extra-adrenal phaeochromocytomas). Phaeochromocytomas are rare tumors, accounting for about 0.2-0,6% of all cases of sustained hypertension and hypertensive crisis. Catecholamine-secreting tumors can result in extremely high levels of circulating catecholamines (epinephrine, norepinephrine and dopamine). The elevated catecholamine levels induce systemic vasoconstriction, with cardiac stimulation leading to a substantial increase in arterial blood pressure and tachycardia (22).

Thyroid and parathyroid diseases

Dysregulation of thyroid function is reversible cause of secondary hypertension. Thyroid disorders lead to various hemodynamic changes that contribute to elevated blood pressure through their effects on endothelial function, vascular reactivity, renal hemodynamics, and the RAAS system. In hyperthyroidism, the increased endothelial responsiveness is a result of shear stress from the hyperdynamic circulation, which helps lower vascular resistance. On the other hand, hypothyroidism leads to a marked reduction in sensitivity to sympathetic agonists, resulting in higher peripheral vascular resistance and arterial stiffness. Thyroid disorders, specifically hypothyroidism and hyperthyroidism, have also been on the rise in recent decades and can certainly be important causes of secondary hypertension. Sporadic primary hyperparathyroidism is an endocrine disorder often characterized by persistent fasting hypercalcemia, caused by the autonomous overproduction of parathyroid hormone due to parathyroid adenoma or hyperplasia (hypercalcemic primary hyperparathyroidism). Primary hyperparathyroidism is associated with a higher risk of arterial hypertension (23-26).

Cushing's syndrome

In Cushing's syndrome arterial hypertension develops due to multiple pathophysiological mechanisms that contribute to increased plasma volume, peripheral vascular resistance, and cardiac output. Glucocorticoids may also affect blood pressure control by acting on the central nervous system, where they activate both glucocorticoid and mineralocorticoid receptors. As a result, glucocorticoids lead to changes that elevate cardiac output, total peripheral resistance, and renovascular resistance, which contributes to persistent hypertension. It is also known that the incidence of Cushing's syndrome have been increasing in the last period. Present in about 80% of Cushing's syndrome patients, secondary

hypertension is one of the pathology's most prevalent features (27-29).

Pregnancy-induced secondary hypertension

Pregnancy-induced secondary hypertension refers to a spectrum of hypertensive disorders unique to pregnancy, with preeclampsia and Hemolysis, Elevated Liver Enzymes, and Low Platelet (HELLP) syndrome being the most severe forms. Women with HELLP syndrome are at the highest risk for cardiovascular morbidity, including pulmonary edema and cardiac dysfunction. Preeclampsia, diagnosed after 20 weeks of gestation, is marked by new-onset hypertension, often accompanied by proteinuria or evidence of organ damage. Large studies published in recent years have also shown that there is an increase in the prevalence of pregnancy-induced hypertension. Obese women over 35 years of age have an increased risk of developing pregnancy-induced hypertension and preeclampsia, which can be a major cause of maternal and perinatal morbidity and mortality (30-35).

Aortic coarctation

Coarctation of the aorta, a congenital narrowing of the aorta, is a rare but significant cause of secondary hypertension, accounting for less than 1% of cases. It causes a narrowing of the descending aorta, usually located at the insertion of the ductus arteriosus distal to the left subclavian artery, which typically results in a left ventricular pressure overload. The obstruction reduces blood pressure in the lower body while raising pressure in the head and upper limbs. Coarctation is diagnosed by comparing blood pressure readings in the upper and lower limbs. Typically, these pressures are comparable, but in coarctation, blood pressure in the upper limbs is often significantly higher than in the lower limbs (36,37).

Mechanisms of obesity-induced hypertension and Discussion

Obesity is a common health disorder that develops from the interaction between genotype and environment and involves social, behavioral, cultural, physiological, metabolic and genetic factors. There is much evidence that obesity has a significant negative impact on population health. Therefore an important role is assigned to the treatment of this condition and its associated comorbidities such as arterial hypertension, hyperlipidemia, hyperinsulinemia, and insulin resistance. Obesity is a major global health problem and the prevalence of obesity is constantly increasing in most countries in the world, dominantly in younger-aged individuals both women and men. Sedantery behavior, constantly lower physical activity, urbanization, unhealthy nutrition contribute to obesity (38,39).

Link between obesity and arterial hypertension involves multiple mechanisams of origin such as sympathetic nervous system (SNS) overactivation, stimulation of the renin-angiotensin-aldosterone system (RAAS), alterations in adipose-derived cytokines such as leptin, insulin resistance and hyperinsulinaemia, elevated cortisol levels, as well as structural and functional renal changes (40).

Activation of the sympathetic nervous system (SNS) has been considered to have a crucial function in the pathogenesis of hypertension among obese individuals. Sympathetic nervous system overactivity include elevations in heart rate, cardiac output, and renal tubular sodium reabsorption, as a direct result of a α-adrenergic and β-adrenergic receptor stimulation and indirectly through activation of other systems such as the renin-angiotensin-aldosterone system RAAS. Causative mechanisms of SNS activation in obesity include abnormal adipokine secretion from adipose tissue, stimulation via the RAAS, insulin resistance, and baroreceptor dysfunction (40).

The arterial pressure control mechanism of diuresis and natriuresis according to the principle of infinite feedback gain seems to be shifted toward higher BP values in obese patients. Abnormalities in these mechanisms that would tend to raise blood pressure increase sodium and water excretion through pressure natriuresis and diuresis. As long as excretion exceeds intake, extracellular-fluid volume decreases reducing venous return and cardiac output until blood pressure returns to normal. Conversely, when blood pressure decreases, the kidney retains salt and water until arterial pressure returns to normal. Thus, pressure natriuresis acts as the key component of the feedback system that normally stabilizes blood pressure and body-fluid volumes. During the early phases of obesity, before loss of nephron function because of glomerular injury, primary sodium retention occurs as a result of increase in renal tubular reabsorption. This may be compensated by renal vasodilation, increased glomerular filtration rate and increased filtered amount of water and electrolytes. As a consequence of an incomplete compensation, however, extracellular-fluid volume is expanded, resulting in a hypertensive

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adjustment of the pressure natriuresis. This resetting of the kidney-fluid apparatus to a hypertensive level is consistent with the model of hypertension because of volume overload. Another significant cause of shift of pressure natriuresis toward higher blood pressure levels in obesity is the possibility of alterations in intrarenal forces caused by histological changes in the renal medulla that may compress the loops of Henle and vasa recta. Increased renal sodium reabsorption and volume expansion play an important role in initiating hypertension associated with obesity. Ultimately, however, the elevated glomerular hydrostatic pressure leads to progressive glomerular sclerosis and impaired renal function, and a deleterious cycle ensues in which nephrons are injured, sodium retention is exacerbated, and arterial pressures rise to maintain sodium delivery to the macula densa (41).

Obesity is associated with a state of insulin resistance and hyperinsulinaemia, which may contribute to hypertension. Insulin is known to act as a vasodilator, but in obese individuals with chronic hyperinsulinemia this response is blunted secondary to endothelial dysfunction, resulting in a state of increased vasoconstrictor tone. Chronic hyperinsulinemia has been associated with impairment of the vasodilator action of insulin. Hyperinsulinemia promotes an altered profile of vascular function. Vascular dysfunction seems to be the important factor in understanding the long-term implication of insulin in the causation of hypertension. Finally, insulin resistance has also been exhibited as an effect of heightened sympathetic drive, through b-adrenergic stimulation and/or vasoconstriction with subsequent reduction of muscular blood flow (42).

Also the leptin has been shown to stimulate sympathetic nervous system activity in the central nervous system and exerts a presssor effect on the cardiovascular system. Endothelial dysfunction has also been reported as another important aspect of leptin's effects. This has led to the notion that hyperleptinemia, largely through activation of the SNS, may contribute to obesity-related hypertension (42).

Adipose tissue is a heterogeneous endocrine organ. The deposition of fat tissue and the type (white versus brown) in obese individuals plays equally a large role in the development and progression of hypertension. Therefore, we can say that white adipose tissue represents the largest proportion of fat in the entire body and can be found around the major organs and vasculature in the abdominal cavity and subcutaneously. White adipose tissue serves to maintain energy homeostasis, storing excess in the form of triglycerides. Individuals with increased accumulation of white adipose tissue particularly in visceral depots have a higher prevalence of hypertension, dyslipidemia, and insulin resistance compared with those with less visceral fat. Ectopic fat surrounding the vasculature is also important in blood pressure regulation through excess proinflammatory response and the release of inflammatory adipokines, such as tumor necrosis factor-alpha, interleukins, resistin, visfatin, and leptin (Figure 1) (43).

Overweight and obesity are well-established risk factors that can lead to cardiovascular morbidity and mortality. There is also a multifaceted and dynamic relationship between obesity and cancer. Obesity can serve as a risk factor for cancer development (43).

In this framework, a key factor in the development of hypertension in obesity is genetic susceptibility. Genome-wide association studies have identified over 50 single-nucleotide polymorphisms associated with hypertension and over 250 genes/loci involved in obesity. Recent clinical and preclinical studies investigate gene-environment interactions in the genesis of obesity-related hypertension, including data to support maternal and offspring obesity-related cardiovascular disease. Epigenetic modifications, including DNA methylation, noncoding RNAs,
and histone modifications, are defined as mitotically and meiotically heritable modulation of gene function in these early life origins of hypertension (Figure 1) (43).

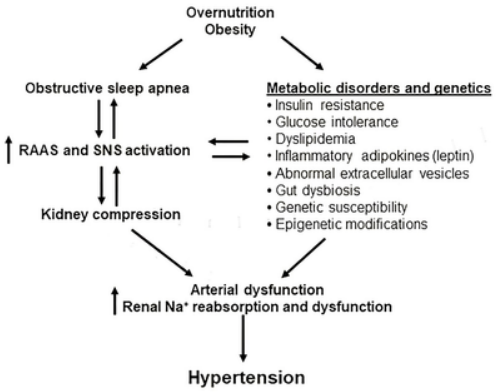


Figure 1. Mechanisms of obesity-induced hypertension

Obesity frequently coexists with obstructive sleep apnea, which results in chronic intermittent hypoxia and leads to the activation of carotid body chemoreceptors that reflexively upregulate SNS activity. Obese individuals have

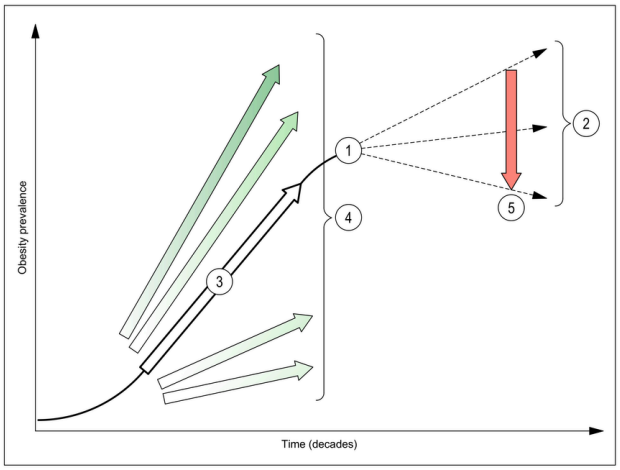
higher levels of plasma renin activity, angiotensinogen, angiotensin-converting enzyme (ACE), and aldosterone. Activation of the RAAS leads to increased formation of angiotensin II, which induces systemic vasoconstriction and simulates the production of aldosterone. Both angiotensin II and aldosterone increase renal tubular sodium reabsorption and water retention, resulting in intravascular volume expansion and hypertension. The prevalence of arterial hypertension in mild, moderate, and severe OSA is different, with the highest prevalence expected in severe forms of sleep apnea. The OSA severity index and the apnea–hypopnea index (AHI) are significant independent predictors of both systolic blood pressure and diastolic blood pressure. It has been shown that systolic blood pressure and diastolic blood pressure increase in line with increasing OSA severity, but there is a more significant increase in diastolic blood pressure. Obstructive sleep apnea is also an important risk factor in the development of resistant hypertension (44).

Obesity simultaneously leads to an increase in the prevalence of both primary and secondary arterial hypertension. The increase in the prevalence of obesity is certainly one of the dominant reasons for the increase in the prevalence of secondary hypertension. As shown above, obesity significantly contributes to the increase of the most common causes of secondary hypertension, such as chronic kidney disease, primary hyperaldosteronism, sleep apnea, etc.

In the mid-20th century, several large long-term prospective cohort studies (Framingham Heart Study, Nurses Health Study, CARDIA Study) were initiated and are still ongoing. These studies show that obesity is an independent significant risk factor contributing to the potential development of coronary heart disease, heart failure, stroke, arterial hypertension etc. (45-47).

In Figure 2. we can see the aims of obesity modeling at the population level. Descriptive studies quantify the present burden and potential future trends of obesity. Explanatory studies analyse the causes of the rise in obesity prevalence with time and the variability across populations. Evaluative models assess the likely effect of interventions to reduce future prevalence (48).

Figure 2. Diagram of the major uses of modelling of population prevalence of obesity



The black line is the trajectory of increases in obesity prevalence with time, with the present burden (1) and projected future burdens (2) being descriptive uses of modelling. Explanatory uses of modelling include explaining the rise in obesity with time (3) and the differences in prevalence rates (4). Evaluative uses include assessment of the potential for solutions to reduce the future burden of obesity (5) (48).

Some forms of secondary hypertension, if left untreated, cause more severe cardiac damage than primary hypertension and are associated with a higher cardiovascular risk. Cardiac damage includes not only myocardial hypertrophy, but also inflammation, fibrosis, apoptosis, and necrosis. Complications of secondary hypertension include hypertensive crisis, stroke, aortic dissection, myocardial infarction, arrhythmias, and congestive heart failure. Excessive secretion of catecholamines, aldosterone, angiotensin II, and cortisol leads to myocardial damage in secondary hypertension, and in addition to myocardial hypertrophy, it can cause both systolic and diastolic dysfunction, stress-induced cardiomyopathy, myocarditis, and dilated cardiomyopathy (49).

CONCLUSION

Secondary hypertension is more often resistant hypertension, which means that it is difficult to achieve target blood pressure values and takes more time. The possibility of existence of secondary hypertension should be considered in the diagnosis and treatment of all hypertensive patients. Blood pressure can be effectively reduced by identifying its etiology and treating the

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condition. Therefore, it is important to timely conduct appropriate examinations and begin treatment promptly. The use of personalized medical approaches allows for greater precision in patient treatment. In conclusion, if healthy lifestyle, increasing physical activity and dietary habits are not implemented, we can certainly expect a further rise in the prevalence of secondary hypertension in the future, in younger and middle-aged individuals, as well as partly in older patients.

On the one hand, it seems that since the appearance of the first drug for the treatment of primary arterial hypertension in the last year of the 19th century, it is much easier to achieve good blood pressure regulation, considering that several groups of antihypertensive medications have been developed in the meantime until today. This has resulted in the use of proven effective therapies to progressively improve control rates of hypertension, leading to reductions in cardiovascular, stroke, and kidney outcomes. On the other hand, today at the beginning of the 21st century, the increase in secondary hypertension and the discovery of its causes, which sometimes require a much more complex approach, are more worrying. And we can freely say that we have "A stable tree that grows like primary hypertension and a wind that shakes the canopy like secondary hypertension."

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PRAXISMEDICA

PRIMENA PLAZME BOGATE TROMBOCITIMA U LEČENJU ATROFIČNIH OŽILJAKA OD AKNI

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UVOD: Atrofični ožiljci nastaju kao česta posledica nelečenih akni, usled smanjene sinteze kolagena i poremećenih mehanizama reparacije tkiva. Plazma bogata trombocitima (PRP) se poslednjih godina sve češće koristi u terapiji ožiljaka zahvaljujući svojim regenerativnim sposobnostima, kao što su stimulacija sinteze kolagena, angiogeneza i remodelovanje tkiva.
PRIKAZ BOLESNIKA: Prikazan je slučaj pacijentkinje starosti 33 godine sa atrofičnim ožiljcima od akni tipa icepick i boxcar, lokalizovanim obostrano na obrazima. Sprovedena su tri PRP tretmana u razmaku od 4-6 nedelja. Korišćen je komercijalni PRP set, a dobijena plazma aplikovana je intradermalno iglom do 30G na dubini od oko 2mm. Sprovedena je klinička evaluacija i fotodokumentacija pre i posle serije tretmana. Nakon sprovedene terapije zabeleženo je značajno kliničko poboljšanje.
ZAKLJUČAK: PRP terapija se pokazala kao efikasna, bezbedna i dobro podnošljiva terapija u lečenju atrofičnih ožiljaka od akni. Iako standardizovan protokol u lečenju atrofičnih ožiljaka ne postoji, ovaj prikaz slučaja podržava PRP kao vrednu samostalnu ili kombinovanu terapijsku proceduru.
KLJUČNE REČI: Plazma bogata trombocitima, atrofični ožiljci od akni

APPLICATION OF PLATELET-RICH PLASMA IN THE TREATMENT OF ATROPHIC ACNE SCARS

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INTRODUCTION: Atrophic scars commonly develop as a consequence of untreated acne due to decreased collagen synthesis and impaired tissue repair mechanisms. Platelet-rich plasma (PRP) has increasingly been used in scar therapy in recent years because of its regenerative properties, including stimulation of collagen synthesis, angiogenesis, and tissue remodeling.
CASE OUTLINE: We present the case of a 33-year-old female patient with atrophic icepick and boxcar acne scars localized bilaterally on the cheeks. Three PRP treatments were performed at intervals of 4–6 weeks. A commercial PRP kit was used, and the obtained plasma was applied intradermally using a 30G needle at a depth of approximately 2 mm. Clinical evaluation and photographic documentation were conducted before and after the treatment series. Significant clinical improvement was observed following the therapy.
CONCLUSION: PRP therapy proved to be an effective, safe, and well-tolerated treatment for atrophic acne scars. Although a standardized protocol for the treatment of atrophic scars does not yet exist, this case report supports PRP as a valuable standalone or adjunctive therapeutic option.
KEYWORDS: Platelet-rich plasma, atrophic acne scars

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INTRODUCTION

Akne predstavljaju hroničnu bolest folikula dlake i sebacealnih žlezda koja zahvata 9,4% svetske populacije. U više od 85% slučajeva bolest se javlja u pubertetu, pogađajući podjednako oba pola, ali se može javiti i kod odraslih, pretežno žena. Najčešće su lokalizovane na licu, vratu, dekolteu i leđima, u vidu komedona, papula, pustula, nodusa i cisti. [1]

Etiopatogeneza akni je multifaktorijalna i povezana je sa produkcijom androgena u pubertetu, retencionom folikularnom hiperkeratozom, hiperprodukcijom i sekrecijom sebuma, proliferacijom Cutibacterium acnes i imunskim odgovorom na povećano prisustvo ove bakterije u sebacealnom folikulu. [1,2] Ovi procesi pokreću kaskadu inflamatornih reakcija sa oslobađanjem proinflamatornih citokina i hemokina, regrutacijom neutrofila u folikul i nastankom pustula i apscesa, Navedeni mehanizmi dovode do infrainfundibularne inflamacije, rupture folikula i formiranja perifolikularnih apscesa, čime se aktivira proces zarastanja rane. [3, 4]

Zarastanje rana predstavlja kompleksan biološki proces koji prolazi kroz nekoliko faza. U inicijalnoj, inflamatornoj fazi, tokom hemostaze, prolazna vazokonstrikcija zamenjuje se vazodilatacijom koja se klinički manifestuje pojavom eritema. Aktiviraju se fibroblasti, makrofagi, granulociti i neutrofili koji oslobađaju inflamatorne medijatore i pripremaju okolinu za sledeću fazu zarastanja. [5,6] U fazi stvaranja granulacionog tkiva dolazi do zamene oštećenog tkiva i intenzivne neoangiogeneze. Neutrofili se postepeno zamenjuju monocitima koji diferenciraju u makrofage i oslobađaju brojne faktore rasta, koji stimulišu migraciju i proliferaciju fibroblasta. Fibroblasti sintetišu komponente ekstracelularnog matriksa – glikozaminoglikane i kolagen, pri čemu se inicijalno stvara kolagen tip III, koji se kasnije zamenjuje kolagenom tipa I. [6]

U završnoj fazi fibroblasti i keratinociti sintetišu matriksne metaloproteinaze (MMP) i tkivne inhibitore matriksnih metaloproteinaza (TIMP), enzime odgovorne za kontrolisanu razgradnju kolagena i remodelovanje ekstracelularnog matriksa. Disbalans između aktivnosti MMP i TIMP tokom procesa zarastanja dovodi do patološkog remodelovanja dermisa, usled čega može doći do prekomerne degradacije kolagena, stvaranja defekta u koži i nastanka atrofičnih ožiljaka ili, u slučaju prekomerne sinteze kolagena, do razvoja hipertrofičnih ožiljaka. [7]

Ožiljci se klasifikuju kao atrofični, hipertrofični i keloidni, pri čemu su atrofični ožiljci najzastupljeniji. Atrofični ožiljci su podeljeni u nekoliko subkategorija na osnovu oblika, širine i dubine defekta koji stvaraju na koži:

1. ledeničasti (eng. Icepick) - uski, duboki i tačkasti ožiljci koji mogu da se protežu duboko u dermis,
2. kutijasti (eng. Boxcar) – široki, okrugli ili ovalni udubljeni ožiljci, jasno ograničeni vertikalnom ivicom, mogu biti površinski (manji od 0.5mm) ili duboki (veći od 0.5mm),
3. talasasti (eng. Rolling) ožiljci - površinski talasasti ožiljci koji koži daju neujednačen izgled [6]

Ne postoji standardizovana terapija u lečenju atrofičnih ožiljaka, primenjuju se različite hirurške tehnike (subcizija, punch graft ili punch ekscizija), hemijski pilinzi (alfa- i beta-hidroksi kiseline), ablativni i neablativni laseri i minimalno invazivne procedure kao što su microneedling i plazma bogata trombocitima (engl. platelet rich plasma, PRP), koje dovode do smanjenja vidljivosti ožiljaka i značajnog kliničkog poboljšanja. [8]

PRP je autologni preparat plazme koji sadrži višestruko veću koncentraciju trombocita u odnosu na perifernu krv. Alfa granule trombocita sadrže brojne faktore rasta koji doprinose sintezi kolagena, elastina i drugih komponenti ekstracelularnog matriksa, ćelijskoj proliferaciji, migraciji i angiogenezi, čime PRP ima važnu ulogu u regeneraciji i remodulaciji tkiva. [8-10]

Indikacije za primenu plazme bogate trombocitima u dermatologiji su: atrofični ožiljci od akni, rejuvenacija kože, androgenetska i cicatrijalna alopecija i tretman strija. [11] Iako se PRP smatra dobro podnošljivom terapijom, postoje jasne kontraindikacije za njegovu primenu, koje obuhvataju poremećaje koagulacije, trombocitopeniju, aktivne infekcije, sistemske inflamatorne bolesti i malignitete. Posebnu pažnju treba posvetiti pacijentima sa aknama ili onima koju su na istovremenoj sistemskoj i/ili lokalnoj terapiji, kod kojih je neophodna adekvatna vremenska distanca pre započinjanja PRP tretmana. [11,12]

PRP procedura se sprovodi isključivo u kontrolisanim uslovima, uz poštovanje aseptičnih mera, od strane stručno osposobljenih i sertifikovanih lica, pre svega specijalista dermatovenerologije ili plastične i rekonstruktivne hirurgije. Pre započinjanja terapije neophodna je detaljna procena pacijenta u cilju obezbeđivanja maksimalne bezbednosti i optimalnog terapijskog ishoda. [12]

PRIKAZ SLUČAJA

Anamneza, klinički pregled i dopunske dijagnostičke metode

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Pacijentkinja starosti 33 godine dolazi na pregled na Kožno odeljenje Kliničko-bolničkog centra u Kosovskoj Mitrovici zbog prisustva ožiljaka lokalizovanih na obrazima obostrano. Pacijentkinja navodi pojavu papulo-pustuloznih akni na licu u 16. godini života koje nisu bile lečene. Promene su trajale 8 godina, a nakon spontane regresije za sobom su ostavile ožiljke. Nije bilo kasnijih egzarcerbacija akni. Pacijentkinja je navela da je dobrog opšteg zdravstvenog stanja, bez komorbiditeta i aktuelne medicinske terapije.

Kliničkim pregledom ustanovljeno je prisustvo atrofičnih ožiljaka tipa icepick i boxcar, a uvidom u kompletnu krvnu sliku dobijen je podatak o referentnim vrednostima broja eritrocita, leukocita i trombocita.

U cilju smanjenja vidljivosti ožiljaka predložena je terapija plazmom bogatom trombocitima. Pacijentkinja je bila detaljno upoznata sa protokolom, tehnikom aplikovanja i očekivanim tokom oporavka nakon tretmana.

Predložena terapija sprovedena je u periodu od januara do aprila 2025. godine na Kožnom odeljenju Kliničko-bolničkog centra u Kosovskoj Mitrovici.

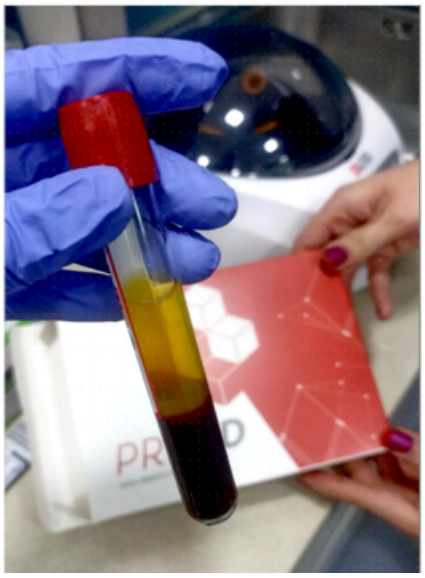
Pretretman lica

Pretretman je podrazumevao čišćenje lica i nanošenje anestetik kreme (Lidokaiin- Hlorid 5% gel, Galenika) u trajanju od 30 minuta. Nakon uklanjanja anestetika i dezinfekcije lica antiseptikom (sprej Octenisept), koža je bila spremna za aplikovanje PRP-a.

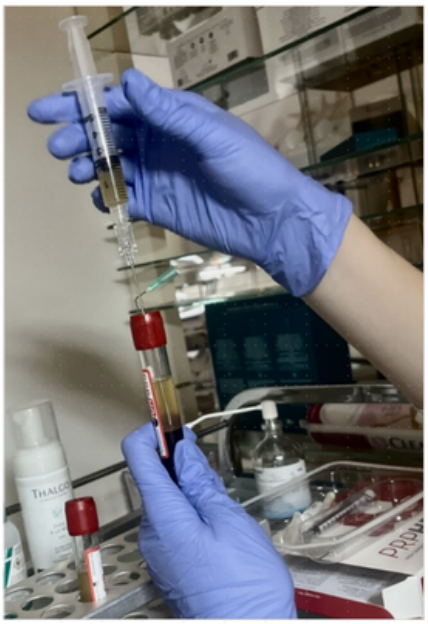
Protokol dobijanja plazme bogate trombocitima i aplikacija

Za dobijanje visoko-koncentrovane frakcije trombocita korišćen je komercijalni set PRP HD kit (Elpida, Srbija), zatvoreni sistem za jednokratnu upotrebu. Protokol je obuhvatao venepunkciju krvi iz kubitalne vene u dve eprutevete od po 10ml, koje su sadržale 0.1ml 3.2% koncentrovanog Na citrata. Uzorci su potom centrifugirani u centifugi (Dlab DM0506 Low Speed Centrifuge) na 500 RCF tokom 6 minuta, u skladu sa preporukama proizvođača seta (Slika 1). Nakon centrifugiranja, iz svake epruvete izdvojeno je po 2ml plazme (sloj plazme neposredno iznad eritrocita) (Slika 2), koja je potom resuspendovana u trećoj epruveti. Dobijeni PRP je zatim prebačen u špriceve i aplikovan intradermalno metodom papule, koristeći iglu od 30G 4mm na dubini od oko 2mm, u željenoj regiji, u razmacima od oko 1cm. Ukupno je utrošeno 4ml PRP-a po tretmanu. Pacijentkinja je praćena tokom procedure i narednih 48h, komplikacije nisu bile zabeležene. Neposredno nakon tretmana uočen je eritem koji je očekivan i prolazan u prvih par sati.

Slika 1. Dobijena plazma nakon centrifugiranja



Slika 2. Izvlačenje 2ml plazme (sloj iznad eritrocita)



Postproceduralna nega podrazumevala je nanošenje antipirinske kreme, dvadesetčetvoročasovno izbegavanje direktnog izlaganja UV zracima, intenzivne fizičke aktivnosti, saune i agresivnih kozmetičkih procedura.

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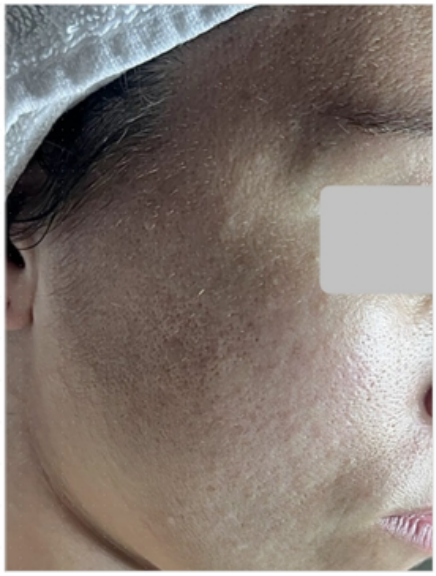
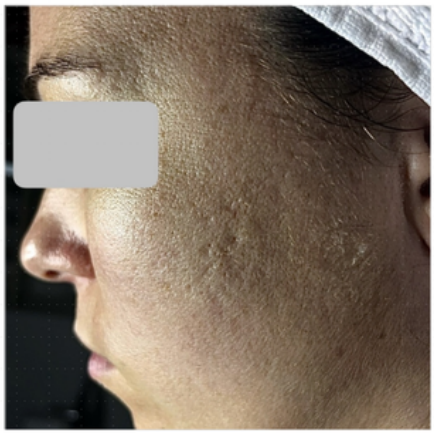
Sprovedena su tri PRP tretmana u razmaku od 4-6 nedelja, uz praćenje i fotografisanje pre (slika 3, 4) i posle kompletne serije tretmana (Slika 5,6).

Slika 3. Prikaz atrofičnih ožiljaka na desnom obrazu pre PRP terapije



Slika 4. Prikaz atrofičnih ožiljaka na levom obrazu pre PRP terapije



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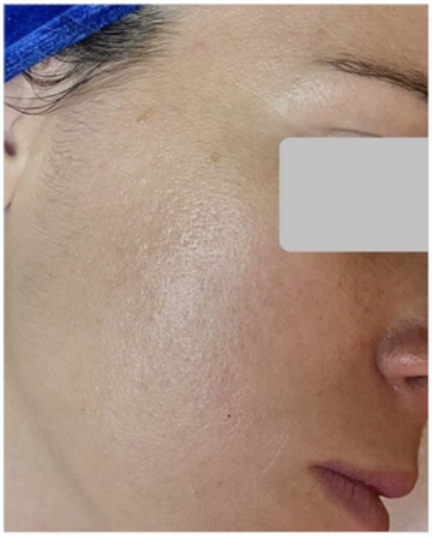
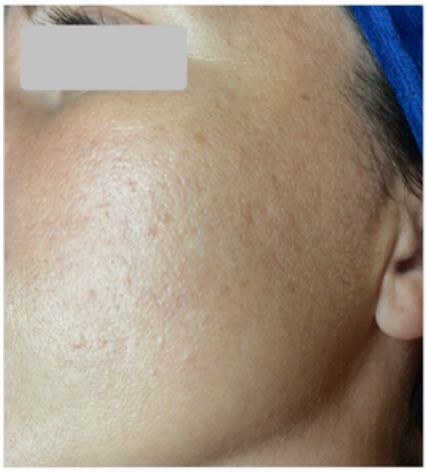
Slika 5. Izgled kože desnog obraza nakon PRP terapije



Slika 6. Izgled kože levog obraza nakon PRP terapije



REZULTATI

Evaluacijom pacijentkinje 4 nedelje posle trećeg tretmana uočen je značajan stepen kliničkog poboljšanja, koji se manifestovao smanjenjem broja i dubine atrofičnih ožiljaka, redukcijom vidljivosti pora i finih bora, ujednačenijim tonom i poboljšanim tonusom kože.
Poboljšanje je utvrđeno kliničkim pregledom i subjektivnom procenom pacijentkinje, koja je izrazila visok stepen zadovoljstva postignutim ishodom lečenja.

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DISKUSIJA

Plazma bogata trombocitima (PRP) poslednjih godina nalazi primenu u mnogim granama medicine, kao što su ortopedija, fizikalna medicina, plastična hirurgija, stomatologija i dermatologija. Zahvaljujući svojim sposobnostima regeneracije tkiva, angiogeneze i remodelovanja ekstracelularnog matriksa PRP se široko primenjuje u dermatološkoj praksi. Budući da atrofični ožiljci nastaju kao posledica nedovoljne sinteze kolagena i poremećaja reparativnih mehanizama kože, primena PRP-a predstavlja jasnu terapijsku indikaciju, bilo kao samostalna terapija ili u kombinaciji sa drugim procedurama. [13, 14]

Schoenberg E. i saradnici ističu da kombinacija frakcionog ablativnog lasera i PRP-a skraćuje period oporavka, smanjuje postproceduralni edem i eritem i doprinosi boljim kliničkim rezultatima u odnosu na monoterapiju laserom. [14] Iako većina kliničkih ispitivanja o terapiji atrofičnih ožiljaka od akni uključuje PRP u kombinaciji sa drugim procedurama, dostupni su i podaci o njogovoj primeni kao monoterapije. U randomizovanoj studiji koju su sproveli Gulanikar A.D. i saradnici, a koja je obuhvatila 30 pacijenata sa atrofičnim ožiljcima od akni, primena PRP-a kao samostalne terapijske procedura dovela je do statistički značajnog kliničkog poboljšanja. [15]

Aktivacijom trombocita oslobađaju se brojni citokini i faktori rasta, te visoka koncentracija trombocita u koncentrovanoj plazmi daje obećavajuće rezultate u obnovi oštećene kože. [12,14]

Degranulacijom alfa granula iz trombocita oslobađaju se trombocitni faktor rasta (platelet-derived growth factor, PDGF), transformišući faktor rasta beta (transforming growth factor-beta, TGF-β), vaskularni endotelni faktor rasta (vascular endothelial growth factor, VEGF), insulinu sličan faktor rasta (insulin-like growth factor, IGF), faktor rasta fibroblasta (fibroblast growth factor, FGF) i epitelni faktor rasta (epidermal growth factor, EGF). [16,17] Oslobođeni faktori rasta vezuju se za transmembranske receptore ciljnih ćelija - mezenhimalnih matičnih ćelija, fibroblasta, osteoblasta, endotelnih i epidermalnih ćelija. Vezivanjem za ove receptore, posredstvom intracelularnih signalnih pruteva, dolazi do ekspresije gena odgovornih za ćelijsku proliferaciju, angiogenezu i remodulaciju tkiva. Kao rezultat proliferacije fibroblasta dolazi do sinteze kolagena i ostalih komponenti ekstracelularnog matriksa, koje doprinose obnovi strukture derma. [16-18] Ovaj proces najintenzivniji je u prvom satu nakon aktivacije trombocita i nastavlja se tokom narednih 5 do 10 dana, što obezbeđuje produžen regenerativni efekat [18] Min S. i saradnici su istraživali molekularne mehanizme kombinovane terapije frakcionog CO2 lasera i PRP-a u lečenju ožiljaka od akni. Imunohistohemijskom analizom ustanovljeno je da koža tretirana kombinovanom terapijom sadrži više kolagena tip I i III, TGF-β1 i TGF-β2 u poređenju sa regijom tretiranom isključivo laserom. Autori navode da je povećana produkcija kolagena povezana sa pojačanom aktivnošću TGF-β, koji stimuliše proliferaciju fibroblasta i sintezu kolagena, čime se objašnjava efikasniji reparativni odgovor kod kombinovane terapije. [19]

Pored direktnog uticaja na fibroblaste, trombociti posredstvom citokina i hemokina utiču na inflamatorni odgovor kože aktivacijom reparativnog fenotipa makrofaga (M2). M2 makrofagi podstiču angiogenezu, sintezu kolagena i regulišu aktivnost MMP. Na taj način doprinose očuvanju novoformiranog kolagena i izgradnji vezivne komponente derma, što je od posebnog značaja u lečenju atrofičnih ožiljaka. [20] Uchiyama R. i saradnici navode da PRP može uticati na polarizaciju makrofaga iz proinflamatornog M1 fenotipa u reparativni M2 fenotip, čime se aktiviraju antiinflamatorni i regenerativni mehanizmi u tkivu. Upoređujući dve frakcije PRP-a: PRP bogatu leukocitima (LR-PRP) i PRP siromašnu leukocitima (LP-PRP), autori su pokazali da LR-PRP smanjuje ekspresiju proinflamatornih citokina i povećava aktivnost M2 makrofaga zahvaljujući većoj koncentraciji antiinflamatornih faktora - interleukina-10 i TGF-β, što dodatno doprinosi reparaciji oštećenog tkiva. [21]

U lečenju ožiljaka od akni, PRP posredstvom stimulacije sinteze kolagena, regeneracije tkiva i modulacije inflamatornog odgovora doprinosi popunjavanju atrofičnih ožiljaka, unapređenju teksture i volumena kože, dok angiogeneza poboljšava vaskularizaciju ožiljaka i ishranu kože. Antiinflamatorna svojstva PRP-a smanjuju eritem i edem, uz formiranje ujednačenijeg i zdravijeg izgleda kože. [22]

Rezultati našeg prikaza slučaja u skladu su sa dostupnom literaturom [22,23], budući da je kod pacijentkinje zabeleženo vidljivo poboljšanje strukture kože, smanjenje dubine atrofičnih ožiljaka i ujednačenija pigmentacija kože nakon sprovedene PRP terapije. Ovakav klinički odgovor može se objasniti do sada opisanim mehanizmima delovanja PRP-a, koji uključuju stimulaciju sinteze kolagena, angiogenezu i modulaciju inflamatornog odgovora.

Dodatna prednost PRP terapije je njena izuzetna bezbednost, s obzirom da se koristi autologna plazma, čime je rizik od alergijskih i imunskih reakcija je minimalan.

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[24] U poređenju sa drugim invazivnim procedurama, period oporavka je kratak, a postproceduralni eritem i edem su minimalni i prolazni. [25]

Važno je napomenuti da efekat PRP terapije zavisi od individualnih karakteristika pacijenata, tipa atrofičnih ožiljaka, tehnike pripreme (centrifugalna sila, vreme centrifugiranja, tip epruveta), primenjene tehnike aplikacije, koncentracije trombocita, prisustva leukocita, učestalosti i broja tretmana. S obzirom na to da standardizacija PRP protokola i dalje nije postignuta i da način pripreme zavisi od proizvođača, postoji potreba za daljim istraživanjima koja bi tačno definisala protokol terapije, metod pripreme, način aplikacije i broj tretmana. [26]

Kliničke fotografije uključene u ovaj prikaz slučaja omogućavaju vizuelnu procenu terapijskog ishoda, međutim odsustvo validiranih skala za objektivnu i kvantitativnu analizu atrofičnih ožiljaka predstavlja metodološko ograničenje. Ipak, uočeni rezultati primene PRP-a u našem prikazu doprinose kliničkom iskustvu i dodatno potvrđuju njegovu efikasnost kao minimalno invazivne terapijske procedure u lečenju atrofičnih ožiljaka od akni.

ZAKLJUČAK

Dosadašnja istraživanja ukazuju da PRP ima značajne prednosti zahvaljujući svojim regenerativnim svojstvima, dobroj podnošljivosti i potencijalnim dugoročnim rezultatima. Iako su potrebne dodatne studije, koje uključuju standardizaciju protokola pripreme PRP-a i sprovođenje većih randomizovanih kontrolisanih studija, dostupni podaci potvrđuju da PRP terapija predstavlja efikasnu i sigurnu proceduru u tretmanu atrofičnih ožiljaka od akni, samostalno ili u kombinaciji sa drugim terapijskim pristupima.

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UPUTSTVO AUTORIMA

OPŠTA UPUTSTVA
• Word
• latinica
• Times New Roman
• 12 pt
• sve margine 2,5 cm
• stranica A4
• levo poravnanje
• uvlačenje pasusa 10 mm
• literatura u tekstu u zagradama [...]

PRVA STRANICA
• Naslov rada bez skraćenica
• Puna imena i prezimena autora
• Zvaničan naziv ustanova, mesto, država
• Kontakt-adresa, telefon, e-mail

POSEBNA STRANICA
Kratak sadržaj (100-250 reči)
Originalan rad:
• Uvod
• Cilj rada
• Metode rada
• Rezultati
• Zaključak
• Ključne reči (3-6)
Prikaz bolesnika:
• Uvod
• Prikaz bolesnika
• Zaključak
• Ključne reči (3-6)
Ostali tipovi radova:
• nema segmenata

TEKST RADA
Originalan rad (do 5.000 reči):
• Uvod
• Cilj rada
• Metode rada
• Rezultati
• Diskusija
• Zaključak
• (Zahvalnica)
• Literatura (Vankuverski stil)
Prikaz bolesnika (do 3.000 reči):
• Uvod
• Prikaz bolesnika
• Diskusija
• (Zahvalnica)
• Literatura (Vankuverski stil)
Pregled literature, saopštenje, rad iz istorije medicine, rad za "Jezik medicine"
(do 5.000 reči):
• Uvod
• Odgovarajući podnaslovi
• Zaključak
• (Zahvalnica)
• Literatura (Vankuverski stil, pet autocitata)

POSEBNA STRANICA
• Naslov rada na engleskom
• Puna imena i prezimena autora
• Zvaničan naziv ustanova na engleskom, mesto, država

POSEBNA STRANICA
Summary (100-250 words)
Original article:
• Introduction
• Objective
• Methods
• Results
• Conclusion
• Keywords (3-6)
Case report:
• Introduction
• Case outline
• Conclusion
• Keywords (3-6)
Articles for other columns:
• nema segmenata

PRILOZI
Tabele (Word):
• Tabela 1. (srpski)
• Table 1. (English)
Grafikoni (Excel, link u Word):
• Grafikon 1. (srpski)
• Graph 1. (English)
Slike (original, skenirano)
• Slika 1. (srpski)
• Figure 1 (English)
Sheme (CorelDraw ili Adobe Illustrator)
• Shema 1. (srpski)
• Scheme 1. (English)

OSTALO
• skraćenice u latinici podvući
• decimalni brojevi u srpskom tekstu sa zarezom, u engleskom i prilozima sa tačkom
• jedinice SI

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UPUTSTVO AUTORIMA

Opšta uputstva. Tekst rada kucati u programu za obradu teksta Word, latinicom (Serbian Latin kodni raspored), sa dvostrukim proredom, isključivo fontom Times New Roman i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, veličinu stranice na format A4, a tekst kucati s levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije). Ne koristiti tabulatore i uzastopne prazne karaktere (spejsove) radi poravnanja teksta, već alatke za kontrolu poravnanja na lenjiru i Toolbars. Posle svakog znaka interpunkcije staviti samo jedan prazan karakter. Ako se u tekstu koriste specijalni znaci (simboli), koristiti font Symbol. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u uglastim zagradama – npr. [1, 2], i to onim redosledom kojim se pojavljuju u tekstu. Stranice numerisati redom u okviru donje margine, počev od naslovne strane.

Koristiti kratke i jasne rečenice. Prevod pojmova iz strane literature treba da bude u duhu srpskog jezika. Sve strane reči ili sintagme za koje postoji odgovarajuće ime u našem jeziku zameniti tim nazivom. Za nazive lekova koristiti isključivo generička imena. Uređaji (aparati) se označavaju fabričkim nazivima, a ime i mesto proizvođača treba navesti u oblim zagradama. Ukoliko se u tekstu koriste oznake koje su spoj slova ibrojeva, precizno napisati broj koji se javlja kao eksponent ili kao indeks (npr. 99Tc, IL-6, O2, B12, CD8).

Ukoliko je rad deo magistarske teze, odnosno doktorske disertacije, ili je urađen u okviru naučnog projekta, to treba posebno naznačiti u napomeni na kraju teksta. Takođe, ukoliko je rad prethodno saopšten na nekom stručnom sastanku, navesti zvaničan naziv skupa, mesto i vreme održavanja.

Rukopis rada dostaviti odštampan jednostrano na beloj hartiji formata A4 u tri primerka. S obzirom na to da se rad kuca latinicom, a članak u časopisu štampa ćirilicom, važno je da se u jednom primerku rukopisa koji se predaje za štampu crvenom olovkom podvuku reči (fraze, nazivi, skraćenice itd.) koje će ostati u latinici (npr. jedinice mera, nazivi lekova, hemijske formule, skraćenice koje potiču od stranih izraza i slično).

Klinička istraživanja. Klinička istraživanja se definišu kao istraživanja koja se odnose na ispitanike obuhvaćene jednom zdravstvenom intervencijom ili više njih, radi ispitivanja uticaja na zdravstveni ishod. Registarski broj istraživanja treba da se navede u poslednjem redu Kratkog sadržaja.

Etička saglasnost. Rukopisi o humanim medicinskim istraživanjima ili istorijama bolesti pacijenata treba da sadrže izjavu u vidu pisanog pristanka ispitivanih osoba u skladu s Helsinškom deklaracijom, odobrenje lokalnog etičkog odbora da se istraživanje može izvesti i da je ono u skladu s pravnim standardima. Eksperimentalna istraživanja na humanom materijalu i ispitivanja vršena na životinjama treba da sadrže izjavu etičkog odbora institucije i treba da su u saglasnosti s lokalnim pravnim standardima.

Izjava o sukobu interesa. Uz rukopis se prilaže izjava svih autora kojom se izjašnjavaju o svakom mogućem interesu ili izjava da nemaju sukob interesa. Za dodatne informacije o različitim vrstama sukoba interesa videti na internet stranici Svetskog udruženja urednika medicinskih časopisa (World Association of Medical Editors – WAME; http://www.wame.org) pod "Politika izjave o sukobu interesa".

Autorstvo. Sve osobe koje su navedene kao autori rada treba da se kvalifikuju za autorstvo. Svaki autor treba da je učestvovao dovoljno u radu na rukopisu kako bi mogao da preuzme odgovornost za celokupan tekst i rezultate iznesene u radu. Autorstvo se zasniva samo na: bitnom doprinosu koncepciji rada, dobijanju rezultata ili analizi i tumačenju rezultata; planiranju rukopisa ili njegovoj kritičkoj reviziji od znatnog intelektualnog značaja; u završnom doterivanju verzije rukopisa koji se priprema za štampanje.

Autori treba da prilože opis doprinosa u rukopisu za svakog koautora pojedinačno. Finansiranje, sakupljanje podataka ili generalno nadgledanje istraživačke grupe sami po sebi ne mogu opravdati autorstvo. Svi drugi koji su doprineli izradi rada, a koji nisu autori rukopisa, trebalo bi da budu navedeni u zahvalnici s opisom njihovog rada, naravno, uz pisani pristanak.

Naslovna strana. Na posebnoj, prvoj stranici rukopisa treba navesti sledeće: naslov rada bez skraćenica; puna imena i prezimena autora (bez titula)indeksirana brojevima; zvaničan naziv ustanova u kojima autori rade, mesto i državu (redosledom koji odgovara indeksiranim brojevima autora); na dnu stranice navesti ime i prezime, adresu za kontakt, broj telefona, faksa i e-mail adresu autora zaduženog za korespondenciju.

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UPUTSTVO AUTORIMA

Kratak sadržaj.Uz originalni rad, saopštenje, pregled literature, prikaz bolesnika, rad iz istorije medicine, rad za rubriku "Jezik medicine" i rad za praksu, na posebnoj stranici treba priložiti kratak sadržaj rada obima 100-250 reči. Za originale radove kratak sadržaj treba da ima sledeću strukturu: Uvod, Cilj rada, Metode rada, Rezultati, Zaključak; svaki od navedenih segmenata pisati kao poseban pasus koji počinje boldovanom reči. Navesti najvažnije rezultate (numeričke vrednosti) statističke analize i nivo značajnosti. Za prikaze bolesnika kratak sadržaj treba da
ima sledeće: Uvod, Prikaz bolesnika, Zaključak; segmente takođe pisati kao poseban pasus koji počinje boldovanom reči. Za ostale tipove radova kratak sadržaj nema posebnu strukturu.

Ključne reči. U Ključnim rečima ne treba da se ponavljaju reči iz naslova, a treba da budu relevantne ili opisne. Ispod kratkog sadržaja navesti ključnereči (od tri do šest). U izboru ključnih reči koristiti Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).

Prevod na engleski jezik. Na posebnoj stranici priložiti naslov rada na engleskom jeziku, puna imena i prezimena autora (bez titula) indeksirana brojevima, zvaničan naziv ustanova na engleskom jeziku, mesto i državu. Na sledećoj posebnoj stranici priložiti sažetak na engleskom jeziku (Summary) sa ključnim rečima (Keywords), i to za radove u kojima je obavezan kratak sadržaj na srpskom jeziku, koji treba da ima 100-250 reči. Za originalne radove (Original articles) sažetak na engleskom treba da ima sledeću strukturu: Introduction, Objective, Methods, Results, Conclusion; svaki odnavedenih segmenata pisati kao poseban pasus koji počinje boldovanom reči. Za prikaze bolesnika (Case reports) sažetak na engleskom treba da sadrži sledeće: Introduction, Case outline,Conclusion; segmente takođe pisati kao poseban pasus koji počinje boldovanom reči. Prevesti nazive tabela, grafikona, slika, shema, celokupni srpski tekst u njima i legendu.

Treba se pridržavati jezičkog standarda BritishEnglish. Radovi koji se u celini dostave na engleskom jeziku imaju prioritet u objavljivanju.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano. Originalni rad treba da ima sledeće podnaslove: Uvod, Cilj rada, Metode rada, Rezultati, Diskusija, Zaključak, Literatura. Pregled literature čine: Uvod, odgovarajući podnaslovi, Zaključak, Literatura. Autor preglednog rada mora da navede bar pet autocitata (reference u kojima je bio prvi autor ili koautor rada) radova publikovanih u časopisima sa recenzijom. Koautori,ukoliko ih ima, moraju da navedu bar jedan autocitat radova takođe publikovanih u časopisima sa recenzijom. Prikaz bolesnika čine: Uvod, Prikaz bolesnika, Diskusija, Literatura. Ne treba koristiti imena bolesnika ili inicijale, brojeve istorije bolesti, naročito u ilustracijama. Prikazi bolesnika ne smeju imati više od sedam autora.

Skraćenice. Koristiti samo kada je neophodno, i to za veoma dugačke nazive hemijskih jedinjenja, odnosno nazive koji su kao skraćenice već prepoznatljivi (standardne skraćenice, kao npr. DNK, sida, HIV, ATP). Za svaku skraćenicu pun termin treba navesti pri prvom navođenju u tekstu, sem ako nije standardna jedinica mere. Ne koristiti skraćenice u naslovu. Izbegavati korišćenje skraćenica u kratkom sadržaju, ali ako su neophodne, svaku skraćenicu ponovo objasniti pri prvom navođenju u tekstu.

Decimalni brojevi. U tekstu rada na srpskom decimalne brojeve pisati sa zarezom, a u tekstu na engleskom, u tabelama, na grafikonima i drugim prilozima, budući da se i u njima navodi i prevod na engleskom jeziku, decimalne brojeve pisati sa tačkom (npr. u tekstu će biti 12,5±3,8, a u tabeli
12.5±3.8). Kad god je to moguće, broj zaokružiti na jednu decimalu.

Jedinice mera. Dužinu, visinu, težinu i zapreminu izražavati u metričkim jedinicama (metar m, kilogram – kg, litar – l) ili njihovim delovima. Temperaturu izražavati u stepenima Celzijusa (°C), količinu supstance u molima (mol), a pritisak krvi u milimetrima živinog stuba (mm Hg). Sve rezultate hematoloških, kliničkih i biohemijskih merenja navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).

Obim rukopisa. Celokupni rukopis rada – koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku – mora iznositi za originalni rad,
saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak i rad za "Jezik medicine" do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu Word kroz podmeniTools–Word Count ili File–Properties–Statistics.

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Tabele. Svaka tabela treba da bude sama po sebi jasno razumljiva. Naslov treba otkucati iznad tabele, a objašnjenja ispod nje. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom na srpskom i engleskom jeziku (Table). Tabele raditi isključivo u programu Word, kroz meni Table–Insert–Table, uz definisanje tačnog broja kolona i redova koji će činiti mrežu tabele. Desnim klikom na mišu – pomoću opcija Merge Cells i Split Cells – spajati, odnosno deliti ćelije. U jednu tabelu, u okviru iste ćelije, uneti i tekst na srpskom i tekst na engleskom jeziku – nikako ne praviti dve tabele sa dva jezika! Kucati fontom Times New Roman, veličinom slova 12 pt, sa jednostrukim proredom i bez uvlačenja teksta. Korišćene skraćenice u tabeli treba objasniti u legendi ispod tabele na srpskom i engleskom jeziku. Svaku tabelu odštampati na posebnom listu papira i dostaviti po jedan primerak uz svaku kopiju rada (ukupno tri primerka tabele za rad koji se predaje).

Slike. Slike se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom na srpskom i engleskom jeziku (Figure). Za svaku sliku dostaviti tri primerka ili tri seta u odvojenim kovertama. Primaju se isključivo originalne fotografije (crno-bele ili u boji), na sjajnom (glatkom, a ne mat) papiru, po mogućstvu formata 9×13 cm ili 10×15 cm. Na poleđini svake slike staviti nalepnicu sa rednim brojem slike i strelicom koja označava gornji deo slike. Voditi računa da se fotografije ne oštete na bilo koji način. Slike snimljene digitalnim fotoaparatom dostaviti na CD i odštampane na papiru, vodeći računa o kvalitetu (oštrini) i veličini digitalnog zapisa. Rezolucija treba da bude 300dpi, format slike 10×15 cm, a format zapisa .JPG ili .TIFF. Ukoliko autori nisu u mogućnosti da dostave originalne fotografije, treba ih skenirati kao Grayscaleu rezoluciji 300 dpi i u originalnoj veličini i snimiti na CD.
Slike se mogu objaviti u boji, ali dodatne troškove štampe snosi autor.

Grafikoni. Grafikoni treba da budu urađeni i dostavljeni u programu Excel, da bi se videle prateće vrednosti raspoređene po ćelijama. Iste grafikone linkovati i u Word-ov dokument, gde se grafikoni označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom na srpskom i
engleskom jeziku (Graph). Svi podaci na grafikonu kucaju se u fontu Times New Roman, na srpskom i engleskom jeziku. Korišćene skraćenice na grafikonu treba objasniti u legendi ispod grafikona na srpskom i engleskom jeziku. Svaki grafikon odštampati na posebnom listu papira i dostaviti po jedan primerak uz svaku kopiju rada (ukupno tri primerka za rad koji se predaje).

Sheme (crteži). Sheme raditi u programu Corel Drawili Adobe Illustrator(programi za rad sa vektorima, krivama). Svi podaci na shemi kucaju se u fontu Times New Roman, na srpskom i engleskom jeziku (Scheme, Drawing), veličina slova 10 pt.Korišćene skraćenice na shemi treba
objasniti u legendi ispod sheme na srpskom i engleskom jeziku. Svaku shemu odštampati na posebnom listu papira i dostaviti po jedan primerak uz svaku kopiju rada (ukupno tri primerka za rad koji se predaje).

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