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SADRŽAJ/CONTENTS

ORIGINALNI RADOVI / ORIGINAL ARTICLES

STRUČNI RADOVI / PROFESSIONAL ARTICLES

PRIKAZ SLUČAJA / CASE REPORTS

THE PREVALENCE OF ALCOHOL CONSUMPTION AMONG STUDENTS AT THE UNIVERSITY OF BELGRADE

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SUMMARY

I**ntroduction/Objective** The objective of this study was to determine the prevalence of alcohol use in the student population of the University of Belgrade.
Methods The cross-sectional study was conducted in a population of 2,000 students of the Belgrade University. Four faculties (Medicine, Geography, Economics, Electrical Engineering) from which the students participating in this research were chosen by the method of random choice (by computer listing), conducted in the period April - June 2010.
Results Among our respondents, the highest amount of spirits is consumed by respondents from the Faculty of Electrical Engineering, with 22% of them consuming more than 6 shots on each occasion, while the smallest number of students who drink more than 6 shots on each occasion are from the Faculty of Economics, with 8%. Students from the Faculty of Electrical Engineering, who have the lowest prevalence of cigarette use, consume alcohol in a binge drinking pattern. The highest frequency of binge drinking in the past year and in the past month before the survey was among respondents from the Faculty of Geography.
Conclusion There is a need for developing a conscience about all the effects that alcohol has, especially physical ones which are not usually noticed immediately; taking responsibility for own actions; working on a healthy life style and educating people to enhance and improve their health control.

Keywords: Alcohol, University students, prevalence.

SRPSKI

PREVALENCIJA UPOTREBE ALKOHOLA MEĐU STUDENTIMA UNIVERZITETA U BEOGRADU

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SAŽETAK

Uvod/cilj Cilj ove studije je bio da se odredi prevalencija upotrebe alkohola u studentskoj populaciji Univerziteta u Beogradu.
Metode Sprovedena je studija preseka u populaciji od 2 000 studenata Univerziteta u Beogradu. Četiri fakulteta (Medicinski, Geografski, Ekonomski, Elektrotehnički),čiji su studenti učestvovali u ovom istraživanju u periodu april-jun 2010. godine, bila su izabrana metodom slučajnog izbora (preko kompjuterskog listinga).
Rezultati Među našim ispitanicima, najveću količinu žestokog pića konzumiraju ispitanici sa Elektrotehničkog fakulteta, pri čemu 22% njih konzumira više od 6 čašica u svakoj prilici, dok je najmanji broj studenata koji piju više od 6 čašica u svakoj prilici sa Ekonomskog fakulteta, njih 8%. Studenti Elektrotehničkog fakulteta, koji imaju najnižu prevalenciju upotrebe cigareta, konzumiraju alkohol po „binge" obrascu. Najveća učestalost opijanja u poslednjih godinu dana i poslednjih mesec dana pre anketiranja bila je među ispitanicima sa Geografskog fakulteta.
Zaključak Postoji potreba za razvijanjem svesti o svim efektima koje alkohol ima, posebno fizičkim, koji se obično ne uočavaju odmah, preuzimanjem odgovornosti za vlastite postupke, radom na zdravom načinu života i edukacijom ljudi kako bi se poboljšala kontrola zdravlja.

Ključne reči: Alkohol, studenti, prevalencija.

INTRODUCTION

The World Health Organization (WHO) identified several factors that influence alcohol consumption, including gender, age, health status, economic wealth, lifestyle choices, religion, and cultural norms. In three regions, more than half of the population has consumed alcohol: 59.9% in the European Region, 54.1% in the Region of the Americas, and 53.8% in the Western Pacific Region (1). Alcohol is linked to more than 200 diseases and results in various negative social consequences. The global death toll from all causes increased from 53.5 million in 2010 to 56.4 million in 2016 (1). The results revealed that the majority of people preferred drinking beer (57.7%), followed by alcohol-based smoothies (22.2%). This may be because beer is easily accessible to students, offering a low price and a lighter taste and alcohol content compared to spirits. Additionally, alcohol smoothies, which combine liquor with sweetened drinks, are popular for their appealing flavor and the fact that drinkers don't feel overly intoxicated (2).

Unhealthy alcohol consumption is a significant public health issue, contributing to high rates of morbidity and mortality, and is the leading health risk factor for individuals aged 15-49 worldwide. Students' social environments and academic pressures often promote unhealthy behaviors, including excessive alcohol use; as a result, they typically consume more alcohol than their non-student peers of the same age (3).

Adolescence and youth are periods marked by significant changes in the formation, adoption, or abandonment of consumption habits and lifestyles. Studying the use of substances, such as alcohol, is essential at this stage because of the long-term effects this consumption can have in adulthood (4).

Personal maturation, transitioning to university or the workforce, and the family or social environment are key factors in reinforcing these habits. In particular, family socialization forms the foundation for the development of an individual's personality, attitudes, values, and self-concept (4). Several international studies have found that a family history of alcohol use, along with a background of family dysfunction, increases the likelihood of risky alcohol consumption among young people (5).

Numerous international studies have examined alcohol consumption patterns among university students [6,7,8]. While the prevalence of hazardous drinking and binge drinking varies across different regions, there is a noticeable increase in binge drinking within this population. Research consistently indicates that young people tend to drink more during late adolescence and early adulthood, with young adults being particularly susceptible to binge drinking (9). Therefore, beyond identifying alcohol consumption in this group, it is crucial to understand the pattern of consumption, as the type of alcohol intake plays a key role in the development of alcohol-related issues (9).

The aim of our study is to determine the prevalence of alcohol use in the student population of the University of Belgrade.

METHODS

A cross-sectional study was conducted with a sample of 2,000 students from the University of Belgrade. The participants were randomly selected (via computer listing) from four faculties—Medicine, Geography, Economics, and Electrical Engineering—during the period of April to June 2010. An equal number of students from each faculty, representing different academic years, were surveyed on the day they attended practical training.

The primary data collection tool was a standardized epidemiological questionnaire developed at the Institute of Epidemiology, Faculty of Medicine in Belgrade, which has been used in similar studies. The questionnaire covered demographic information (such as gender, age, faculty and year of study, place of residence, and parents' education) as well as behavioral characteristics (including reasons for starting the habit and attitudes towards its harmful effects). A specific section of the questionnaire focused on alcohol consumption.

To assess depression and anxiety, the Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Rating Scale (HAMA) were used, with evaluations conducted by a psychiatrist. Participation was voluntary and anonymous. The study was approved by the Institutional Review Board, and informed consent was obtained from all students who chose to participate.

RESULTS

A total of 2,000 students from the University of Belgrade participated in the study, consisting of 860 (43%) males and 1,140 (57%) females. The average age of the participants was 21.5 years. An equal number of students (500) from each faculty and academic year were included in the survey. The response rate was 99.8%.

Table 1 shows the distribution of respondents by faculty in relation to the frequency of alcohol consumption. It was observed that the highest number of students who never consume alcohol is from the Faculty of Medicine (26.5%). The largest proportion of students who drink once a month is also from this faculty, compared to the others (43.1%). The table further reveals that the highest frequency of alcohol consumption is among students of the Faculty of Electrical Engineering, while the lowest is among students of the Faculty of Medicine. A statistically significant difference in the frequency of alcohol consumption was found among the surveyed students, with a X^2 test result of (X^2=127.9; p=0.001).

Table 1. Distribution of respondents by faculty in relation to alcohol consumption frequency

Faculty	Frequency of alcohol consumption										Total	
	never		1 per month		2-4 times per month		2-3 times per week		4 or more times per week			
	N	%	N	%	N	%	N	%	N	%	N	%
Medicine	129	26.5	210	43.1	124	25.5	20	4.1	4	0.8	487	100
Geography	96	19.6	169	34.5	157	32.0	57	11.6	11	2.2	490	100
Economics	98	19.8	194	39.3	146	29.6	46	9.3	10	2.0	494	100
Electrical Engineering	50	10.1	149	30.2	173	35.1	104	21.1	17	3.4	493	100
Total	373	19.0	722	36.8	600	30.5	227	11.6	42	2.1	1964	100

Table 2 presents the quantity of strong alcohol consumed in relation to the surveyed faculties. It is observed that the highest number of shots of strong alcohol are consumed by respondents from the Faculty of Electrical Engineering, with 21.6% of them consuming more than 6 shots on each occasion. This amount is consumed by 9.2% of students from the Faculty of Medicine and 12.2% from the Faculty of Geography. The smallest proportion of students who drink more than 6 shots per occasion is from the Faculty of Economics, with 8.1%.

Analyzing the number of shots of strong alcohol among the surveyed students, a statistically significant difference was found using the X^2 test (X^2=23.7; p=0.005).

Table 2. Amount of hard liquor consumed

Faculty	Number of shots of hard liquor								Total	
	1-2 shots		3-4 shots		5-6 shots		more than 6 shots			
	N	%	N	%	N	%	N	%	N	%
Medicine	77	54.2	36	25.4	16	11.3	13	9.2	142	100
Geography	92	48.9	54	28.7	19	10.1	23	12.2	188	100
Economics	97	52.4	53	28.6	20	10.8	15	8.1	185	100
Electrical Engineering	112	41.6	68	25.3	31	11.5	58	21.6	269	100
Total	378	48.2	211	26.9	86	11	109	13.9	784	100

Table 3 presents the quantity of wine consumed in relation to the surveyed faculties. It is observed that the highest number of students from the Faculty of Medicine drink 1-2 glasses of wine (72%), while the largest number of students from the Faculty of Geography consume 5-6 glasses of wine on one occasion. Additionally, the highest proportion of students from the Faculty of Electrical Engineering drink 7-9 glasses of wine, and even more than 10 glasses (4.8% and 6%, respectively).

Analyzing the number of glasses of wine among the surveyed students, a statistically significant difference was found using the X^2 test (X^2=49.1; p=0.001).

Table 3. Amount of wine consumed

Faculty	Number of glasses of wine										Total	
	1-2 glasses		3-4 glasses		5-6 glasses		7-9 glasses		more than 10			
	N	%	N	%	N	%	N	%	N	%	N	%
Medicine	201	72.0	57	20.4	14	5.0	5	1.8	2	0.7	279	100
Geography	165	55.4	78	26.2	37	12.4	8	2.7	10	3.4	298	100
Economics	191	63.7	70	23.3	22	7.3	7	2.3	10	3.3	300	100
Electrical Engineering	154	48.9	89	28.3	38	12.1	15	4.8	19	6.0	315	100
Total	711	59.6	294	24.7	111	9.3	35	2.9	41	3.4	1192	100

The quantity of beer consumed in relation to the surveyed faculties is shown in Table 4. The results indicate that the highest number of students from the Faculty of Medicine drink 1-2 glasses of beer (54.2%), while the largest proportion of respondents from the Faculty of Geography consume 5-6 and 7-9 glasses of beer (17.4% and 10.3%, respectively). The highest number of students from the Faculty of Electrical Engineering drink more than 10 glasses of beer on one occasion.

Tabela 4. Amount of beer consumed

Faculty	Number of glasses of beer										Total	
	1-2 glasses		3-4 glasses		5-6 glasses		7-9 glasses		more than 10			
	N	%	N	%	N	%	N	%	N	%	N	%
Medicine	103	54.2	44	23.2	24	12.6	11	5,8	8	4.2	190	100
Geography	88	34.8	66	26.1	44	17.4	26	10,3	29	11.5	253	100
Economics	110	48.0	61	26.6	33	14.4	11	4.8	14	6.1	229	100
Electrical Engineering	108	29.7	108	29.7	61	16.8	36	9.9	51	14.0	364	100
Total	409	39.5	279	26.9	162	15.6	84	8.1	102	9.8	1036	100

Analyzing the number of glasses of beer among students from these four faculties, a statistically significant difference was found using the X^2 test (X^2=52.9; p=0.001).

The distribution of respondents by faculty in relation to the frequency of consuming 6 or more glasses of alcohol on one occasion is shown in Table 5. It is observed that the highest proportion of respondents who never drink 6 or more glasses of alcohol on one occasion is from the Faculty of Medicine (73.5%), while the highest number of respondents from the Faculty of Electrical Engineering consume alcohol once a month, 2-3 times a week, and 4 or more times a week (50.7%, 8.9%, and 1.7%, respectively). A statistically significant difference was found among the surveyed students regarding the frequency of consuming 6 or more glasses of alcohol on one occasion, as determined by the X^2 test (X^2=145.0; p=0.001).

Table 5. Distribution of respondents by faculty based on the frequency of consuming 6 or more drinks in one occasion

Faculty	Frequency of consuming 6 or more drinks in one occasion								Total	
	never		1 per month or less		2-3 times per week		4 or more times per week			
	N	%	N	%	N	%	N	%	N	%
Medicine	352	73.5	120	25.1	5	1.0	2	0.4	479	100
Geography	273	58.0	171	36.3	23	4.9	4	0.8	471	100
Economics	301	64.5	151	32.3	15	3.2	0	0.0	467	100
Electrical Engineering	187	38.7	245	50.7	43	8.9	8	1.7	483	100
Total	1113	58.6	687	36.2	86	4.5	14	0.7	1900	100

The distribution of respondents by faculty in relation to the frequency of drunkenness in the year prior to the study is shown in Table 6. It was observed that during this period, 67.5% of medical students did not get drunk at all. The highest number of respondents from the Faculty of Electrical Engineering reported getting drunk once a month and 2-3 times a week (53.8% and 10.4%, respectively). However, the largest proportion of students who got drunk 4 or more times a week in the past year were from the Faculty of Geography (1.5%), followed by the Faculty of Electrical Engineering (1.2%), the Faculty of Economics (0.8%), and the fewest were from the Faculty of Medicine (0.4%). A statistically significant difference was found among students from the selected faculties regarding the frequency of drunkenness in the past year, as determined by the X^2 test (X^2=126.0; p=0.001).

Table 6. Distribution of respondents by faculty based on the frequency of binge drinking in the past year in relation to the survey

Faculty	Frequency of binge drinking in the past year								Total	
	never		1 per month or less		2-3 times per week		4 or more times per week			
	N	%	N	%	N	%	N	%	N	%
Medicine	324	67.5	145	30.2	9	1.9	2	0.4	480	100
Geography	230	47.7	217	45.0	28	5.8	7	1.5	482	100
Economics	268	55.7	191	39.7	18	3.7	4	0.8	481	100
Electrical Engineering	166	34.5	259	53.8	50	10.4	6	1.2	481	100
Total	988	51.4	812	42.2	105	5.5	19	1.0	1924	100

Table 7 shows the distribution of respondents by faculty in relation to the frequency of drunkenness in the month prior to the survey. As seen from the table results, medical students are ranked last in terms of drunkenness in the past month, with 80.5% not getting drunk during that period. The highest number of respondents from the Faculty of Electrical Engineering reported getting drunk once a month and 2-3 times a week in the month prior to the study (29.4% and 9.5%, respectively). Students from the Faculty of Geography were the most likely to get drunk 4 or more times a week, with 1.5%, followed by students from the Faculty of Electrical Engineering (1.2%), and finally, an equal number of students from the Faculty of Economics and the Faculty of Medicine (0.4% each). A statistically significant difference was found among the surveyed students regarding the frequency of drunkenness in the past month, as determined by the X^2test (X^2=67.1; p=0.001).

Table 7. Distribution of respondents by faculty based on the frequency of binge drinking in the past month in relation to the survey

Faculty	Frequency of binge drinking in the past month								Total	
	never		1 per month or less		2-3 times per week		4 or more times per week			
	N	%	N	%	N	%	N	%	N	%
Medicine	389	80.5	78	16.1	14	2.9	2	0.4	483	100
Geography	301	63.1	134	28.1	35	7.3	7	1.5	477	100
Economics	350	73.1	106	22.1	21	4.4	2	0.4	479	100
Electrical Engineering	289	59.8	142	29.4	46	9.5	6	1.2	483	100
Total	1329	69.1	460	23.9	116	6.0	17	0.9	1922	100

In our study, according to HAMD, correlation was not found between this harmful habit and depression (ρ=-0,028; p=0,219). According to HAMA, correlation was found between alcohol consumption and anxiety (ρ=-0,057; p=0,015).

DISCUSSION

In our study, on average, 19% of students never consume alcohol. The largest group of students, approximately 37%, consumes alcohol once a month. It was noted that the highest percentage of respondents who never consume alcoholic beverages are students of the Faculty of Medicine (around 27%). At the Faculty of Medicine, University of Zagreb, this number is significantly lower, at around 17% (10).

In our study, the largest number of students from the Faculty of Medicine (around 43%) drink alcohol once a month, compared to others. However, at the Faculty of Medicine in Calgary, Canada, the trend of alcohol consumption is higher than in our case. In this city, 86% of medical students currently consume alcoholic beverages (11).

In a study conducted among student populations from seven European countries, based on questionnaire analysis, it was found that the highest proportion of students who do not consume alcohol at all or only occasionally are those living in Turkey (73% of men and 88% of women), while these proportions are highest among the Danes (8% of men and 15% of women) (12).

Among our respondents, an average of around 14% consume alcohol more than once a week, while this percentage is higher among Spanish (49%:64%, in favor of women) and Bulgarian students (46%:28%, in favor of male respondents) (12). However, our respondents have a higher frequency of alcohol consumption compared to Polish (13%) and Turkish students (11%) (12). In our study, among respondents from the Faculty of Medicine, more than 5% drink more than twice a week, while in Zagreb, nearly 14% of respondents from the Faculty of Medicine consume alcohol this frequently (10).

In our study, an average of around 48% of respondents consume one to two drinks of strong alcohol on each occasion, while 27% of students consume 3-4 drinks. On average, 11% of students drink five to six drinks, and about 14% consume more than six drinks on each occasion. Consuming six or more drinks in one sitting is considered excessive episodic alcohol consumption or "binge drinking," defined as consuming five or more drinks on one occasion for males and four or more drinks for females (13).

Among our respondents, the highest number of drinks of strong alcohol is consumed by students from the Faculty of Electrical Engineering, with 22% of them consuming more than 6 drinks on each occasion. The lowest percentage of students who drink more than 6 drinks per occasion is from the Faculty of Economics, with only 8% (a statistically significant difference, p=0.005). Interestingly, students from the Faculty of Electrical Engineering, who have the lowest prevalence of cigarette use, consume alcohol according to a "binge" drinking pattern.

In Canada, at the Faculty of Medicine, among 86% of current drinkers, the majority (81%) consume fewer than 11 drinks per week, while 15% of men and 1% of women consume 11 or more drinks in the same period (11). In Zagreb, among students at the Faculty of Medicine, 70% reported consuming 3-4 drinks per month or less frequently (10). In Greece, male medical students consume an average of 92 milliliters of alcohol per week, while female students consume an average of 48 milliliters in the same period (14). In Orlando, a study conducted on a college student population found that the average number of drinks per week during the first three months of the study was 10, and 9 during the six-month period (15).

In a study conducted on a college student population in Fargo, North Dakota, male students consumed an average of 10 alcoholic drinks during the week prior to their 21st birthday, while female students consumed an average of 5 (16).

Alcohol consumption is also a common phenomenon among high school students, as evidenced by a study conducted in Georgia in 2007, where 38% of students reported current alcohol use, and 19% reported excessive consumption in the past month. Strong spirits were the most commonly consumed alcoholic beverages (44%) across all groups. Among those who reported current use, significantly more binge drinkers (54%) indicated that they typically consumed spirits, compared to non-binge drinkers (32%) ($p<0.001$). Beer was the second most commonly consumed beverage among high school students (24%), while sweet drinks were the second most common among female students (24%) (17).

The findings of our study show that, on average, 60% of students consume one to two glasses of wine in one sitting, 25% consume three to four glasses, 9% consume five to six glasses, 3% consume seven to nine glasses, and 3.4% consume more than ten glasses.

In Germany, adolescents aged 16-17 consume an average of 2.5 bottles of wine per week, which is significantly higher than the consumption by female adolescents (13).

It is observed that the majority of students from the Faculty of Medicine (72%) drink one to two glasses of wine per sitting. The largest number of students from the Faculty of Geography consume five to six glasses of wine in one sitting, while the highest percentage of students from the Faculty of Electrical Engineering drink seven to nine glasses or even more than ten (4.8%, 6%).

In one sitting, around 40% of our respondents consume one to two glasses of beer, about 27% of students consume three to four glasses, around 16% consume five to six glasses, about 8% consume seven to nine glasses, and around 10% consume more than ten glasses.

The largest number of students from the Faculty of Medicine (about 54%) drink one to two glasses of beer in one sitting, while the highest number of respondents from the Faculty of Geography consume five to six and seven to nine glasses of beer (about 17% and 10%, respectively). The highest percentage of respondents from the Faculty of Electrical Engineering consume more than ten glasses of beer in one sitting. In Germany, in 2007, the average male adolescent aged 16-17 consumed this amount of beer weekly (11 glasses of 0.3 liters) (13).

In Georgia, a study conducted on a sample of high school students found that among current drinkers, beer was the second most commonly consumed alcoholic beverage among male students (24%), right after spirits (17).

Our study revealed that about 36% of students consume alcohol according to a "binge" pattern once a month or less frequently, while 4.5% of students consume this amount 2-3 times per week, and 0.7% drink four or more times a week.

It is observed that the highest percentage of respondents who never drink 6 or more drinks in one sitting is at the Faculty of Medicine (around 74%), while the largest number of respondents from the Faculty of Electrical Engineering consume this amount of alcohol once a month, 2-3 times a week, and 4 or more times a week (around 51%, 9%, and 2%, respectively).

In a study conducted on the student population at the University of Central Florida in Orlando, 28% of students reported heavy drinking. It was found that, both in the three-month and six-month period, the maximum number of drinks consumed in one sitting was eight. On average, students experienced one episode of drunkenness per week during both the three-month and six-month periods (15). A study by Toumbourou et al. (2009) demonstrates that both elementary and high school students excessively consume alcohol. In Washington state, 0.5% of male and 0.3% of female 7th-grade students engage in binge drinking, while in the 1st year of high school, the ratio is 2.4% for boys and 2.2% for girls (18).

In Victoria, according to this pattern, 2.6% of boys and 1.5% of girls in Grade 7 drink alcohol, while in the first year of high school, the ratio is as follows: 6.5% boys and 6.6% girls (18).

In relation to the frequency of intoxication in the past year, a statistically significant difference was found between faculties ($p=0.001$) in our study. Around 51% of respondents reported never getting drunk during this period (the highest percentage being at the Faculty of Medicine, around 68%). About 42% of respondents got drunk once a month or less frequently, 5.5% got drunk 2-3 times a week, and 1% got drunk four or more times a week.

The largest number of respondents from the Faculty of Electrical Engineering got drunk once a month and 2-3 times a week (54% and 10%, respectively). However, the highest percentage of respondents who got drunk four or more times a week in the past year were from the Faculty of Geography (1.5%), followed by the Faculty of Electrical Engineering (1.2%), the Faculty of Economics (0.8%), and the smallest percentage were from the Faculty of Medicine (0.4%).

In other countries, the prevalence of this psychoactive substance use over the past year was also high.

In Washington, in the year prior to the study, the prevalence of alcohol consumption among boys in grade 5 was 10%, and among girls, it was 5%. In Victoria, Australia, the prevalence was 34% for boys and 21% for girls (18).

In relation to the frequency of intoxication in the past month, a statistically significant difference was found between faculties ($p=0.001$) in this study. During this period, around 69% of students did not get drunk at all (the highest percentage being from the Faculty of Medicine, around 81%). About 24% of respondents got drunk once a month or less frequently, 6% of students got drunk 2-3 times a week, and around 1% got drunk four or more times a week.

The highest number of respondents from the Faculty of Electrical Engineering got drunk once a month and 2-3 times a week in the month prior to the study (around 29% and 10%, respectively). Students from the Faculty of Geography were the most likely to get drunk four or more times a week (1.5%), followed by students from the Faculty of Electrical Engineering (1.2%), and an equal number of students from the Faculty of Economics and the Faculty of Medicine, both at 0.4%.

In Orlando, during the month prior to the study conducted in 2005 and 2006, college students reported an average of 9 days of alcohol consumption, with 5 of those days involving heavy drinking (five or more drinks in one sitting for men, and four or more for women) (15).

In Germany, in 2007, the monthly prevalence of excessive drinking among boys aged 15-16 was as follows: 25% of boys consumed alcohol according to a "binge" pattern once or twice a month, 21% drank 3-5 times, 8.5% drank 6-9 times, and 10% drank at least 10 times a month (13).

A high prevalence in the month prior to the study was observed in São Paulo, Brazil, among a sample of students aged 10 to over 18, where the alcohol consumption prevalence rate was 48% (19).

In Washington State, in the month prior to the study, higher prevalence rates of alcohol use were recorded among female students in both elementary and high school. In grade 7 of elementary school, the rates were 11.5% for boys and 13% for girls, in favor of girls, while in the first year of high school, the rates were 23% for boys and 26% for girls, again in favor of girls (18).

In Victoria, the prevalence of alcohol use in grade 7 in the month prior to the study was significantly higher compared to Washington, at 35% for boys and 27% for girls, in favor of boys, while in the first year of high school, the rates were 53% for boys and 55% for girls, in favor of girls (18).

CONCLUSION

n the summary, among our respondents, the highest quantity of spirits is consumed by students from the Faculty of Electrical Engineering, while the lowest number of students who drink more than 6 glasses on each occasion is from the Faculty of Economics.

Students from the Faculty of Electrical Engineering, who have the lowest prevalence of cigarette use, consume alcohol according to the "binge" drinking pattern.

The highest frequency of drunkenness in the last year and in the last month prior to the survey was observed among respondents from the Faculty of Geography.

This study highlighted the prevalence of alcohol consumption among Belgrade University students. Based on that, there is a need for developing a conscience about all the effects that alcohol has, especially physical ones which are not usually noticed immediately; taking responsibility for own actions, because alcohol harms not only the alcohol users, but also harm their families; working on a healthy life style and educating people to enhance and improve their health control.

As our students start with this habit earlier than students in other countries, alcohol-related preventive efforts, would be of vital impact in preventing exposure to alcohol or minimizing alcohol-related health hazards.

Declaration of interest

The authors report no conflicts of interest.

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PREPORUKE ZA PRISTUP PACIJENTIMA SA POREMEĆAJIMA FUNKCIJE ŠTITNE ŽLEZDE U STOMATOLOŠKOJ ORDINACIJI

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SAŽETAK

Hormoni štitne žlezde, tiroksin i trijodtironin, utiču na rad svih organa i organskih sistema. Bilo da su u ekscesu ili u deficitu, dovode do značajnih poremećaja homeostaze organizma, menjajući u prvom redu metaboličke procese i dovodeći do značajnih kliničkih manifestacija, pre svega od strane kardiovaskularnog, ali i drugih organskih sistema. Disbalans tireoidnih hormona takođe ima i oralne manifestacije, koje su često razlog dolaska pacijenata kod stomatologa. Međutim, ono što najviše brine stomatologe jeste mogućnost akutne dekompenzacije hiper ili hipotireoze, sa pojavom tireotoksične oluje ili miksedemske kome, koje predstavljaju vitalno ugrožavajuća stanja. Zbog toga je od velike važnosti valjana preproceduralna evaluacija i priprema pacijenata sa poremećajima funkcije tireoidnih hormona za pre planirane stomatološke intervencije. Tokom dentalnih procedura potrebno je pridržavati se preporuka po pitanju izbora lokalnih anestetika, hemostaze, intereakcije lekova, mogućnosti infekcije i minimiziranja stresa, a sve u cilju izbegavanja akutne dekompenzacije tireoidnog disbalansa.

Ključne reči: tireoidni hormoni, oralne manifestacije, tireotoksična oluja, miksedemska koma

ENGLISH

RECOMMENDATIONS FOR THE APPROACH TO PATIENTS WITH DISORDERS OF THYRIOD GLAND FUNCTION IN THE DENTAL OFFICE

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ABSTRACT

Thyroid hormones, thyroxine and triiodothyronine, affect the work of all organs and organ systems. Whether they are in excess or in deficit, they lead to significant disturbances in the homeostasis of the organism, changing first of all the metabolic processes and leading to significant clinical manifestations, primarily in the cardiovascular, but also in other organ systems. The imbalance of thyroid hormones also has oral manifestations, which are often the reason why patients visit the dentist. However, what worries dentists the most is the possibility of acute decompensation of hyper or hypothyroidism, with the appearance of thyrotoxic storm or myxedema coma, which are life-threatening conditions. Therefore, a valid pre-procedural evaluation and preparation of patients with thyroid hormone function disorders for pre-planned dental interventions is of great importance. During dental procedures, it is necessary to adhere to recommendations regarding the choice of local anesthetics, hemostasis, drug interactions, the possibility of infection and minimizing stress, all in order to avoid acute decompensation of thyroid imbalance.

Key words: thyroid hormones, oral manifestations, thyrotoxic storm, or myxedema coma

UVOD

Štitna žlezda (lat. glandula thyroidea) je najveća endokrina žlezda u organizmu, teška oko 30 grama. Nalazi se sa prednje strane vrata, sastoji se od dva lobusa i istmusa koji podsećaju na štit, po čemu je i dobila ime. Luči tiroidne hormone (TH) – trijodtironin (T3) koji je aktivna forma hormona i prohormon tiroksin (T4) koji se na periferiji konvertuje u aktivnu formu T3. Sekrecija TH odvija se sistemom negativne povratne sprege, uz učešće tireostimulirajućeg hormona (TSH) hipofize i tireotropnog hormona hipotalamusa (1). TH se u cirkulaciji u velikoj meri vezuju za tireoglobuline (TG), a slobodne, nevezane frakcije (free, F) su odgovorne za kliničke manifestacije. Oboljenja štitne žlezde mogu, ali ne moraju, biti povezana sa poremećajima funkcije TH (2).
Tireotoksikoza je klinički sindrom koji nastaje kao posledica povećanih koncentracija TH u cirkulaciji i njihovog "toksičnog dejstva" na periferna tkiva. Hipertireoza je termin koji se često koristi kao sinonim za tireotoksikozu, ali to nije isto. Hipertireoza je širi pojam, koji obuhvata svako povišenje TH (što ne mora nužno biti povezano sa „toksičnim" uticajem na organe)(3). Hipotireoza predstavlja smanjeno lučenje i funkciju TH, a značajnim sniženjem TH nastaje miksedem. Prisutna su i druga oboljenja (tireoiditisi, tumori, strume), koja mogu, ali ne moraju biti u vezi hormonskog disbalansa. Pojmom tireoiditis obuhvaćena je grupa različitih upalnih bolesti štitne žlezde: akutni tireoiditis, subakutni granulomatozni (de Quervainov) tireoiditis, hronični (autoimuni) tireoiditis, limfocitni, postradijacijski, Riedelov tireoiditis i tireoiditis zbog uticaja nekih lekova. Tumori štitne žlezde mogu biti benigni (najčešće adenomi) i maligni - karcinomi (papilarni, folikularni, medularni, anaplastićni). Strume su uvećanja štitne žlezde i predstavljaju benignu, degenerativnu bolest, najčešće bez poremećaja hormonske funkcije (može praviti kompresivne i mehaničke smetnje na susedne organe), ali postoje i tzv. „toksične" strume, kada je povećano lučenje TH(4). Tireoidni hormoni deluju na sve vitalne organe i njihove funkcije, pa disbalans ovih hormona značajno utiče na opšte zdravstveno stanje (5). Zbog toga su poremećaji funkcije TH od mnogo većeg značaja u stomatološkoj praksi nego druge bolesti štitaste žlezde, koje nisu povezane sa disbalansom TH. Takođe, hormonski disbalans TH ostavlja posledice i na zdravlje zuba i drugih oralnih struktura. Ipak, sa stomatološkog stanovišta, najznačajnija je mogućnost pojave akutnih komplikacija disbalansa TH, koji u suštini predstavljaju naglu dekompenzaciju hipertireoze (tireotoksična oluja) ili hipotireoze (miksedemska koma). Zbog toga je važno napraviti adekvatnu preproceduralnu evaluaciju i pripremu pacijenata sa disbalansom TH, poznavati osnovne karakteristike ovih poremećaja, kako bi se blagovremeno posumnjalo na njihovu pojavu i preduzele odgovarajuće profilaktičke i kurativne mere.

Efekti tireoidnih hormona na vitalne funkcije

Tiroidni hormoni utiču na funkcionisanje svih vitalnih organa. Jedan od najznačajnijih efekata je na metabolizam (pospešuju ga i povećavaju potrošnju kiseonika), kako bazalni, tako i na metabolizam svih hranljivih materija (proteina, ugljenih hidrata, masti). Značajne efekte TH ostvaruju na kardiovaskularni sistem, respiratorni sistem, na bubrege, na transport kiseonika, na rast i razvoj tkiva, na nervni i reproduktivni sistem (4).
U hipertireozi, posebno je značajan uticaj ekscesa TH na kardiovaskularni sistem. Dolazi do povećanja srčane frekvence, udarnog volumena i volumena krvi, a smanjenja sistemskog vaskularnog otpora. To ima za posledicu povećanje srčanog rada i hipertrofiju miokarda, povećanje sistolnog arterijskog pritiska i pojavu poremećaja srčanog ritma. Najčešći poremećaj je sinusna tahikardija koja je prisutna kod > 40% bolesnika sa hipertireozom, a mogući su i atrijalna fibrilacija, ventrikularne ekstrasistole (VES). Takođe su mogući i drugi poremećaji i komplikacije, kao što su plućna hipertenzija, anginozne tegobe, tromboembolija Kliničke manifestacije efekata ekscesa TH na druge organe i organske sisteme, prezentuju se najčešće kao: pojačan apetit, praćen gibitkom telesne težine (zbog ubrzanog metabolizma), preosetljivost na toplotu i pojačano znojenje, nervoza, tremor, različiti očni znaci i simptomi (ptoza kapka, egzoftalmus, diplopije, bol, otoci). Gotovo svi pacijenti sa hipertireozom imaju i uvećanu štitnu žlezdu (struma). Mogući su (mada se ređe javljaju) i: ginekomastija, splenomegalija, dijareja, otok nogu, palmarni eritem, promene na koži (3). U lečenju se koriste tri grupe lekova, u skladu sa tri najvažnija cilja lečenja: 1) smanjenje sinteze TH (tireosupresivni lekovi - propiltiouracil i matimazol), 2) smanjenje oslobađanja već sintetisanih TH i uskladištenih u štirnoj žlezdi (preparati joda) i 3) antagonizovanje efekata TH koji su već oslobođeni u cirkulaciju (beta blokatori, najčešće propranolol) (7).
U hipotireozi simtomi i znaci su povezani sa usporenim metabolizmom. Najznačajnije kliničke manifesacije su hipotenzija, bradikardija, hipoventilacija, hipotermija, a može se javiti i adrenalna insuficijencija (u slučaju hipotenzije refraktarne na standardnu terapiju). Najznačajnije laboratorijske promene su: hematološki poremećaji (anemija, trombocitopenija poemećaji koagulacije), hipoglikemija i elektrolitni poremećaji (naročito hiponatremija). Ovi pacijenti dobijaju na telesnoj težini uprkos slabijem apetitu (zbog usporenog metabolizma), osećaju umor, slabost, usporenost (do letargije), imaju mijalgije, atralgije, menstrualne poremećaje, koža je suva, gruba i hladna, nokti su krti, kosa gruba, istanjena, opada, česti su periferni i periorbitalni edemi, a mogu biti prisutni i pleuralni i perikardni izlivi, opstipacija, promuklost, intolerancija hladnoće. Lečenje se bazira na primeni sintetskih TH (9.10).

Oralne manifestacije disbalansa TH

Kod pacijenata sa disbalansom TH dolazi do pojave oralnih manifestacija, kako kod hipertireoze, tako i kod hipotireoze. Na verovatnoću pojave oralnih manifestacija utiču starosno doba pacijenta, vreme trajanja i težina bolesti, pa su češće u slučajevima loše kontrolisane bolesti. Iako su oralne manifestacije disbalansa TH čest razlog odlaska pacijenata kod stomatologa, nikada nisu razlog nastanka hitnih stanja u stomatološkoj ordinaciji (11). Najznačajnije oralne manifestacije disbalansa TH prikazane su u tabeli 1.

Tabela 1. Oralne manifestacije disbalansa TH

Hipertiroidizam	Hipotiroidizam
1. Povećana sklonost ka karijesu 2.povećana sklonost ka parodontalnim bolestima 3.uvećanje ekstraglandularnog tiroidnog tkiva 4. Sindrom „gorućih" usta 5. Ubrzana erupcija zuba 6. maksilarna i mandibularna osteoporoza 7. Razvoj bolesti vezivnog tkiva (kao Sjorgen Sy ili SLE)	1. Uvećanje pljuvačnih žlezda 2. Makroglosija, glositis 3. Ugroženo zdravlje parodoncijuma - odložena resorpcija kostiju 4. Compromised periodontal health – delayed bone resorption 5. Odložena dentalna erupcija 6. Disgeusija 7. Otvoren prednji zagriz 8. Mikrognatija 9. Debele usne 10. Disanje na usta 11. Hipoplazija gleđi (manje izražena u trajnoj denticiji)

U hipertireozi, moguće je pojava sledećih oralnih manifestacija: sindrom „gorućih" (ili „peckajućih") usta, osteoporoza maksile i mandibule, povećanje ekstraglandularnog tkiva štitne žlezde, tremor usana i jezika, sklonost gingivalnom krvarenju, kserotomija idr. Uočeno je da je kod ovih pacijenata povećana incidenca karijesa i parodontalnih bolesti. Kod dece sa hipertireozom dolazi do prerane denticije (ubrzani gubitak mlečnih žlezda i ubrzana erupcija trajnih zuba). Hipertireoza potencira već postojeću parodontopatiju, pa ona prelazi u težu formu, sa jako izraženom supuracijom iz gingivalnih džepova. Povećana je aktivnost odontoblasta (direktna posledica povišenog T4), pa se stvara sekundanri dentin, dolazi do obliteracije koronarnog i radikularnog dela pulpe i proširenja oba dela kavuma pulpe. Pojava obliteracije pulpe i dentikula kod intaktnih zuba je najraniji stomatološki znak hipertireoidizma. Ova pojava često uzrok neobjašnjivih bolova u predelu pulpe, a tokom endototskog tretmana otežava prohodnost radikularnog dela kavuma pulpe (12).
U hipotireozi, često su prisutni: makroglosija, edem oralne sluznice, povećanje pljuvačnih žlezda, glositis, hipoplazija gleđi u mlečnoj i trajnoj denticiji, mikrognatija, disanje na usta, otvoreni zagriz, bleda oralna sluznica, zakasnelo nicanje zuba, disgeuzija i generalno, narušeno je parodontalno zdravlje. Od posebnog značaja, sa stomatološkog stanovišta, povećana je sklonost ka infekcijama usne duplje (najčešće Candidom albicans), prisutni su poremećaji hemostaze (povećana sklonost ka krvarenju) i usporeno zarastanje rana. (11,12)

Preproceduralna evaluacija pacijenata sa disbalansom TH

Prilikom preproceduralne evaluacije pacijenata sa dibalansom TH potrebno je imati u vidu da su stomatološke procedure i intervencije uglavnom elektivne, retko hitne, te da stomatolozi imaju dovoljno vremena na raspolaganju da se ovi pacijenti adekvatno pripreme. Obim preproceduralne evaluacije i pripreme zavisi od vrste poremećaja funkcije TH, težine i kontrole bolesti štitne žlezde (12).
Osnovni elementi preproceduralne evaluacije su: uvid u hormonski status, upoznavanje sa vrstom, težinom i dužinom trajanja bolesti,

terapijom koju prima, sagledavanje komorbiditeta koji su povezani sa disbalansom TH (ili nezavisni od njega), kao i procena potrebe za preproceduralnom konsultacijom sa endokrinologom (i/ili endokrinim hirurgom) (tabela 2). Najvažnije je da se postigne stabilno stanje bolesti, kako bi se minimizirao rizik od akutne dekompenzacije (13).

Tabela 2. Elementi preproceduralne evaluacije pacijenata sa disbalansom TH

Elementi evaluacije	Napomene – objašnjenja
Hormonski status	cilj: eutiroidno stanje ± 10%
Upoznavanje sa vrstom i težinom poremećaja TH i terapijom koju prima	dužina trajanja bolesti, poslednja kontrola kod endokrinologa
Razmotriti mogućnost nastanka akutnih kompliakcija tireoidnog disbalansa	Simptomi i znaci tireotoksične krize i miksedemske kome
Sagledati komorbiditete pacijenta	povezane sa disbalansom TH i ostale
Proceniti da li je potrebna konsultacija sa endokrinologom ili endokrinim hirurgom	ev. potreba za promenom terapije ili za tiroidektomijom pre stomatološke intervencije

Najvažnije je da vrednosti TH budu u granicama referentnih vrednosti. Međutim, određen broj pacijenata (oko tri promila) sa hipertireozom veoma loše podnose tireosupresivnu terapiju, imaju brojne neželjene efekte, pa je praktično nemoguće postići eutireoidno stanje. Kod ovih pacijenata je preporuka da, kada se postignu vrednosti koje ne odstupaju više od 10% od referentnih, da se tada najpre uradi tireoidektomija, a nakon toga stomatološka intervencija.
Stomatolog mora biti svestan nuspojava lekova koje se koriste u lečenju disbalansa TH. Bolesnik sa hipertireozom, na terapiji tionamidima, može razviti agranulocitozu (neutropeniju)., kada je značajno povećan rizik od bakterijskih i gljivičnih infekcija i njihova težina. Agranulocitoza je praćena simptomima kao što su temperatura, groznica, glavobolja, malaksalost. Kod pacijenata sa agranulocitozom, potrebno je uputiti pacijenta hematologu i odložiti stomatološku proceduru dva meseca, do regeneracije bele krvne loze. Osim agranulocitoze, kao najteže komplikacije primene tireosupresivne terapije, mogu biti prisutne
i druge neželjene pojave ove terapije, kao što su hepatitis ili sindrom sličan lupusu eritematodesu (11,13).
Takođe, potrebno je razmotriti i prisustvo drugih poremećaja koji mogu biti povezani sa disbalansom TH. Odstupanja od normalnih vrednosti TH mogu biti povezana ne samo sa vrednostima krvnog pritiska, već i sa nivoom holesterola u krvi, pojavom i težinom dijabetesa melitusa i dr (5).
Upoznavanje sa kliničkim manifestacijama bolesti je takođe od velike važnosti. Tako, na primer, neki pacijenti, u sklopu hipertireoze imaju egzoftalmus, a mogu imati i tešku oftalmopatiju, zbog koje primaju kortikosteroide. Kod takvih pacijenat je potrebno razmotriti da li je potrebna periproceduralna suplementacija kortikosteroidima. Takođe je veoma važno, naročito kada su u pitanju stomatološke operacije i dugotrajne procedure, da se zaštite oči pacijenata sa egzoftalmusom jer su mogući postproceduralni bolovi u očima i sušenje konjuktiva. U svrhu zaštite očiju mogu se koristiti posebno dizajnirani štitnici za oči i tzv. „veštačke suze“ (lat. lacrimae arteficiales) (13).
Kriterijumi za adekvatnu preproceduralnu evaluaciju pacijenata sa disbalansom TH su: mišljenje endokrinologa da se može pristupiti proceduri (ne starije od 10 dana), kardiološki status u granicama normale, što podrazumeva dobru frekvencu pulsa (ne >85 otkucaja/min niti < 55 otkucaja/min), odsustvo ventrikularnih ekstrasistola (VES) ili VES<5/min, i EKG bez svežih ishemijskih lezija), kao i laboratorijske analize u referentnim vrednostima (ne starije od 14 dana). Pri interpretaciji laboratorijskih analiza, najvažnije je da FT4 bude u granicama normale (jer najbolje korelira sa kliničkom slikom), dok je poželjno, ali nije neophodno da i TSH, T3 i T4 budu takođe u granicama normalnih vrednosti. Ovo se naročito odnosi na TSH još dugo ostaje suprimiran, čak veoma nizak, pa nije potrebno čekati da TSH bude normalan (14).

Preporuke za postupanje sa pacijentima sa disbalansom TH u stomatološkoj ordinaciji

Stomatolog mora da prilagodi izvođenje dentalnog zahvata razmatrajući: primenu lokalnih anestetika, sklonost razvoju infekcija, postizanje hemostaze, dejstvo i interakcije lekova. Takođe, mora biti osposobljen da posumnja na akutnu dekompenzaciju tireoidne funkcije i blagovremeno i adekvatno pristupi tom, životno ugrožavajućem problemu (11).
Preporuke za postupanje prilikom stomatoloških intervencija kod pacijenata sa tireotoksikozom sadržane su u sledećih nekoliko uputstava: (15)
1. Izbegavati lokalne anestetike (LA) koji sadrže adrenalin - koristiti ili „čiste“ anestetičke rastvore ili LA koji u sebi, kao vazokonstriktor, sadrže felipresin (prilokain). Naime, dodavanjem vazokonstrikora u LA produžuje se vreme trajanja i smanjuje apsorpcija LA, pa je samim tim smanjeno krvarenje tokom procedure. Najčešći vazokonstriktor je adrenalin koji deluje agonistički na α (α1 i α2) i ß receptore (ß1, ß2, ß3), dovodeći do stimulacije srca sa pozitivnim hronotropnim i ionotropnim delovanjem, a vazodilatacije u koronarnim krvnim sudovima, bronhodilatacije idrugih efekata. T4 i T3 deluju sinergistički sa adrenalinom povećavajući osjetljivost tkiva na kateholamine i povećavaju ekspresiju adrenergičkih receptora. Osim toga, imaju i pozitivno inotropno i hronotropno dejstvo, što može rezultirati fibrilacijom pretkomora (7, 11).
2. Imati u vidu interreakcije lekova koji se koriste u lečenju tiroidne disfunkcije i lekova koji se koriste tokom i/ili posle stomatološke procedure. To se pre svega odnosi na nesteroidne antiinflamatorne lekove (NSAIL) koje treba izbegavati u terapiji postproceduralnog bola jer smanjuju vezivanje T4 za tireoglobuline (TG), čime povećavaju FT4, pa može doći do tireotoksične oluje. Takođe, treba izbegavati sve lekove koji imaju slično dejstvo kao adrenalin (atropin, jod, jodoform). Budući da pacijenti sa hipertireozom koriste u terapiji beta blokatore, najčešće propranolol (jer jedini sprečava perifernu konverziju T4 u T3) moguća je interakcija propanolola i adrenalina, sa različitim i neizvesnim ishodima, uključujući bradikardiju i srčani zastoj (7). Potrebno je imati u vidu da fluoridi efikasno smanjuju aktivnost štitne žlijezde jer imaju antagonistički odnos prema jodu, pa se povećane količine fluorida povezuju s nedostatkom joda. Ti pacijenti mogu koristiti zubne paste bez fluorida.
3. U kontroli hemostaze rukovoditi se karakteristikama disbalansa TH. Ukoliko pacijent ima hipertenziju i tahikardiju u sklopu hipertireoze, važan je duži lokalni pritisak za postizanje hemostaze nakon zahvata. Od značaja je i činjenica da je metabolizam faktora koagulacije pojačan, što rezultira povećanom osetljivošću na oralne antikoagulanse. Tokom lečenja antitireoidnim lijekovima može biti potrebno povećati dozu oralnih antikoagulansa kako bi se postigao zadovoljavajući nivo njihovog antikoagulacijskoga učinka (što se posebno odnosi na terapiju propiltiouracilom) (14).
4. Smanjiti stres pacijenta (tj. oslobađanje adrenalina) primenom protokola za sedaciju
5. Pratiti krvni pritisak i puls (pre, tokom i posle intervencije).
6. Ako pacijent ima dentogenu infekciju, obavezno ga posle intervencije uputiti endokrinologu, jer to može izazvati dekompenzaciju TH (16).

Akutne komplikacije disbalansa TH

Najveći problem kod stomatoloških pacijenata koji imaju neki poremećaj funkcije TH jeste svakako mogućnost dekompenzacije tog poremećaja, koja je praćena dramatičnom kliničkom slikom i potrebom za promptnom reakcijom. Zbog toga je fokus u preproceduralnoj evaluaciji ovih pacijenata prevencija tireotoksične krize i tireotoksične oluje, kao i prevencija miksedema i miksedemske kome.
Tireotoksična oluja (TO) je akutno, brzo pogoršanje (dekompenzacija) hipertireoze. Najčešće je posledica neprepoznate kliničke slike hipertireoze u uslovima druge bolesti ili nakon hirurške intervencije. TO je retko (1-2%), ali životnougrožavajuće stanje praćeno visokom smrtnošću (20-40 %). Smrt nastupa zbog aritmije i srčanoga zastoja.
Klinička slika tireotoksične oluje, koja je u stomatološkoj ordinaciji i najznačajniji element dijagnoze pokazuje prisustvo četiri kardinalna znaka TO, tj. manifestacije: hipertermija >38°C koja ne reaguje na antipiretike (uz profuzno znojenje), tahikardija koja je ekstremna i može dovesti do kritičnog poremećaja srčane funkcije (srčane insuficijencije i pretkomorske fibrilacije), poremećaj mentalnog stanja sa teškom uznemirenošću (agitacija) i postojanje osnovnog uzroka koji je doveo do dekompenzacije nedijagnostikovane ili neлečene hipertireoze (hirurška intervencija, DKA, HHS...). Od ostalih kliničkih manifestacija, mogu biti prisutne groznica, mučnina, povraćanje, proliv, palpitacije, aritmija, gubitak svesti idr.
Laboratorijska potvrda TO najčešće nije dostupna u stomatološkoj ordinaciji, ali je neophodna za potvrdu dijagnoze. Prisutno je značajno povećanje vrednosti TH u krvi, kao i njihovih slobodnih frakcija (T3, FT3, T4 i FT4), TSH značajno snižen, povišeni su ureja (zbog dehidratacije), kalcijum i serumski enzimi, a prisutna je i blaga hiperglikemija (17).
Miksedemska koma je akutna dekompenzacija loše kontrolisane ili nelečene ili nedijagnostikovane hipotireoze. Češća kod starijih i u prisustvu predisponirajućih faktora: lekovi koji suprimiraju disanje (sedativi, anestetici, antidepresivi), infekcije (pneumonija), kongestivno zatajenje srca, infarkt miokarda, gastrointestinalno krvarenje, sepsa, izlaganje hladnoći. Kao i TO, to je životno ugrožavajuće stanje sa visokim procentom smrtnosti (18).

U kliničkoj slici miksedemske kome dominiraju: poremećaj svesti (do sopora i kome), hipoventilacija (koja vodi hipoksiji i hiperkapniji), hipotermija (23 - 32,2°C), hipotenzija, bradikardija i periferni edemi. Laboratorijske analize, takođe najčeše neizvodljive u stomatološkoj ordinaciji, pokazuju značajan hormonski, elektrolitni, metabolički i acidobazni disbalans.Vrednosti T3, T4 i TSH mogu biti različite, u zavisnosti od vrste hipotireoze, na kom „terenu“ je nastala miksedemska koma. T4 i FT4 su uvek sniženi, kod svih vrsta hipotireoze, dok je T3 takođe snižen, ali u mnogo manje nego T4 (kod primarne hipotireoze). Vrednost TSH varira: povišen kod tireoidne i strumogene forme hipotireoze, a normalan, snižen ili nemerljiv kod hipofizne ili hipotalamusne hipotireoze (18,19).

Protokoli lečenja akutne dekompenzacije TH u stomatološkoj ordinaciji.

Tireotoksična oluja i miksedemska koma, kao najteže forme tireoidnog disbalansa imaju tri zajedničke karakteristike: da su to životno ugožavajuća stanja, da je visoka smrtnost i da je obavezna hospitalizacija za adekvatno lečenje. Ako se ova stanja dogode u stomatološkoj ordinaciji, obavezno je pratiti protokole koji su predviđeni za takve situacije (2, 11). Prvi korak u oba protokola je isti, a to je: obavezan prekid svih stomatoloških procedura. Poslednji korak protokola, nakon ukazane prvi pomoći je takođe isti: hitan transpost u bolnicu (12).
Protokol lečenja tireotoksične oluje u stomatološkoj ordinaciji obuhvata prekid svih stomatoloških procedura, ordiniranje kiseonika, monitoring vitalnih funkcija, plasiranje IV kanile i hlađenje pacijenta (16). Dalja terapija, koja se najčešće ne može sprovoditi u stomatološkoj ordinaciji, već u bolnici uključuje: propiltiouracil (velike doze - inicijalno 600 mg, kasnije 200 do 300 mg svakih šest sati) peroralno, preko nazogastrične sonde ili rektalno; propanolol (40 do 60 mg peroralno na 4 sata ili 2 mg intravenski); glukokortikoide (2 mg dekstametazona svakih 6 sati) i antibiotike (u slučaju infekcije) (16,17).
Protokol lečenja miksedemske kome oluje u stomatološkoj ordinaciji podrazumeva prekid svih stomatoloških procedura, plasiranje IV kanile, monitorng krvnog pritiska i frekvence pulsa (po mogućnosti i drugih vitalnih funkcija, glikemije i dr.), primenu infuzionih rastvora, utopljavanje, uz paralelnu organizaciju hitnog transporta u bolnicu.
Pri primeni ovih simptomatskih mera inicijalnog lečenja treba biti veoma oprezan. Zbog očekivane hipoglikemije, može se primeniti glukoza, a zbog očekivane hiponatremije hipotoni slani rastvri, ali je neophodna velika obazrivost jer bolesnici sa hipotireozom slabije izlučuju vode, a može doći i do retencije vode. Isto tako, potrebno je biti oprezan prilikom davanja lekova budući da se sporije metabolišu. Utopljavanje bolesnika takođe mora biti veoma oprezno, i nakon pokretanja metabolizma. Spoljašnje zagrevanje indikovano je samo ako je temperatura niža od 300C, budući da jako naglo zagrevanje može rezultirati hipotenzijom i aritmijama, pa i kardiovaskularnim kolapsom. Unutršnje zagrevanje (topli m iinfuzionim rastvorima vrši se u hospitalnim uslovima. Kod izražene hipotenzije i sumnje na udruženu adrenalnu insuficijenciju, mogu se primeniti kortikosteroidi (hidrokortizon, u dozi 50-100 mg IV, a kasnije se ova terapija nastavlja, na 6 sati) (19, 21).
U hospitalnim uslovima, nastavlja se simptomatska terapija infuzionim rastvorima, vrši se dalja korekcija hipoglikemije i korekcija acidobaznog, metaboličkog i elektrolitnog disbalansa (niponatremije, acidoze, hipoksije i tkivne oksigenacije). Po potrebi, primenjuje se i mehanička ventilacija pluća ako je PaO2 < 60 mmHg (8 kPa), ili PaCO2 raste tokom opservacije, uz obavezno lečenje precipitirajućeg oboljenja koje je do ove dekompenzacije i dovelo (najčešće su u pitanju infekcije, pa se primenjuju antibiotici) (19).

Suplementacija tiroidnim hormonima mora biti veoma oprezna, naročito kada su u pitanju starije osobe. Započinje se visokim početnim dozama levotiroksina, obično u bolusu od 500 µg IV. Uobičajena je doza održavanja 50 do 100 µg IV, jednom dnevno. Alternativa je liotironin u dozi od 10 do 25 µg IV na 8-12, ali se izbegava zbog mogućih aritmija.
Pri primeni ovih simptomatskih mera inicijalnog lečenja treba biti veoma oprezan. Zbog očekivane hipoglikemije, može se primeniti glukoza, a zbog očekivane hiponatremije hipotoni slani rastvri, ali je neophodna velika obazrivost jer bolesnici sa hipotireozom slabije izlučuju vode, a može doći i do retencije vode. Isto tako, potrebno je biti oprezan prilikom davanja lekova budući da se sporije metabolišu. Utopljavanje bolesnika takođe mora biti veoma oprezno, i nakon pokretanja metabolizma. Spoljašnje zagrevanje indikovano je samo ako je temperatura niža od 300C, budući da jako naglo zagrevanje može rezultirati hipotenzijom i aritmijama, pa i kardiovaskularnim kolapsom. Unutršnje zagrevanje (topli m iinfuzionim rastvorima vrši se u hospitalnim uslovima. Kod izražene hipotenzije i sumnje na udruženu adrenalnu insuficijenciju, mogu se primeniti kortikosteroidi (hidrokortizon, u dozi 50-100 mg IV, a kasnije se ova terapija nastavlja, na 6 sati) (19, 21).
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ZAKLUČAK

Disbalans tireoidnih hormona reperkutuje se na celokupno opšte zdravlje, a takođe i na oralno zdravlje. Karijes, bolesti parodoncijuma, oštećenje zubne gleđi, prerana ili zakasnela denticija i mnoge druge oralne manifestacije čest su razlog odlaska pacijenata u stomatološku ordinaciju. Ipak, stomatologe najviše brine neregulisani disbalans tiroidnih hormona koji bi mogao dovesti do akutne dekompenzacije i pojave vitalno ugrožavajući stanja kao što su tireotoksična oluja i miksedemska koma. Postoje preporuke za preproceduralnu evaluaciju i pripremu pacijenata sa disbalansom TH pred zakazanu dentalnu intervenciju kojih se treba pridržavati. Isto tako, u slučaju da tokom stomatološke procedure ipak dođe do akutnih komplikacija povezanih sa disbalansom TH, neophodno je postupati po protokolima za takve situacije.

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INTRAKRANIJALNA TRANSLUCENCA KAO ULTRASONOGRAFSKI MARKER ZA RANU DETEKCIJU OTVORENE SPINE BIFIDE

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SAŽETAK

Ovaj članak se fokusira na tehniku sonografskog pregleda za procenu intrakranijalne translucencije tokom ultrasonografije u prvom tromesečju. Odgovarajuće poznavanje sonografskih markera prvog trimestra je najvažniji faktor za procenu normalne i abnormalne strukture mozga, a ovaj pregledni članak može omogućiti otkrivanje otvorene spina bifide i Arnold-Chiari anomalije u ranoj fazi fetalnog razvoja.

Ključne reči: intrakranijalna translucencija, nuhalna translucencija, sonografija prvog trimestra, anatomija mozga, otvorena spina bifida

ENGLISH

EXAMINATION OF INTRACRANIAL TRANLUCENCY AS A MARKER FOR EARLY DETECTION OF OPEN SPINA BIFIDA

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ABSTRACT

This aricle focuses on the sonographic axamination techique for evaluation of intracranial translucencies during the first trimester ultrasound scan. Appropriate knowledge of sonographic landmarks is the most important factor for evaluation normal as well as abnormal brain structure, and this examination may enable detection of open spina bifida and Arnold – Chiari anomaly at an early stage of fetal develpoment.

Key words: intracranial translucency, nuchal translucency, first trimester sonography, brain anatomy, open spina bifida

Nicolaides i sar. su prvi opisali povezanost otvorene spine bifide (OSB) sa ultrasonografskim nalazom frontalne kosti (lemon sign) i kaudalnog premeštanja cerebeluma (banana sign) kod fetusa u 16-23 nedelji gestacije1. To su manifestacije i Arnold-Chiari malformacije koja je uvek udružena sa OSB. Ovi kranijalni znaci su lako prepoznatljivi i procenat ultrasonografske detekcije za OSB u drugom trimestru je skoro 100%, dok je procenat otkrivanja ove anomalije u prvom trimestru znatno manji i kreće se između 33-44% 2-4,17 .

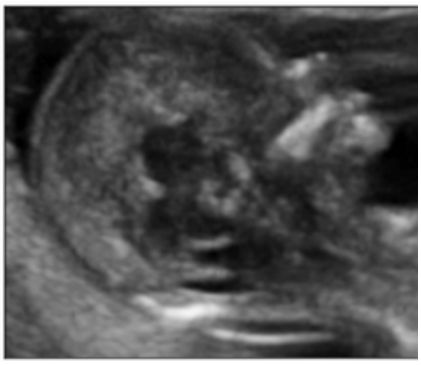
Chaoui i sar. su objavili indikativne podatke da otvorena spina bifida već postoji u prvom trimestru i da je moguće postaviti sumnju kada se četvrta moždana komora ili intrakarnijalna translucenca ne može videti u tkz. NT (nuhalna translucenca) srednje-sagitalnom preseku 5.

Ultrasonografski skrining trudnoće između 11 i 13 nedelje gestacije se danas sprovodi ne samo za merenje nuhalnog zadebljanja (NT), već i za detekciju ozbiljnih malformacija i indentifikaciju trudnoća koje su u visokom riziku za nepovoljan fetalni i matermalni ishod. Adekvatna aparatura, temeljno poznavanje normalnih i patoloških anatomskih karakteristika i pravilna sonografska tehnika preduslov su za rano ultrasonografsko otrkivanje ili sumnnju u fiziološki morfološki status skoro svih organa i sistema. To se odnosi i na nervni sistem, odnosno u ovom slučaju na spinu bifidu. Veliki ultrasonografski dijagnostički izazov u prvom trimestru predstavlja otkrivanje otvorene OSB 5. Chaoui i sar.5,6 su prvi objavili način izvođenja, standardizaciju preseka i stepen izvodljivost u ranom otkrivanju OSB kroz anomaliju zadnje lobanjske jame u vreme sprovođenja skrininga za nuhalnu translucencu, a to je vizuelizacija intrakranijalne translucence (IT). Treba naglasiti da je u skoro svim slučajevima otvorena spina bifida udružena sa Arnold-Chiari malformacijom koja je rezultat curenja cerebrospinalne tečnosti u amnionsku šupljinu i smanjenog pritiska u subarahnoidalnom prostoru koji vodi kaudalnom premeštanju mozga i obstruktivnom hidrocefalusu. U prvom trimestru trudnoće kaudalno premeštanje mozga rezultuje kompresijom četvrte moždane komore i gubitkom normalne vizuelizacije IT, a u drugom trimestru Arnold-Chiari se ispoljava kao "lemon" i "banana" znak 1,5,7.

Sasvim je moguće da se između 11 i 13 nedelje dijagnostikuju ozbiljne anomalije centralnog nervnog sistema (holoprosencefalija, ventrikulomegalija, akranija, egzencefalija, encefalokea). Unutar periodaod 11 do 13 nedelja anteroposteriorni dijametar IT raste od 1,5 mm pri dužini fetusa (crown rump lenght – CRL) od 45 mm, pa do 2,5 mm kada je CRL 85 mm. Obimne sonografske studije koje se bave razvojem humanog centralnog nervnog sistema govore da je četvrtu moždanu komoru relativno lako identifikovati od 8 nedelje kao hipoehogenu strukturu, ali za dijagnozu otvorene spine bifide pre 11 nedelje još treba dokaza i studija. Nakon 13 nedelje IT je sonografski je laka identifikaciju jer njen dijametar raste sa gestacijom 8.

Pregled bi trebalo da se radi primenom aparata sa visokom rezolucijom, sa transabdominalnom multifrekventnom sondom od 4 – 8 MHz ukoliko je moguće i pratećim sonografskim sistemom koji sadrži visoko harmoničan prikaz, široko skeniranje (cross-beam), spikularnu redukciju, dinamični domet, sivu mapu. Fetus se prikazuje i srednje-sagitalnom preseku, u istoj ravni koja se primenjuje za merenje NT (prema preporukama Fetal Medicine Fondation). Dužina teme-trtica mora biti između 45 i 84 mm, a slika fetusa bi trebalo da zauzme najmanje 75% ekrana. Za pravilno merenje NT, sonda treba da je pod onim uglom kojim se izbegava zigomatični nastavak, a meri se maksimalna „on to on“ distanca. Kod takvog prikaza pri sagledavanju moždanog stabla četvrta moždana komora se prikazuje kao intrakranijalno rasvetljenje paralelno sa NT.
U 11 – 13 nedelji gestacije moždano stablo je hipoehogeno (tamno sivo) dok je IT anehogena (crna). Iza IT je smeštena buduća cisterna magna. U srednje-sagitalnom preseku IT je neznatno zakrivljena i najširi anteroposteriorni dijametar je srednji deo četvrte moždane komore. Za merenje IT, kao i za merenje NT, preporučuje se selektovanje rasvetljenja sa najširim promerom i plasiranje kalipera na prednju i zadnju ivicu. (sl. 1)

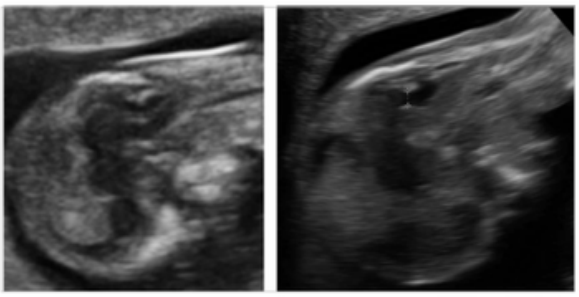
Slika 1. Egzaktni srednje sagitalni presek fetalnog lica u 13 nedelji. Prikazana je nosna kost (NB), nuhalna translucenca (NT), talamus, srednji mozak (MB), moždano stablo (BS), cisterna magna (CM) i četvrta komora. Četvrta komora se prikazuje kao intrakranijalna anehogena (IT) zona između dve ehogene linije; posteriorna granica moždanog stablna pred i horoidni pleksus četvrte moždane komore pozadi.



Pozicija fetusa za procenu IT

Kao i kod merenja NT i nosne kosti, procena IT zahteva položaj fetusa kada je lice usmereno ka sondi. Iako se četvrta komora može prikazati kada je fetus u dorzoanteriornom položaju, adekvatan pregled fetalnog mozga često otežan osenčenjem zbog fetalne okcipitalne kosti.

Slika 2. Osenčenje uzrokovano okcipitalnom kosti. a) transabdominalni prikaz, b) transvaginalni prikaz.



Transabdominalna i transvaginalna procena IT

Tačan srednje-sagitalni prikaz fetalnog lica neophodan za merenje NT i vizuelizaciju nosne kosti dobija se znatno lakše transabdominalnim nego transvaginalnim pristupom, zato što manipulacija vaginalnom sondom ograničena. Pored toga, transvaginalno, u srednje sagitalnoj ravni, razlika u kontrastu između IT i okolnog moždanog tkiva je često mala. Međutim rezolucija i intimniji pristup uterusu a samim tim i plodu obezbeđuje vaginalnim pristupom znatno bolju procenu fetalne anatomije i morfologije, tako da sonografisti za podrobniji pregled u ranoj trudnoći često koriste oba pristupa. (sl. 2)

Trodimenzionalna ultrasonografska procena IT

Trodimenzionalni ultrasonografski prikaz je koristan u proceni IT naročito onda kada je teško dobiti dvodimenzionalni srednje-sagitalni presek fetalnog lica. U takvim slučajevima transverzalni presek fetalne glavice u nivou četvrte komore nam daje informaciju o IT. Zbog veće i bolje rezolucije transvaginalni pristup ima prednost. Referentna tačka se nalazi u centru četvrte moždane komore i slika se rotira u sve tri ravni i usklađuje se sa srednjom linijom te se na taj način dobija srednje-sagitalna linija mozga i najbolji presek za procenu IT. Isti način se koristi da se u drugom trimestru sagledaju i druge fetalne intracerebralne strukture, kao što su korpus kalozum i vermis 9.
Mozak fetusa koji je pogođen otvorenom spinom bifidom u 11 – 13 nedelji se može opisati kao tkz. “presušen mozak“ , a sonografske karakteristike uključuju:

1. Iregularan oblik lateralnih ventrikula
2. Proširen horoidni pleksus
3. Kolabirana treća moždana komora
4. Kaudalno i posteriorno pomeren mezencefalon (i mozak u celini)
5. Uzak akvedukt
6. Mali mozak nije vidljiv
7. Obliterirana četvrta moždana komora

Kod fetusa sa meningomijelokelom u 11 – 13 nedelji gestacije intrakranijalna kolekcija cerebrospinalne tečnosti bitno se redukuje, a smanjuju se i dijametri lateralnih ventrikula, treće moždanih komora, Silvijusovog akvedukta i četvrte moždane komore. Ovaj fenomen je jasno detektabilan primenom 3D neurosonografije prvenstveno vaginalnim pristupom 10-16.

Ipak postoje radovi koji ukazuju da i pored toga što IT nije i ne može biti prikazana u optimalnom NT preseku nije uvek povezana sa OSB. Nemogućnost vizuelizacije IT je nekada otežana i skopčana je više sa tehničkim faktorima nego sa eventualnom fetalnom anomalijom. Fong i sar. su stoga zaključili da su potrebne veće prospektivne studije i dodatna potvrda pre uvođenja IT u ultrasonografski skrinig. Za sada je preporuka, prema ovim autorima, ukoliko se sumnja na postojanje OSB u prvom trimestru, potrebna je ekspektativna ultrasonografska pretraga u drugom trimestru 11,14,15.

Veliki broj autora su sagledavanje IT uvrstili u obavezni ultrasonografski skrining prvog i ranog drugog trimestra tako da ovaj marker poprima značajnu ulogu u sagledavanju anatomije fetalnog centralnog nervnog u 11-13 nedelji. 18

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THE IMPORTANCE OF EARLY DETECTION OF DIABETES INSIPIDUS IN CHILDHOOD - CASE REPORT

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SUMMARY

The discovery that sunlight can cure rickets was first scientifically confirmed in 1919. Shortly thereafter, in 1924, it was found that inactive lipids in the diet and skin are converted into antirachitic substances under the influence of UV light. Vitamin D (Vit D), also known as the "sunshine vitamin," was first identified in 1931. In recent decades, it has regained the focus of interest among the broader scientific community and dermatologists. Specifically, certain dermatoses have been associated with low Vit D levels, leading to its supplementation in patients. On the other hand, some dermatoses worsen with sun exposure, necessitating strict avoidance of sunlight and the therapeutic use of Vit D preparations.We are witnessing a growing number of cases of melanoma and non-melanoma skin cancers, with excessive sun exposure being the primary etiological factor in most cases. This paper provides a literature review on the historical discovery of Vit D and presents findings from studies examining Vit D levels not only in various dermatoses but also in other diseases. The number of studies, as well as the spectrum of diseases in which the role of Vit D is being investigated, continues to increase.

Keywords: Vitamin D, sunshine vitamin, antirachitic substance, calcium, phosphorus, skin.

SRPSKI

VITAMIN D- „SUNČANI VITAMIN“

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SAŽETAK

Da sunčeva svetlost može izlečiti rahitis prvi put je naučno otkriveno 1919. godine. Uskoro, 1924. godine utvrđeno je da se inaktivni lipidi u ishrani i koži pod dejstvom UV svetla pretvaraju u antirahitične supstance. Vitamin D (vit D), takođe poznat kao „sunčani“, prvi put je otkriven 1931. godine. Ovaj vitamin se u poslednjim decenijama ponovo nalazi u žiži interesovanja i šire naučne zajednice i dermatologa. Naime, postoje dermatoze kod kojih je utvrđen nizak nivo Vit D, i kod pacijenata se primenjuje njegova suplementacija. Sa druge strane, postoje dermatoze koje se pogoršavaju sa izlaganjem sunčevom svetlu, pa im se zabranjuje izlaganje suncu. Kod njih se u terapijske svrhe moraju primeniti preparati Vit D. Svedoci smo sve većeg broja obolelih od melanomskih i nemelanomskih karcinoma kože. Kod većine njih etiološki agens je prekomerno izlaganje suncu.U ovom radu iznosimo pregled literature u vezi istorijata otkrića Vit D i rezultate studija ispitivanja novoa Vit D ne samo kod različiti h dermatoza, već i drugih bolesti. Studija je sve više, kao i spektra bolesti kod kojih se ispituje uloga Vit D. Tako da je Vit D sa pravom ponovo u žiži naučnog interesovanja.

Ključne reči: Vitamin D, sunčani vitamin, antirahitična supstanca, kalcijum, fosfor, koža.

INTRODUCTION

History

The first scientific discoveries related to the antirachitic effect of sunlight date back to 1919, as noted by Bergqvist and Ezzedine. A few years later (1924), it was discovered that inactive lipids in the diet and skin could be converted by UV light into substances with antirachitic effects (1). Vitamin D (vit D), also known as the "sunshine vitamin," was first identified in 1931. In recent decades, this vitamin has once again become a focal point of interest for the broader scientific community and dermatologists (1, 2, 3, 4).

The primary source of vitamin D is skin exposure to sunlight and the action of ultraviolet B (UVB) rays, accounting for over 80% of the total vitamin D produced. Exposure of even a small skin area to UVB rays is sufficient for vitamin D synthesis. There are only a few natural sources of vitamin D: cod liver oil, cheese, mackerel, salmon, egg yolk, beef liver, and tuna (3, 5). Supplementation through external intake of vitamin D can be achieved via various supplements or medications, as well as cosmetic products, primarily in the form of oil-based solutions (alcoholic, sucrose, or glycol types) and capsules for external use (5, 6). Maintaining higher serum vitamin D levels significantly improves the prognosis of numerous systemic diseases. However, determining the necessary concentration is challenging due to various factors affecting absorption (7).

Externally or internally applied vitamin D supplementation is highly beneficial for sensitive, capillary, and mature, aging skin. Studies to date have shown polymorphisms in vitamin D receptors, which are significantly more common in patients with atopic dermatitis. These findings suggest a crucial role of vitamin D in the pathogenesis of the disease. Additionally, experimental research conclusions indicate that the human antimicrobial peptide LL-37 is often insufficiently expressed in patients with atopic dermatitis. The deficiency of this peptide disrupts the re-epithelialization process. Clinical studies confirm that vitamin D supplementation increases LL-37 expression in these patients and reduces disease severity (5, 6).

Since obtaining sufficient amounts of vitamin D solely from natural dietary sources has proven inadequate, many countries have begun fortifying foods with vitamin D, particularly orange juice, milk, yogurt, and cereals. Additionally, various forms of vitamin D supplements are widely available over-the-counter in the form of vitamin D3 and D2, with or without calcium, at affordable prices. Vitamin D supplements also safely increase serum vitamin D levels, although not as effectively or quickly as sunlight exposure (3).

Synthesis of Vitamin D and Its Metabolites

The function of keratinocytes in relation to vitamin D is unique because they not only serve as the primary source of vitamin D for the body (containing the precursor 7-dehydrocholesterol (7-DHC)), but they also metabolize the produced vitamin D into active metabolites through enzymatic mechanisms. This process is referred to as the photoendocrine system of vitamin D. It should be emphasized that vitamin D itself regulates the proliferation and differentiation of keratinocytes (1,7).

From the vitamin D precursor, 7-DHC, exposure to UVB rays of shorter wavelengths opens the B-ring of the steroid, forming previtamin D3. After thermal isomerization is completed, cholecalciferol (vitamin D3) is formed. Two separate hydroxylation reactions occur to produce the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)D). The first hydroxylation reaction takes place in the liver, resulting in 25-hydroxyvitamin D (25(OH)D), the primary circulating form of vitamin D. Its concentration can be measured in serum to determine vitamin D status. The second hydroxylation reaction occurs predominantly in the kidneys, although many other cells, such as keratinocytes, use the same enzymes to produce 1,25(OH)D. The kidneys facilitate the uptake of 25(OH)D3 using a vitamin D-binding protein. If glomerular filtration decreases due to chronic kidney disease, serum vitamin D levels also decline. 25(OH)D regulates cell proliferation, immune response, and serum calcium and phosphorus levels. Inhibition of cAMP protein production induced by 1,25(OH)2D3 enhances the growth of mycobacteria (7,14,15).

Apart from cholecalciferol (vitamin D3), vitamin D is also available as ergocalciferol (vitamin D2). Its hormonal role is expressed as dihydroxycholecalciferol (calcitriol) (16). Sun exposure provides vitamin D in the form of D3. Dietary sources can supply both forms, which are officially considered equivalent and interchangeable, though this is only partially accurate. D2 and D3 differ in their efficacy in raising serum 25-hydroxyvitamin D levels, as the metabolites of vitamin D2 do not bind to the vitamin D-binding protein in plasma with the same efficiency, and this ability is reduced. Additionally, vitamin D2 has a non-physiological metabolism and a shorter shelf life. However, in current practice, vitamin D preparations are more frequently used in the form of vitamin D2 rather than vitamin D3 (3).

In addition to the production of previtamin D3, further UVB exposure leads to the production of two isomeric forms of vitamin D, which do not affect calcium homeostasis. During UVB exposure, the skin converts approximately 15% of 7-dehydrocholesterol into previtamin D3. Studies have shown that UVB exposure of the skin not only results in the production of previtamin D3 but also generates two isomers of vitamin D and some other metabolites if UVB exposure continues. Importantly, none of these metabolites have activity in calcium modulation, ensuring the safe production of vitamin D under UVB radiation. Any additional previtamin D3 is broken down. The formation of vitamin D3 in the skin offers multiple benefits to the body, even from the isomerized degradation metabolites, compared to dietary supplementation of vitamin D3. It is now known that the effects of these degradation photoproducts may be beneficial in the prevention of tumors (including skin cancers) and their genesis, as well as exerting antiproliferative effects on keratinocytes (6,7).

According to the Clinical Practice Guidelines of the US Endocrine Society, vitamin D deficiency is defined as serum 25-OH D levels <50 nmol/L (below 20 ng/mL). Vitamin D insufficiency is defined as serum 25-OH D levels between 50 and 75 nmol/L (21–29 ng/mL) (2).

The gold standard for analyzing vitamin D status is the measurement of its main circulating metabolite, 25-hydroxyvitamin D3 (25(OH)D3), using high-performance liquid chromatography (HPLC) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) (17).

Roles of Vitamin D

Vitamin D is a liposoluble steroid hormone with a key role in calcium and phosphate homeostasis and maintaining bone health by promoting the absorption of calcium and phosphorus and ensuring their adequate concentrations. Vitamin D is essential for the growth and remodeling of osteoblasts and osteoclasts, leading to a positive correlation between vitamin D status and bone health (18). Endogenously produced 1,25(OH)D maintains calcium homeostasis, as osteoblasts require calcium ions for collagen matrix synthesis. Vitamin D deficiency is associated with elevated parathyroid hormone levels, which help maintain calcium balance in the serum and bones. Parathyroid hormone extracts calcium from the bones into the bloodstream and expels phosphorus through urine. Hypervitaminosis D can result in hypercalciuria and hypercalcemia, accompanied by symptoms such as weakness, headaches, confusion, and polyuria. Although achieving hypervitaminosis D requires a high intake of vitamin D, toxicity is rare because the kidneys perform the final regulatory mechanism during hydroxylation. However, the effects of vitamin D are not limited to bones. It acts on nearly all organ systems in the human body. Vitamin D is essential for other physiological functions and is considered a crucial component for muscle performance and immunity (2, 3, 5, 7, 8, 9, 10). Given its role in regulating numerous cellular functions, vitamin D plays a versatile role in almost all organs and organ systems, influencing the cardiovascular, neurological, immune, and endocrine systems (parathyroid glands, pancreas), as well as reproductive organs (placenta, uterus, ovaries, and testes). Vitamin D is significant in the development of autoimmune diseases and infections, playing a crucial role in defense against opportunistic infections (1, 11, 12, 13). Vitamin D deficiency increases the risk of ischemic stroke and is also associated with type 2 diabetes (14). Recent meta-analyses suggest that several diseases, including type 2 diabetes, cancer, depression, COVID-19, and acute respiratory infections, can be mitigated or prevented with vitamin D supplementation. Thus, vitamin D can serve as a dietary-based prevention and treatment strategy. For vitamin D to exert its effects, it must bind to its nuclear receptor (VDR), which is distributed across most human tissues. Research has shown that VDR also functions as a tumor suppressor, and inhibition of its expression is associated with melanoma progression (7).

Factors That Reduce Vitamin D Production

Several factors can diminish vitamin D production. Skin type

according to the Fitzpatrick scale can negatively affect the ability to maintain vitamin D production. It has been observed that as the Fitzpatrick skin type progresses from I to VI, from lighter to darker skin, vitamin D production decreases. Based on this, it can be concluded that darker skin requires higher doses of UV radiation to produce the same level of vitamin D that lighter skin generates. This is likely because the higher melanin content characteristic of darker skin provides greater protection from UV radiation compared to lighter skin. Fitzpatrick skin types I and II have lower minimal erythema doses (the amount of UV radiation required to cause sunburn) compared to types V and VI. As a result, UV radiation penetrates more effectively, stimulating greater vitamin D production in skin types I and II. Supporting this, an experimental study showed that 30 minutes of exposure in lower Fitzpatrick phototypes converted 3% of skin 7-dehydrocholesterol (7-DHC) into previtamin D3, while higher Fitzpatrick phototypes converted only 0.3%. This characteristic of lower Fitzpatrick skin types also increases the risk of skin cancer and other UV-induced dermatoses (7).

Some studies have provided interesting data indicating that individuals with higher Fitzpatrick skin types may have vitamin D deficiencies because melanin competes with 7-DHC for UV absorption. On the other hand, individuals with lighter Fitzpatrick skin types can produce more than 50 nmol/L of 25(OH)D from just 30 minutes of daily sun exposure, whereas darker skin may require up to two hours of exposure to achieve the same production level (7).

Other factors that reduce vitamin D production include clothing and avoidance of UV radiation, which should be considered when taking a patient's medical history. Raymond-Lezman and Riskin cite a Turkish study that found women who traditionally cover most of their bodies had severe vitamin D deficiencies compared to women with greater skin exposure to sunlight (7).

Vitamin D3 production depends on the penetration and absorption of UVB radiation, making geographic location an important factor when determining the need for increased vitamin D intake in at-risk populations. In some regions, vitamin D is not produced during winter and spring due to latitude, regardless of skin type. Additionally, cloud cover significantly reduces UV radiation absorption, leading to vitamin D deficiency.

With the rise of air pollution following the industrial revolution, rickets incidence increased significantly. The same authors referenced a study conducted in Delhi that showed lower 25(OH)D levels in children as pollution levels rose. Similarly, in the United Kingdom, vitamin D deficiency was found to be most common in adolescent girls, likely due to reduced outdoor time. Interestingly, natural light passing through windows does not initiate vitamin D synthesis, but UV tanning beds have been shown to increase vitamin D levels (7).

Vitamin D and Various Disorders and Diseases, with Emphasis on Dermatoses

An increasing number of dermatoses are linked to vitamin D status, particularly atopic dermatitis, psoriasis, vitiligo, and skin cancers (7, 19, 20). Most studies have investigated the efficacy of the combination of calcipotriol/betamethasone dipropionate in various formulations for topical treatment of psoriasis, demonstrating good therapeutic outcomes, improvement in patients' quality of life, and clinical presentation (21, 22, 23, 24, 25).

Like other organs, the skin undergoes a phase of progressive decline in its physiological, morphological, and functional properties during aging. Aging is a natural, genetically predisposed process, but skin functions are essential for homeostasis and survival. The skin is the largest organ in our body. Together with the hypodermis (subcutaneous fat), it serves as both a source and a target organ for several hormones and neuromediators, making it an independent peripheral endocrine organ. It is crucial to emphasize that the skin has the capacity to produce prohormonal vitamin D and transform it into active metabolites. These metabolites can exert various effects on keratinocytes and fibroblasts, the primary skin cells, as well as on immune cells. These effects are mediated through the activation of the nuclear vitamin D receptor (VDR). Vitamin D plays a critical role in skin homeostasis and contributes to its barrier function. As essential components of a functional immune system, active forms of vitamin D modulate skin immunity (7).

Beyond studying vitamin D levels in different dermatoses, research is being conducted in other fields. For example, Riccardi et al. highlight that numerous epidemiological studies have shown that low circulating vitamin D concentrations negatively correlate with skin manifestations and bone abnormalities, significant clinical features of neurofibromatosis type 1 (NF1). The conclusions of these studies are anticipated to evaluate the therapeutic efficacy and role of vitamin D in NF1, based on preclinical and clinical research. Current studies show a clinical correlation between vitamin D status and NF1, providing important insights into the disease's pathogenesis and new possibilities for targeted therapy. Recent findings indicate that vitamin D or its analogs have been used to treat skin and bone lesions in NF1 patients, either alone or in combination with other therapeutic agents (8).

In research by Islam et al. (9), it was emphasized that patients with primary antiphospholipid syndrome had significantly lower serum vitamin D concentrations and poorer clinical parameters. This aligns with findings from studies on systemic lupus erythematosus (SLE) (26, 27).

Based on the above, it is suggested that vitamin D supplementation could benefit patients with primary antiphospholipid syndrome, helping to maintain clinical stability, improve overall health, and potentially reduce disease severity (9).

Vitamin D deficiency is a global health issue affecting individuals of all ages. A variety of factors contribute to deficiencies, with the most important being lack of sun exposure and poor dietary intake. It has been found that the average prevalence of vitamin D deficiency in the US population is 37.5%. This deficiency is associated with various metabolic, neoplastic, and immunological disorders, such as atherosclerosis, diabetes mellitus, autoimmune diseases, and colorectal cancer (2, 17).

Multivitamin supplements may contain either vitamin D2 or D3, but it is a noticeable trend among pharmaceutical companies to reformulate their products and introduce supplements that contain vitamin D in the D3 form, as highlighted by Mostafa and Hegazy (3).

DISCUSSION

It can be said that almost a century has passed since the "discovery" of Vitamin D, first as an anti-rickets substance, and then as a liposoluble vitamin with numerous functions in our body, meaning multisystemic effects, as there is no organ and/or organ system in our body that it does not affect. Since the primary source of this vitamin is the action of UV light, it earned the name "sunshine" vitamin/hormone. Renewed interest in Vitamin D began before the Covid-19 pandemic, and during this pandemic, it seemed to be at the "peak" of attention from both the scientific community and the general public worldwide. It was at the center of both experimental and clinical research in numerous scientific studies around the world, and as the results of these studies were published, knowledge about the role of Vitamin D in various diseases and disorders spread. It is crucial for the homeostasis of calcium and phosphate, maintaining bone health. However, today, the spectrum of diseases associated with Vitamin D deficiency primarily includes skin diseases, autoimmune diseases, neurological disorders, cardiovascular diseases, and mental health issues. Research on the topical application of Vitamin D preparations in the treatment of psoriasis began in the last century. Studies published in 1975 analyzed the therapeutic applications of topically applied Vitamin D preparations. The best results in the topical treatment of psoriasis have been achieved with a combination of Calcipotriol/betamethasone dipropionate in cream or gel formulations. There is significantly less research on the topical treatment of atopic dermatitis. As previously mentioned, for all other dermatoses, oral Vitamin D preparations are recommended. The role of Vitamin D in the skin aging process is also being explored. Numerous studies are still ongoing, so new results are expected. The media has played a significant role in writing about and publishing (marketing) new Vitamin D supplementation products, whether they contain only Vitamin D or are combined with other components. Recently, products for topical Vitamin D supplementation, either for therapeutic use in dermatoses (psoriasis) or for slowing the skin aging process, have increasingly appeared.

Another important aspect of Vitamin D in dermatology is that some dermatoses worsen with sun exposure, so they should not be exposed to UV rays. Vitamin D preparations must be used for them. However, patients should be regularly monitored, as, as mentioned earlier, there are no universal recommendations, or precisely determined Vitamin D concentrations in the blood of the patient that are best for a specific dermatosis, taking into account factors such as gender, age, season,

etc. We are also witnessing an increase in the number of younger patients with melanoma and non-melanoma skin cancers in the last decade or two. Additionally, a deficiency of Vitamin D has been observed in melanoma patients.

According to Hernigou et al., Vitamin D became one of the most frequently used "medications" in the 20th century, as a substitute for insufficient UVB exposure for people, for various reasons. Although throughout the century, the understanding of Vitamin D metabolism has constantly grown, other diseases and disorders, not just rickets, have emerged before orthopedic surgeons. Recently, studies have been conducted on Vitamin D deficiency as a factor associated with various bone pathologies, such as fractures and prosthetic infections (4).

In the conclusion of their study, Tong et al. emphasize the need for further research to determine how much Vitamin D is necessary to maintain a healthy life. Considering the many factors that affect the amount of Vitamin D produced by UVB radiation, it must be concluded that there is no universal approach for recommendations. If a patient's Vitamin D level is below 16 ng/mL, they are at higher risk for morbidity and mortality. When the Vitamin D level is increased above 20 ng/mL, improvements in clinical condition, patient status, and disease outcomes are observed. The focus of research now also includes many projections for malignancies and high-risk diseases, as results from some studies have shown the benefits of achieving higher serum concentrations of Vitamin D. It is recommended to precisely monitor Vitamin D levels, which can help improve the quality of life for patients, reduce the burden of the disease, and extend the lives of patients. As previously stated, and as Tong et al. repeat, Vitamin D toxicity is very rare. The body has self-regulating mechanisms through the kidneys that function during Vitamin D synthesis induced by UV radiation. Patients should be monitored, and tests should be done to check for hypercalciuria and hypercalcemia with symptoms similar to hyperparathyroid hormone. If neither is present, simply reducing UVB exposure or taking supplementation will result in a reduction in calcium levels (28).

Raymond-Lezman et al. believe that the self-regulating and safe nature of Vitamin D is very important and should encourage individuals to safely increase their UV exposure while also regularly checking their skin. Patients should be educated that they must not allow sunburns to develop and should always use sunscreen as recommended by dermatologists. In this way, higher concentrations of Vitamin D can be achieved while completely reducing the risks associated with UV radiation. When UV light is not available sufficiently due to season or geographic location, Vitamin D supplementation is recommended, which will only benefit health (7).

Various factors are associated with Vitamin D status, especially skin type, gender, body mass index, physical activity, smoking, alcohol consumption, and Vitamin D receptor polymorphism. Patients with photosensitive disorders must avoid sun exposure, potentially leading to a risk of Vitamin D deficiency. It is crucial to emphasize that maintaining Vitamin D levels in the serum within normal physiological ranges is essential for patients with conditions such as atopic dermatitis, psoriasis, vitiligo, polymorphic light eruption, mycosis fungoides, alopecia areata, systemic lupus erythematosus (SLE), and melanoma (5).

It must be emphasized that today a significant portion of the urban population has a Vitamin D3 deficiency, as they do not expose their skin to the sun or spend time outdoors due to air pollution and other reasons, and as the global population ages, they lose reserves of 7-dehydrocholesterol in the epidermis due to aging. As previously mentioned, the consequences of Vitamin D deficiency include bone diseases and other health issues such as malignancies, asthma, arthritis, hypertension, osteoporosis, and mental, neurological, and cardiovascular diseases. Symptoms of Vitamin D deficiency may include bone pain and muscle weakness. Vitamin D has significant applications in the cosmetic industry, as the topical use of these cosmetic preparations with Vitamin D prevents photoaging, photodamage, wrinkles, and other skin changes associated with the aging process. Topical Vitamin D preparations are also very effective in the treatment of psoriasis (6).

Vitamin D supplementation (either externally or internally) can be extremely beneficial for sensitive, capillary, and mature, older skin, and is increasingly recommended for such patients. Vitamin D receptor polymorphisms are more common in patients with atopic dermatitis, leading to the conclusion of Vitamin D's key role in the pathogenesis of this common skin condition in patients of all ages. The human antimicrobial peptide LL-37 is often insufficiently expressed in individuals with atopic dermatitis, impairing the reepithelialization process. Clinical studies have shown that Vitamin D supplementation increases LL-37 expression in patients and reduces the severity of the disease, though this is still under experimental investigation (5).

Topical Vitamin D analogs exhibit significant anti-inflammatory and antiproliferative effects (inhibition of IL-2, IL-6, IL-8, IFN-γ, and IL-10 secretion, and stimulation of T-cell differentiation). This leads to inhibition of the production of psoriasis and Koebner proteins. A key element of this issue is the connection of Vitamin D's specific metabolism, simply put, with lumisterol or 7-dehydrocholesterol. These are crucial for regulating the skin's protective barrier and controlling immune functions. For Vitamin D3 to be biologically active, it must be activated by cytochrome P450 (5).

Immune-mediated dermatoses are a group of skin diseases, such as: alopecia areata, atopic dermatitis, psoriasis, systemic lupus erythematosus, and autoimmune blistering dermatoses. Vitamin D is known for its classic pleiotropic effects. Results from recent studies have shown that Vitamin D is catalyzed into its biologically active form [1,25(OH)2D], and then, in correlation with its receptor (Vitamin D receptor), plays a crucial role in many pathophysiological processes, including autoimmune and immune-related dermatoses (5).

It is well-known that the world's population is aging, industrial air pollution is high, and the number of smokers is increasing, all of which contribute to Vitamin D deficiency becoming a larger public health issue globally, especially in industrialized countries. Considering the cumulative and dosed effects of smoking on Vitamin D deficiency, the rise in smokers among the younger population is likely to lead to a significant increase in future public health burdens related to osteoporosis and other numerous cardiovascular, pulmonary, infectious, immune, and other diseases. Smoking has a significant negative impact on circulating Vitamin D levels, although this concentration can return to levels similar to those of non-smokers after quitting smoking. Given the harmful effects of smoking on Vitamin D deficiency and its associated consequences on bone health and other systems, preventing Vitamin D deficiency and smoking cessation must be prioritized, and preventive measures (education, flyers, lectures, etc.) should be implemented (10).

CONCLUSION

Given its multisystemic effects in our body, Vitamin D is rightfully at the forefront of interest for scientists, doctors, and the general public. Through various preventive measures, efforts should be made to raise awareness among the average population about the importance of maintaining physiological levels of Vitamin D, particularly among doctors. Dermatologists, in particular, must explain to their patients the impact of this vitamin on the health of our bodies. Dermatologists are already attempting to do this through various actions and activities, and indeed, further efforts are needed to educate as many people as possible, even at the school level. By doing so, we invest in the future of the nation, ensuring that it remains healthy. When diagnosing a dermatological condition, it is important to explain to patients the significance of sun exposure or avoidance, as well as the application of Vitamin D supplements.

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IDIOPATHIC PULMONARY HYPERTENSION – CASE PRESENTATION

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SUMMARY

Pulmonary hypertension (PH) is a hemodynamic condition characterized by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 240 dyn·s·cm^{-5}. The annual incidence of pulmonary arterial hypertension (PAH) is approximately 3–10 new cases per million adults. It is estimated that the prevalence of pulmonary hypertension in individuals over 65 years of age is around 10%.The aim of this study is to present the case of a female patient with progressive dyspnea in whom PAH remained undiagnosed for a prolonged period.A 74-year-old female patient, M.P., was hospitalized in the Coronary Care Unit of the Clinical Center in Kosovska Mitrovica due to symptoms of shortness of breath, choking, fatigue, leg swelling, and weakness. The admission ECG revealed: sinus rhythm, normal axis, high R wave in V2, ST depression, and negative T waves in leads II, III, aVF, and V4–V5. Echocardiography findings showed right ventricular enlargement (2.9 cm), pulmonary artery dilation (3.3 cm), 1–2+ pulmonary regurgitation, and 3+ tricuspid regurgitation, with a systolic pulmonary artery pressure (SPAP) of up to 126 mmHg. The right ventricle measured 5.3 cm in the 4Ch view, with a TAPSE of 1.8 cm. Right heart catheterization revealed the following pressures: PA 78/34/57 mmHg, RV 74/8/10 mmHg, RA 6/6/7 mmHg, CO 4.3 l/min, and LV 99/10/8 mmHg.
Although primary pulmonary hypertension is predominantly a disease of younger individuals, it should also be considered in older patients presenting with progressive dyspnea in the absence of structural heart disease.

Keywords: pulmonary hypertension, echocardiography, SPAP

SRPSKI

IDIOPATSKA PLUĆNA HIPERTENZIJA - PRIKAZ SLUČAJA

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SAŽETAK

Plućna hipertenzija (PH) predstavlja hemodinamsko stanje koje karakterišu: srednji pritisak u plućnoj arteriji (PAPm) ≥ 25 mmHg u mirovanju, plućni arterijski klinasti pritisak (PAWP) ≤ 15 mmHg i plućni vaskularni otpor (PVR) > 240 dyn·s·cm^{-5}. Godišnja incidencija plućne arterijske hipertenzije (PAH) iznosi približno 3–10 novih slučajeva na milion odraslih osoba. Smatra se da prevalencija plućne hipertenzije kod osoba starijih od 65 godina iznosi oko 10%.Cilj ovog rada je da prikaže slučaj pacijentkinje s progresivnom dispneom, kod koje je PAH ostala dugo neprepoznata. Pacijentkinja M.P., 74 godine, hospitalizovana je u Koronarnu jedinicu Zdravstvenog centra Kosovska Mitrovica zbog osećaja otežanog disanja, gušenja, zamaranja, otoka nogu i malaksalosti. EKG na prijemu pokazao je: sinusni ritam, normogram, visok R talas u V2, ST depresiju i negativan T talas u odvodima D2, D3, aVF i V4–V5. Na ehokardiografiji je desna komora uvećana (2,9 cm), plućna arterija dilatirana (3,3 cm), prisutna 1–2+ pulmonalna regurgitacija i 3+ trikuspidna regurgitacija, sa sistolnim pritiskom u desnoj komori (SPDK) do 126 mmHg. Dimenzije desne komore u 4Ch projekciji iznose 5,3 cm, dok TAPSE iznosi 1,8 cm. Tokom kateterizacije desnog srca, izmereni su sledeći pritisci: PA 78/34/57 mmHg, RV 74/8/10 mmHg, RA 6/6/7 mmHg, CO 4,3 l/min, LV 99/10/8 mmHg.
Iako je primarna plućna hipertenzija predominantno bolest mlađih ljudi, na nju treba misliti i kod starijih osoba, posebno u prisustvu progresivne dispnee bez strukturne bolesti srca.

Ključne reči: plućna hipertenzija, ehokardiografija, SPDK

INTRODUCTION

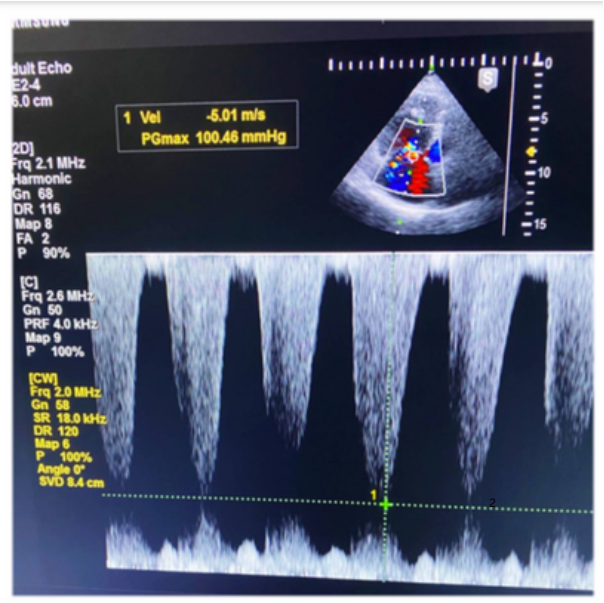
Pulmonary hypertension represents a hemodynamic condition characterized by a mean pulmonary artery pressure (PAPm) ≥ 25 mm Hg at rest, a pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg, and a pulmonary vascular resistance (PVR) >240 dyn·s·cm^{-5}. Pulmonary arterial hypertension (PAH) refers to a subgroup of pulmonary hypertension with pre-capillary pulmonary hypertension characterized by elevated pulmonary vascular resistance (PVR), i.e., PAPm ≥ 25 mm Hg with normal PAWP ≤ 15 mm Hg and PVR > 240 dyn·s·cm^{-5} (1,2). The annual incidence of pulmonary arterial hypertension is around 3-10 new cases per million adults. Pulmonary hypertension affects about 1% of the global population and is not considered a rare disease. The prevalence of pulmonary hypertension in individuals older than 65 years is estimated to be around 10% (3). In Germany, the incidence of pulmonary arterial hypertension in 2014 was 3.9 per 1 million adults, with a prevalence of 25.9 per million adults (4). Initially, it was believed that pulmonary arterial hypertension mainly affected young women; however, in recent years, the median age of patients diagnosed with pulmonary arterial hypertension in Germany has steadily increased, currently standing at 65 years (4, 5). The expected lifespan of patients with pulmonary arterial hypertension has increased over the last three decades. The three-year survival rate for this group is now 70-80% (5), compared to 40% in the 1980s.The cardinal symptom of any form of pulmonary hypertension is progressive dyspnea upon exertion, often accompanied by fatigue and exhaustion. In patients with pulmonary hypertension, frequent syncope even with minimal exertion clearly indicates the presence of a life-threatening condition associated with high mortality. Physical examination of patients with compensated pulmonary hypertension often does not reveal abnormalities. The most common signs are central and peripheral cyanosis, though these are very subtle, and occasionally an auscultatory murmur from tricuspid regurgitation. To diagnose pulmonary hypertension, an ECG and measurement of natriuretic peptide levels are necessary. If both do not show abnormalities, it is unlikely that pulmonary hypertension is present (8). Echocardiographic assessment of right ventricular pressure is often unreliable, but when combined with signs of right heart overload, echocardiography usually provides clear signs of pulmonary hypertension, indicating the type of investigation that should follow (1,2). Pulmonary hypertension can only be definitively confirmed by right heart catheterization, which is absolutely indicated only for patients suspected of having pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, while other forms may not require it. According to guidelines, oxygen therapy is indicated whenever there is manifest hypoxemia with arterial pO2 < 60 mm Hg. Any anemia or iron deficiency without anemia should be corrected. Venipuncture is rarely indicated in patients with polycythemia. When it comes to diuretics in PAH therapy, we use loop diuretics in combination with mineralocorticoids. Anticoagulation is no longer recommended for general use (1,2,9).

Patients with idiopathic or hereditary pulmonary arterial hypertension, or PAH associated with medications, are initially treated with calcium channel antagonists. However, this form of treatment is an option for less than 5% of PAH patients (1,2). For the treatment of idiopathic pulmonary hypertension, specific medications are used, classified into five groups. These drugs are used either alone or in combination. Despite all the assumed treatment modalities, pulmonary arterial hypertension remains an incurable disease with high mortality and poor prognosis. The goal of treatment is to control the disease, i.e., to stabilize the patient at a satisfactory clinical level (Functional Class I or II of the WHO), without signs of right heart failure and ideally without disease progression. In one randomized study using initial combination therapy (10), this goal was achieved in 40% of patients. The choice of medication partially depends on the severity of the pulmonary arterial hypertension. According to mortality risk, PAH patients are categorized into low, medium, and high-risk groups. Patients with newly diagnosed "typical" pulmonary arterial hypertension and low or medium risk receive initial or early combination therapy, which includes an endothelin receptor antagonist (ERA) combined with a phosphodiesterase-5 (PDE5) inhibitor or soluble guanylate cyclase (sGC) stimulator (10–12). For high-risk patients, the recommended initial treatment is a triple combination of ERA, PDE5 inhibitors or sGC stimulators, and an intravenous prostacyclin analog. The patient's response to therapy is assessed after 4-12 weeks initially. If the patient has not achieved the primary treatment goal, i.e., reaching the low-risk category, after initial treatment, the next step is double or triple combination therapy.

The aim of this work is to present a case of a patient with progressive dyspnea who had long remained undiagnosed with PAH.

Patient: M.P., 74 years old, was admitted to the Coronary Unit of ZC KM due to difficulty breathing, suffocation, fatigue, leg swelling, and malaise. These symptoms had persisted for the past 2 years but intensified over the past few days. She has been treated for high blood pressure and varicose veins for several years and denies any allergies to food or medication.
Upon admission, she was alert, oriented, eupnoic, acyanotic, and had normal skin and mucous membrane color. She had a medium skeletal muscular build and normal nutrition. Her chest was cylindrical, and both sides showed normal respiratory movement. On auscultation, a slightly harsh inspiratory wheeze was heard at both basal lung regions. Cardiac rhythm was regular, with an accentuated P2 and a systolic murmur at the apex. Upon admission, her blood pressure was 140/100 mmHg, and her heart rate was 80 bpm. Her abdomen was soft to palpation, non-tender, with no palpable liver or spleen enlargement. Discreet pretibial edema was noted, with pronounced varicosities on the left inner knee. Peripheral arterial pulses were symmetrical and palpable.
The patient was clinically, echocardiographically, and radiologically evaluated upon admission. Her ECG showed sinus rhythm, normogram, high R in V2, ST depression, and negative T in D2, D3, aVF, V4-5.
Blood tests, echocardiography, and further diagnostics were carried out.
Echocardiogram: The aorta has normal width at the root and ascending segment, measuring 31 mm. The aortic valve is tricuspid, with preserved leaflet separation. The left atrium is of normal size, measuring 3.4 cm, and there is 1+ mitral regurgitation. The mitral apparatus is not significantly morphed. An aneurysm of the interatrial septum is observed, oriented towards the left atrium. Color Doppler does not show clear signs of a shunt at this level. The left ventricle has normal dimensions, 41/25 mm, with slowed relaxation, no segmental kinetic abnormalities, and preserved overall systolic function. A D-shaped left ventricle is noted. The right ventricle is enlarged, measuring 2.9 cm. The pulmonary artery is dilated to 3.3 cm. 1-2+ pulmonary regurgitation is registered. There is 3+ tricuspid regurgitation, with an SPAP of 126 mmHg. RV 4Ch is 5.3 cm, TAPSE is 1.8 cm. The pericardium shows no changes. The inferior vena cava (IVC) is dilated, compressible during inspiration up to 1/3. (Figure 1)

Figure 1.



In the laboratory tests, Troponin T is 12, CK is 35, BNP is 502, NT-proBNP is 4518, D-dimer is 0.86, and the remaining laboratory values are within the reference range.
Gas analysis: pH 7.52, pO2 20, pCO2 68, glucose 5.2, lactate 0.7, HCO3 16.3, standard HCO3 21.5, BE -4.2, BEecf -6.6.

Given the significantly elevated pressure in the right ventricle and the suspicion of pulmonary thromboembolism, the patient urgently underwent MSCT PA according to the pulmonary embolism protocol. The pulmonary artery trunk is dilated, with the left lung (LL) reaching 44mm, large left pulmonary artery (LPA) 25mm, and right pulmonary artery (DPA) 27mm, showing a complete defect in the segmental branch for S4-S5 on the CT scan, with discretely hypoperfused parenchyma in the peripheral S4 region. No signs of PTE were observed in other areas. No changes in the parenchyma.

Since the diagnostic procedures performed could not explain the cause of the elevated pressure in the right heart, the patient was referred to the UKCS Belgrade for further diagnostics. During hospitalization, right heart catheterization was performed: In the ostial segment of the main stem, stenosis up to 30% was observed. The LAD (left anterior descending artery) showed no angiographically significant stenoses in the proximal, medial, and distal segments. The distal segment of the LAD was tortuously altered. The circumflex coronary artery showed no stenoses in its proximal and distal segments. The RCA (right coronary artery) showed no stenoses in its proximal, medial, and distal segments. Pressures were measured in the right heart: PA (pulmonary artery) 78/34/57 mmHg, RV (right ventricle) 74/8/10 mmHg, RA (right atrium) 6/6/7 mmHg, CO (cardiac output) 4.3 L/min, LV (left ventricle) 99/10/8 mmHg. (Figure 2.)

Figure 2.

Supplementary diagnostics were performed:

Ergospirometry on an ergocycle: EKG showed no ST-T changes during exertion and recovery. The test indicates preserved functional heart capacity, severely reduced ventilatory function, and signs of pronounced pulmonary hypertension.
Spirometry: Normal ventilation, FVC 108% (2.08L), FEV1 130% (2.031), FEV1%/FVC 97.30%.
Vascular surgery and lower leg vein CDS: Iliac, femoral, popliteal, anterior and posterior tibial veins were normal, with no signs of thrombosis. The right great saphenous vein had varicose branches, but no thrombotic masses. The left leg showed varicosities in the trunk and branches of the great saphenous vein, but again, no thrombotic masses.
During hospitalization, the patient was treated with calcium channel blockers, ACE inhibitors, trimetazidine, PPIs, anticoagulant therapy, and symptomatic treatment. After the right heart catheterization and confirmation of pre-capillary pulmonary hypertension, specific PAH therapy with sildenafil and bosentan was introduced. During hospitalization, the patient was asymptomatic, with no significant rhythm disturbances or conduction abnormalities registered."

CONCLUSIONS

The diagnosis of primary pulmonary hypertension is often delayed. Although primary pulmonary hypertension predominantly affects young individuals, it should also be considered in older patients whenever progressive dyspnea is present in the absence of structural heart disease.

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PRAXIS MEDICA

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• Case outline
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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

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).

K**linička 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.

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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.

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.

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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.

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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55 GODINA ČASOPISA PRAXIS MEDICA