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URINARY IODINE CONCENTRATION: PREDICTOR OF BIRTH WEIGHT OR BIOMARKER FOR ASSESSING THE IODINE STATUS IN HEALTHY PREGNANT WOMEN, ONLY?

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Introduction: This study determined urine iodine concentration (UIC) during gestation, assessed the maternal iodine nutrition status and correlated it with gestational age at birth (GAB) and birth weight (BW).The measurement of UIC provides the best single measurement of the iodine nutritional status in population. Objective: Determination of UIC in pregnant women in North Macedonia. ***Methods:*** This prospective study assessed the iodine nutrition status during the course of pregnancy with reference of median UIC among 364 healthy pregnant women in different gestational age (in trimester and 5-week intervals). ***Results:*** The overall and the 1st to the 3rd trimester median UIC were: 183.7, 207, 189.75 and 169.28 [μg/L], respectively. The median UIC (μg/L) results according to 5-week interval in advancing gestation were: 232.34, 200.13, 152.81, 194.39, 181.28, 160.28, 169.41 and 175.24, respectively. We detected 5.22% (19/364) and 74.72% (272/364) with the median UIC < 50 μg/L and UIC ≥ 100 μg/L, respectively. In multiple regression, the median UIC (β = 0.0000767, P = 0.929) had no statistically significant prediction to the GAB. Disease prevalence results for mean UIC in detecting BW had no statistical significance: area under curve (AUC) = 0.521, z-statistic (0.340), sensitivity (45.83%), specificity (66.27%), predictive (6.59%) and P value (0.734). ***Conclusion:*** Iodine status of pregnant women in our study is generally sufficient by World Health Organization recommendations. The median UIC in each trimester and 5-week interval has statistically insignificant decrease in accordance to the advancing gestation. The median UIC has no significance in predicting GAB and BW.

Key words: pregnancy, urinary iodine concentration, iodine nutritional status, birth weight, gestational age at birth, thyroid metabolism

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INTRODUCTION

Impaired maternal thyroid metabolism and thyroid hormones status are associated with poor outcomes for the mother and the developing newborn, preterm delivery, low birth weight, irreversible damage to the nervous system and intelligence of the fetus (1). Iodine is required for the production of thyroid hormones, which play a crucial role in fetal organogenesis, and in particular in brain development (2). Pregnancy is

associated with substantial changes in thyroid physiology and represents a major stress on maternal homeostasis. The need for iodine in pregnancy is increased (3) due to an increase in maternal thyroxine production to maintain maternal euthyroidism and for transfer of thyroid hormones to the fetus in early pregnancy, before the fetal thyroid begins functioning (4).

The majority of iodine absorbed by the body is excreted in urine. Urine iodine excretion is largely a passive process (5) dependent on glomerular filtration rate (GFR).

The maternal GFR is increased during pregnancy resulting in increased renal loss of ingested iodine, which results with an additional increase in urinary iodine concentration (UIC). In pregnancy, oncotic pressure is substantially decreased because of expansion of the plasma volume, thus contributing to a rise in GFR (6, 7).UIC in nonpregnant women on a stable diet represents a dynamic equilibrium between dietary intakes, thyroidal iodine extraction, the total body thyroid hormone pool, and GFR (5). Pregnancy is a vasodilated state mediated by elevated levels of progesterone.GFR increases continuously within the first month of pregnancy, and reaches its maximum of 40-50% above the level before conception. In the second trimester GFR reached a plateau, and slowly decreased in the third trimester toward the pregnancy concentration (7). Pregnancy is a vasodilated state mediated by alterations in sensitivity to angiotensin II and elevated levels of progesterone. Progesterone has a diuretic effect which is related to aldosterone antagonism which results in increases of GFR (5 - 7). Increased nitric oxide production that occur during normal pregnancy results in cardiac output rising and abets the expansions of plasma volume by stimulating renal sodium and water retention. Both increased renal blood flow and decreased oncotic pressure due to plasma volume expansion contribute to higher GFR (3).

A higher GFR during pregnancy results in decreased circulating creatinine and a possible trend toward lower urinary creatinine concentrations (7, 8). Hence, pregnancy can be expected to result in increased renal iodine losses. In circumstances of borderline or overt iodine deficiency, increases in GFR could deplete total body iodine reserves without the capacity for replenishment if dietary intake remains low (5, 9).The main reasons for increased iodine requirements during pregnancy are: increased thyroid hormone production in pregnancy; the increase in maternal GFR because of increased losses of ingested iodine; fetal and placental consumption of maternal iodine and thyroid hormone proportion. Therefore, the fetal iodine store-supported exclusively by maternal intake, must be continuously refreshed (6).

The excretion of iodine in the urine is a good measure of iodine intake. The median UIC is easily obtainable indicator for iodine status, and it is considered a sensitive marker of current iodine intake that reflects recent changes in iodine status (8, 10).

The measurement of urine iodine excretion provides the best single measurement of the iodine nutritional status of a population (10), but this indicator does not provide direct information about thyroid function (11). UICs are, therefore, not useful for the diagnosis and treatment of individuals, because an individual's UIC can vary daily, or even within the same day but it provides a useful measure of the iodine status of populations (12). UIC can be used as a tool to evaluate the status of iodine nutrition of population (13) and serves as a sensitive parameter of recent iodine intake which reflects the equilibrium between intake and excretion (14). Although there are several methods for UIC quantification reviewed by Dunn *et al.* (15). World Health Organization (WHO) currently recommends the Sandell-Kolthoff-method for epidemiological studies (16). The status of iodine nutrition of a population is determined by measurements of UIC since it is considered an indicator of the adequacy of the iodine intake of that population (5,8,10).

A joint task force of the WHO, the United Nations Children's Fund (UNICEF), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) (17) recommends as parameter for the adequacy of the iodine intake in pregnant women, UIC range from 150 to 249 μg/L. UIC less than 150 μg/L have been defined as iodine deficiency (18).

North Macedonia is historically iodine deficient, but due to the long standing and effective preventive measures, it has been considered iodine replete since 2003 (19). Several studies were conducted in 2002, 2003, and 2007 to monitor the iodine status of the Macedonian population and the pregnant women too. These studies have confirmed sustainable sufficient iodine nutrition in the country (20,21).

The aims of this study were divided into primary and secondary. The primary aims were: First, to assess the impact of advancing gestation on UIC in normal pregnancy according to the different determined reference intervals (trimesters or 5 weeks intervals); second, to compare the results of UIC variations over the course of pregnancy with other studies and third, to assess the maternal status of iodine nutrition determined by measurement of UIC and compare it with maternal iodine status in other studies. The secondary aim of our study was to estimate the impact of UIC on some neonatal outcomes [gestational age at birth (GAB) and birth weight].

PARTICIPANTS AND METHODS

Participants

We prospectively investigated UIC in 364 healthy pregnant women in different gestational week (g.w.), without known thyroid disorder that gave birth at the University Clinic of Gynecology and Obstetrics - Skopje. They had a mean age 29.2 ± 5.6 years, and their mean body mass index (BMI) was 27.14 ± 4.79 kg/m^2. They signed an informed consent, and the Ethics Committee of our institution approved the study.

Inclusion criteria were singleton pregnancy in any gestational age without previous history of thyroid disease of the mother or treatment with thyroid drugs. The exclusion criteria were as follows: mothers who smoke cigarettes, mothers with any chronic disease (diabetes mellitus, hypertension), mothers who has personal history of thyroid disease or a visible (palpable goiter). The subjects who took thyroid-related medicine and who had some other gynecologic condition (uterine fibroids and any fetal anomaly diagnosed with amniocentesis or ultrasound) were excluded, too.The data about maternal age, parity, obstetric history and gestational age at the time of birth were noted from the medical history. Birth weight for all newborns was measured by the midwife attending the birth.

Procedures and criteria

A sample of 2 mL of urine was taken with special pipette from each participant and added in Eppendorf tube. Because of within-day and circadian rhythmicity in UI excretion, we collected the urine sample in the same time (fasting morning urine samples) specified time period between 9 to 10 h P.M. (22). The test tubes were marked with identification number (ID) and frozen at T = -20°C, before being transported. UIC in urine samples was analyzed at the National Institute for Health and Welfare (THL) in Helsinki (ICP) by mass spectrometry (MS) using Agilent 7800 ICP-MS system integrated with Agilent SPS 4 auto sampler, with the Pinell-modified Sandell Kolthoff method (23), described previously.

The threshold criteria for UIC data filtering [(UIC < 50 μg/L, UIC ≥ 100 μg/L) in 5 week (wk) gestation intervals group analysis and (150 μg/L < UIC ≤ 249 μg/L in trimester analysis, also (UIC < 150 μg/L) in predictor's analysis] for adequacy of iodine nutrition during calculations were given by WHO, UNICEF and ICCIDD recommendations (16, 17, 24).To assess the iodine status of a population, the median [not the mean ± SD (standard deviation)] UIC is recommended (25). The median, percentiles and interquartile range (IQR) is the preferred measure of central tendency, rather than mean and SD, are most commonly used to describe the distribution of UIC data (17, 26)

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software version 19.1.3 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2019). Normally distributed variables were presented as mean and SD. Non-normally distributed variables were presented as median and IQR. Some results were presented as N (number) or % (percent). Appropriates Kruskal – Wallis H test or Mann-Whitney U test were used to found difference between UIC values among gestation trimester groups or among 5 wk gestational age interval (between more than 3 groups, or between two groups), respectively. A t Test for independent samples was used to find the difference between symmetrically distributed data. Kernel density plot was created to visualize the distribution of UIC data over a continuous interval. Bivariate Pearson's correlation test was used to measure the strength and direction of relationships between variables. Summary plot of notched box-and-whisker diagram with trend line were created to show UIC results for each 5 wk gestation age period. Multiple backward regression analysis was used to show predictable values of independent variables (maternal BMI, UIC and age as predictors) on the dependent variable GAB and birth weight. Summarized essential information of UIC in meta-analysis according trimester compared with our study, according to the WHO recommendation, was presented as Forest plot diagram. A disease prevalence diagram was created to show prediction value of UIC in detection of birth weight.

RESULTS

During the fourth-month period, from April to July 2017, UIC was assessed in 364 healthy pregnant women in any gestational week (mean age 29.2 ± 5.6 years).

Maternal and fetal outcomes characteristics

Sample characteristics of 364 pregnant women and some of their fetal outcomes are presented in Table 1. In the first trimester of pregnancy (up to 12 g.w.) a total of 67 (18.41 %) were examined, in the second trimester (12 - 28 g.w.) were examined 100 (27.47 %) and in the third trimester (≥ 28 g.w.) were examined 197

(54.12 %). The mean age of the cohort was 29.2 ± 5.6 years, with their mean BMI of 27.14 ± 4.79 kg/m^2 and the mean time of urine sampling was 29.0 ± 10.1 g.w.

The median UIC values in each trimester did not deviate from the median reference values according to the WHO value range (150 – 249 μg/L): in the first (207 μg/L, 95% Confidence Interval [CI] = 197.06 – 221.60), in the second (189.75 μg/L, 95% CI = 181.97 – 217.0) and in the third trimester (169.28 μg/L, 95% CI = 178.76 – 212.7). The overall median UIC during pregnancy (183.7 μg/L) and 95% CI (166.71 to 203.66) were within the WHO's reference range, too.

Appropriate IQR (equal to the difference between 75th and 25th percentiles) for the trimesters are presented in round brackets. We did not found statistically significant difference between median UIC values among trimesters (P = 0.418, T statistic = 1.7447; Kruskal – Wallis H test) and neither between nor within trimester groups (P = 0.747, P = 0.297 and P = 0.289; Mann-Whitney U test). Some of the newborn data (GAB and birth weight) are shown at the bottom of the table 1, too.

The 5th to 95th percentiles range of UIC values for overall, first, second and third trimester of pregnancy were: 48.024 to 438.023 μg/L, 42.493 to 586.963 μg/L, 54.453 to 459.778 μg/L and 44.362 to 422.890 μg/L, respectively. The 25th to 75th percentiles range results for UIC are showed in Table 1, too.

Table 1.
Demographic, clinical and other characteristics according to gestational trimesters

Variables	Mean ± SD Median (IQR)	95% Confidence Interval 25th - 75th percentiles *	group	P - value	group	P - value	group	P - value	
Age (years)	29.2 ± 5.6	28.7 - 29.8							
BMI (kg/m^2)	27.14 ± 4.79	26.64 - 27.63							
Examination time (g.w.)	29.0 ± 10.1	27.9 - 30.2							
UIC (μg/L)	183.7 (161.21)	110.71 - 271.92 *							
UIC (150 - 249 μg/L), WHO[1]	201.5 (47.1)	223.9 - 176.8 *							
UIC (1st trimester)	207 (72.29)	170.39 - 242.68 *	1st	0.747			1st		
UIC (2nd trimester)	189.75 (63.2)	154.60 - 217.8 *	2st		2st	0.297		0.289	
UIC (3rd trimester)	169.28 (50.85)	150.89 - 201.74 *			3st		3st		
GAB (g.w.)	38.4 ± 2.5	38.2 to 38.7							
Birth weight (g)	3127.3 ± 563.4	3068.7 to 3185.8							

SD, standard deviation; IQR, interquartile range; g.w., gestaional week; UIC, Urinary Iodine Concentration;
WHO[1], value range according to the World Health Organization; GAB, gestational age at birth; *, percentiles.

Kernel density plot

A density plot visualizes the distribution of data [UIC (μg/L), x_1 – axis] over a continuous interval or time period. Density trace graph presents distribution and the peak of UIC density, which displays where values of UIC are concentrated. The y-axis (y_1, y_2 and y_3) in a density plot is the probability density function for the Kernel density estimation (KDE). The first (blue, 1), the second (red, 2) and the third (green, 3) line are presenting a distribution of a different data according to the stages of pregnancy. The summary diagram of three different KDE curves is shown on Figure 1.

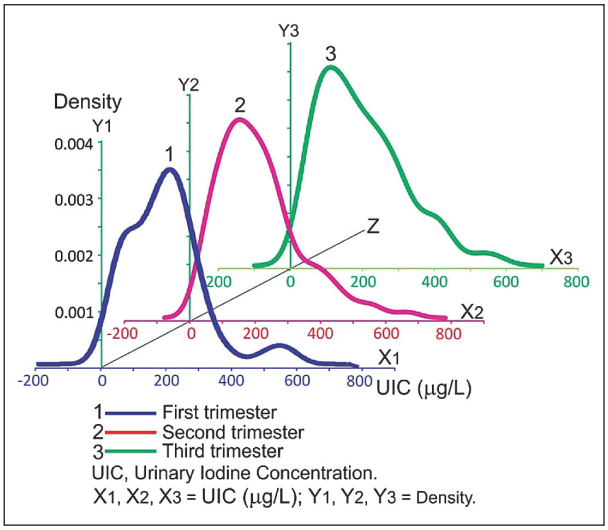

Fig 1. *Kernel density estimation (KDE) and distribution of Urinary Iodine Concentration according to each trimester of pregnancy*

For data density estimation, we used KDE instead histogram, because histogram is not smooth enough to present picture of data distribution as it is KDE. On y-axis is shown the frequency of individuals presented at the corresponding distance – bin. The frequency distribution across space after dispersal event is shown on x-axis: distances from a common origin (binned). The layouts of the frequencies (density from 0 to 0.004) of the UIC have different variability to the value of the mark (UIC). The three KDE curves are positively skewed, or skewed to the right (the mean is greater than the median).

Urinary iodine concentration according to the gestational age

For a more accurate expression of the UIC values variations during pregnancy, we divided the gestation period into 8 subgroups according to a five-week gestational interval. The distribution of UIC with two different UIC threshold values (UIC < 50 μg/L; UIC ≥ 100 μg/L) and Kruskal-Wallis U test between and within groups are shown in Table 2. The UIC results are presented as median according to WHO recommendation (25).

Table 2. *Urinary iodine concentration (UIC) and two different UIC thresholds values in different gestational age groups with results of Kruskal-Wallis H test*

Group	Gestat. Age	N (%)	UIC (μg/L)	UIC < 50 (μg/L)	UIC ≥ 100 (μg/L)	Gestation, wk	Maternal age
Number	wk, [median]	Total 364 (100)	Median (IQR)	N (%), [median]	N (%), [median]	Mean ± SD	Yr, Mean ± SD
1	5 - 9.9 [7]	9 (2.47)	232.34 (149.56)	0	7 (77.7), [258.5]	7.55 ± 1.3	29.1 ± 5.5
2	10 - 14.9 [12]	55 (15,11)	200.13 (142.55)	4 (7.27), [38.41]	39 (70.9), [213.8]	11.49 ± 0.66	29.2 ± 4.9
3	15 - 19.9 [17]	11 (3.02)	152.81 (133.4)	0	7 (63.6), [182.12]	16.8 ± 1.37	31.0 ± 4.7
4	20 - 24.9 [22]	31 (8.51)	194.39 (134.74)	2 (6.45), [42.64]	24 (77.42), [206.98]	21.7 ± 1.26	27.4 ± 6.3
5	25 - 29.9 [28]	61 (16.76)	181.28 (152.15)	2 (3.27), [47.15]	51 (83.61), [214.59]	27.2 ± 1.2	30.6 ± 6.0
6	30 - 34.9 [32]	30 (8.24)	160.28 (167.48)	1 (3.3), [30.6]	21 (70), [230.94]	32.2 ± 1.49	30.5 ± 6.1
7	35 - 39.9 [38]	111 (30.49)	169.41 (177.25)	6 (5.4), [37.5]	86 (77.47), [210.31]	37.7 ± 1.23	28.9 ± 5.4
8	40 - 41.4 [40]	56 (15.38)	175.24 (154.91)	4 (7.14), [40]	37 (66.07), [212.86]	40.41 ± 0.49	28.3 ± 4.8
The results are expressed as: median and interquartile range (IQR), Mean and standard deviation (SD), number N and percent (%). Gest. Age, gestational age; wk, weeks; UIC, Urinary Iodine Concentration;							
Kruskal-Wallis H test							
Test statistic		3.8647					
Corrected for ties Ht		3.8647					
		Degrees of Freedom (DF)		Significance level (P - Value)			
Between Groups		7		0.451			
Within Groups		356		0.795			

The median UIC values in any of the eight gestational age groups did not deviate from the median reference values according to WHO value range (150 – 249 μg/L): 152.81, 160.28, 169.41, 175.24, 181.28, 194.39, 200.13 and 232.34 μg/L, in ascending order, respectively for 3rd, 6th, 7th, 8th, 5th, 4th and 1st gestational age group. There is no statistically significant difference (P = 0.451) in UIC values and maternal age values (P = 0.102) between and within the eight subgroups (Kruskal-Wallis H test and t Test for independent samples, for UIC and age, respectively).

The prevalence of pregnant women in this study with the median UIC < 50 μg/L is only 5.22% (19 cases), and 272 cases (74.72%) from the total were with median UIC ≥ 100 μg/L. Minimal value of median UIC (152.81 μg/L) is registered in third subgroup (15 – 19.9 wk, median 17 wk).

Distribution of the median urinary iodine concentration

The UIC results from each 5-week interval from gestation period [median, 95% CI of the median, 25th percentiles, 75th percentiles and range] are shown by notched box-and-whisker diagram in Fig 2. The median UIC red trend line shows the ascending and descending variation according to the gestational age period. The WHO range determination for UIC (150 – 249 μg/L) is showed by green rectangle. Despite the visible variations of the median UIC during pregnancy showed by red trend line, there is no out of range deviation in UIC, according to the WHO recommendation.

According to the Mann-Whitney test for independent samples we found statistical significance (P = 0.046, test statistic Z = 1.981) between the UIC values in the subgroup A (18 to 21 wk) and the subgroup B (39 to 41.4 wk). The median value for UIC and (95% CI) for the median were 200.85 μg/L (153.62 to 289.85) and 127.27 μg/L (87.17 to 237.99) for subgroup A and B, respectively (Fig. 2).

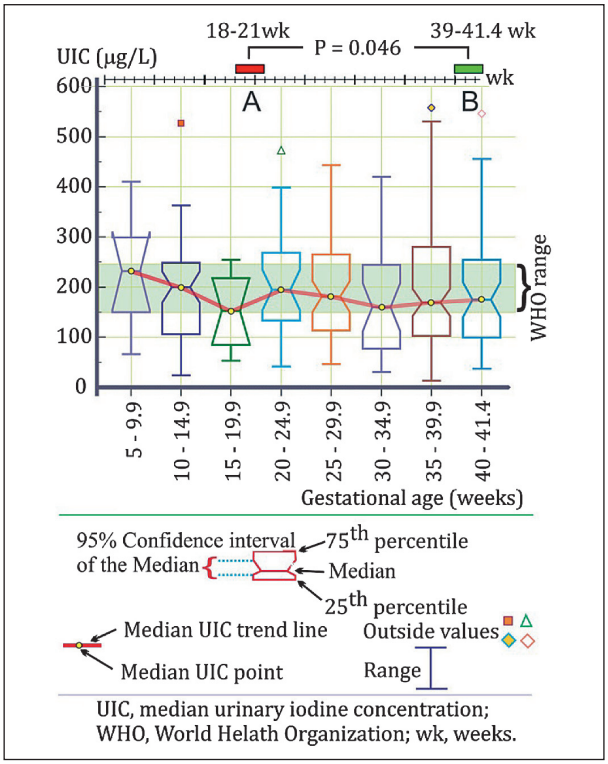

Fig 2. *Distribution of the median urinary iodine concentration through the gestation period*

Bivariate Pearson's correlation analysis

The positive value of Pearson product-moment correlation coefficient (r) as measure of the strength of linear correlation of UIC with maternal and fetal outcome characteristics indicated positive, but not significant correlation between UIC and birth weight (r = 0.05, P = 0.349); UIC and GAB (r = 0.003, P = 0.960); UIC and maternal BMI (r = 0.030, P = 0.568) and UIC and maternal age (r = 0.019, P = 0.72). An inverse significant correlation (P < 0.05) was found between UIC and gestational age of pregnancy (r = - 0.107, P = 0.044).

Multiple backward regression analysis

According to the β standardized Coefficient (βst) and P-value results from multiple backward regression analysis, we found strong positive statistically significant dependency of dependent variable birth weight (βst = 22.5535, P = 0.0004) from maternal BMI as independent variable. This means that any increase of maternal BMI results in an increased birth weight. Independent variables (UIC and maternal age) do not show statistically significant impact on birth weight: (β = 0.1627, P = 0.391) and (β = - 4.7567, P = 0.3782) for UIC and maternal age, respectively.

We found strong inverse statistically significant dependency of dependent variable GAB (β = -0.05560, P = 0.0244) from maternal age as independent variable. This means that any increase of maternal age results in a decreased GAB. BMI (β = 0.004688, P = 0.869) and UIC (β = 0.0000767, P = 0.929) do not show statistically significant predictable value on the dependent variable GAB.

Predictive value of UIC

Selecting option "Plot versus criterion variable (UIC < 150 μg/L)" in MedCalc, we got a curve of disease prevalence i.e. diagram of positive predictive value (%) of UIC < 150 μg/L on birth weight (g). We selected a dichotomous variable (UIC < 150 μg/L) as classification variable: zero (0) for 340 cases with UIC ≥ 150 μg/L and one (1) for 24 cases with UIC < 150 μg/L. Birth weight (g) was selected as estimated variable. The results for positive predictive value variations (%), disease prevalence and associate criterion (birth weight) are shown in Fig. 3.

Disease prevalence was calculated by the next equation: That means.

$$\frac{positive\ cases\ (UIC\ <\ 150mg/\mu gL)}{total\ cases} = \frac{x}{100}\ .\ \text{That means}\ x = \frac{24 \cdot 100}{364} = 6.59\%$$

The maximal sensitivity (45.83%) and specificity (66.27%) of predictor dichotomous variable (UIC < 150 μg/L) in the predicting of birth weight (associate criterion birth weight > 3350 g) is presented as peak (black arrow) of the disease prevalence curve, showed on Fig 3. The receiver operation characteristics (ROC) results were: area under curve (AUC) =0.521, z - statistic = 0.340, P = 0.734, Youden index = 0.121. According ROC, AUC and P – value results, there is no statistical significance in predicting birth weight by classification variable UIC < 150 μg/L.

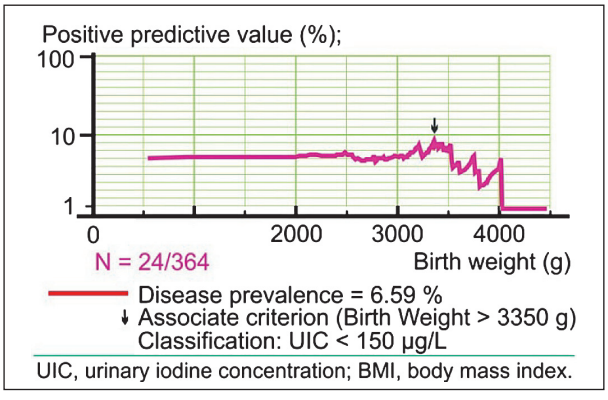

Fig 3. *Prediction value of UIC in detection of birth weight*

Comparison with other studies

The diagram called a forest plot (Fig. 4) summarized essential information of meta-analysis (the name of corresponding author and separate results for median UIC according for each trimester of pregnancy according to the gestation time of urine collection).

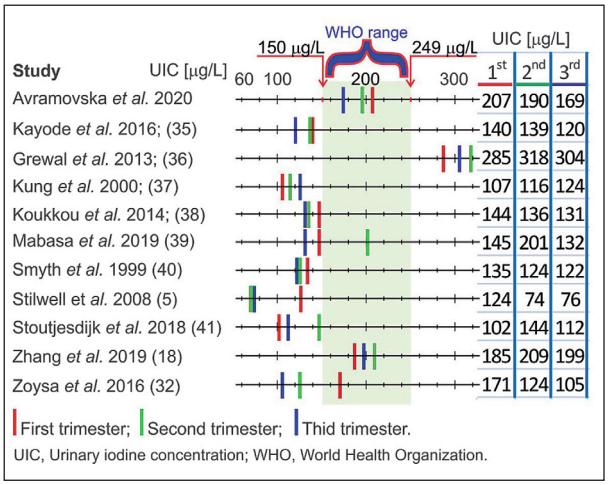

Fig 4. *A forest plot presentation (blobbogram) of median Urinary Iodine Concentration according to the gestation trimester of urine collection*

The vertically placed colored line on numerically divided horizontal line represents the UIC medians for each trimester (red for the 1st, green for the 2nd and blue line for the 3rd trimester). The mutual position of each UIC mean among various studies, as well as their position according to WHO recommended UIC interval (green rectangle, WHO range) for adequate iodine intake in pregnancy, is well understood.

DISCUSSION

We prospectively investigated UIC in 364 healthy pregnant women who consequently came to ambulance of gynecological clinic, regardless of the g.w. of pregnancy, but we selected them by predetermined exclusion criteria. The aims of this study were to determine UIC according to the advancing gestation and to assess the maternal iodine nutrition status, also to correlate the UIC with some neonatal outcomes.

The overall median UIC during pregnancy, median UIC in the first, second and third trimester did not deviate from the median reference value range according to the WHO recommendation (criteria for an acceptable iodine nutritional status in pregnant women) (17). The 25th to 75th percentiles of UIC values in each trimester according to the criteria established by the

WHO indicated an acceptable iodine nutrition status, in women in our study. With the UIC results of 5th to 95th percentiles we detected that 5% of the cohort in our study have median UIC values smaller than 48.0 μg/L (and just as much over 438.0 μg/L). According the results presented in Table 2, only 5.2% from total pregnant women showed UIC < 50 μg/L. Knowing the fact that the adequacy of iodine nutrition is defined by the following criteria: a median UIC ≥ 100 μg/L (with allowed presence 20% of the population having UIC < 50 μg/L) (5, 9), we present adequate population iodine nutrition in our cohort. This percent is almost 4 times smaller than permitted 20% in the general population.

Our results coresponds to the results of Karanfilski *et al.* from 2005-2007, where the median value for UIC for all trimesters in pregnant population was within the interval from 150 - 249 μg/L, which corresponds to an adequate iodine intake (26). These results, compared to the results from their previous study conducted in 2001 (149.7 μg/L for the first, 157.6 μg/L for the second and 130.4 μg/L for the third trimester) suggest an increase in the iodine intake among pregnant women in a population with a confirmed iodine sufficiency (20,26).

However, we must never generalize the given thresholds, range and percent for use in the pregnant population. Changes in iodine requirements and maternal physiology with advancing gestation may invalidate the expected relationship between dietary intake and urine iodine excretion (5, 17). A median UIC of 150 to 249 μg/L has been established to determine the adequate iodine status among pregnant women (17).

Despite the continual downward trend of the mean UIC value from the first to the third trimester, in our study (207, 189.75, 169.28 μg/L), we have not confirmed statistical significant difference neither between nor within the groups (P = 0.418). UIC decreases in the course of pregnancy in our and in most of the previously published studies (27 - 32). During the first trimester and a few weeks later, the fetus relies on maternal thyroid hormones, but as the fetal thyroid gland begins functioning from 15 to 17 weeks gestation, it depends on the maternal iodine supply to maintain thyroid hormone production throughout the remainder of pregnancy (33). The smallest values of the mean UIC (152.81) and IQR (133.4) in the third groups (15 to 19.9 wk, median 17 wk) between series of subgroup's data in our study (Table 2) correlates with requirement of a mother iodine increase confirmed in other studies (5, 30, 33) according to the aforementioned fetal thyroid start-up function. The requirement of a mother iodine increase in pregnancy as result of an increased requirement for thyroxine (T4), a transfer of T4 and iodide from the mother to the fetus and to an increase in the iodine loss due an increase in the renal clearance of iodide (34).

UIC variations during pregnancy sampled by 5 wk intervals are slightly pronounced and gradually downward, so we did not calculate a statistically significant difference neither between (P = 0.451) nor within the groups (P = 0.795). Differences in UIC among gestational groups in studies with inadequate iodine nutrition (depleted iodine status) shown statistical significance (P < 0.001)(5, 33, 37). Unlike them, our and some other studies (18, 32, 39) with better iodine nutritional status, did not showed statistically significant difference between gestational age groups. The most drastic and only one statistically significant (P = 0.046) difference of UIC among two parts of the gestational period A (18 to 21 wk) and B (39 to 41.4 wk) in our study, once again confirms the increased maternal need for iodine during pregnancy.

The trend of median UIC variations throughout pregnancy shown in multiple studies is significantly different: during pregnancy UIC decreases continuously (32, 35, 36, 38, 40); somewhere it increases continuously (37) but elsewhere alternates its trend: first increases from the first to the second trimester, and then decreases from the second to the third trimester (5,18, 36, 39, 41). For better explanation please see a forest presentation shown in Fig. 4. The differences in median UIC values and its trend throughout the pregnancy in the mentioned studies originate from the following characteristics: different time intervals (gestational age) in taking the urine samples (trimesters or 5 wk interval) or in other words diverse referent intervals; difference in the way of taking the urine sample: in what period of the day is it taken (morning, afternoon) and if it was always at the same time, is the sample single (or twice in a day) or is it a collection of 24h urine; differences which are coming from if it UIC results were corrected in accordance with the renal clearance value (GFR); differences that are deriving from the initial UIC value and coming from iodine nutritious status of the pregnant; differences in the number of participants; differences in socio-economy status and ethnic variation, level of education, age and other demographic indicators.

Equalizing the gestational sampling time of 24h urine, UIC correction according to the GFR, assessment of nutritional status with iodine intake and increasing the number of participants are necessary tasks that should be applied so that UIC can be used to assess iodine status in pregnant cohort. The large intra-individual variation in UIC from either spot or 24-hour urine samples means that UIC cannot be used to assess iodine status in an individual pregnant woman. UIC (μg/L) in spot urine samples could to be about

60-65% of the amount excreted in 24 h (42). Thus, multiple factors interact in pregnancy to aggravate of the real UIC value in each examined individual. However, in the absence of clearly defined reference intervals for iodine excretion (UIC) in pregnancy, studies from populations with both adequate iodine nutrition and iodine deficiency provide insight into changes expected in normal pregnancy (5).

We do not found significant correlation between UIC and birth weight (P = 0.349), in accordance with the results of other studies (43, 44). Some studies found positive association between these variables, but these associations were inconsistent across trimesters (45, 46). Therefore, variable, inaccurate with the large intra-individual trimester variation in UIC and non-standardized UIC measurements, make it difficult to correlate with pregnancy outcome. That is why declared inverse correlation between UIC and examination time in our study (P = 0.044) is questionable. In backward multiple regression analysis we found that maternal BMI as independent variable has a positive impact on birth weight (P = 0.0004), only. The included independent variables (UIC and maternal age) do not showed statistically significant impact on birth weight. Including UIC, maternal age and BMI in backward multiple regression analysis for detecting of predictor impact to GAB, we found strong inverse statistically significant dependency of dependent variable GAB (P = 0.0244), only. Opposite to our study results, Rydbeck et al (2014) (47) in cohort of 1617 women [maternal UICs ranged from 0.020 to 10 mg/L (median 0.30 mg/L)], presented that UIC significantly positively associated with birth weight and length for UIC below 1.0 mg/L. Snart *et al.* (2019) (48) collected spot urines samples for UIC in 541 pregnant women with insufficient iodine concentration according WHO. They have not found evidence that UIC is adversely associated with the birth outcomes assessed in their study (48). Due to the different results in our and in the aforementioned studies about UIC association with birth weight, we decided to assess the possible predictive value of UIC on birth weight. We found that there is no statistical significance in predicting birth weight by UIC. Low values of sensitivity and specificity, low AUC (0.521) of predictor dichotomous variable (UIC < 150 μg/L) in predicting birth weight results with no statistical significance (P = 0.734).

More extensive analysis of fetal outcome prediction and analysis of UIC correlation with other iodine and infant parameters was not the main aim of our study, but it may be the motive and goal for future studies on a similar topic.

Our study has several strengths. First, our cohort includes 364 pregnant women, a relatively large sample size for studies of spot urine. Second, we used the Pinell-modified Sandell Kolthoff ICP-MS method, which is a gold standard for quantifying urine iodine. Third, we collected fasting urine spot samples in the same, specified time period (9 to 10h, P.M.) to avoid UIC within-day and circadian rhythmicity variation in UI excretion. Fourth, the UIC results are shown by both, trimester and a 5-week gestational age interval, joined in one study.

STUDY LIMITATIONS

Several limitations to this study should be considered. Analyzing a single spot urine sample instead of multiple spot urinary collections or more efficient repeated 24-hour collections is the first and the main lack in our study. The second limitation is that we did not measure urine creatinine levels to provide UI to creatinine ratio (UI/Cr), as an indicator for assessment of the adequacy UIC, because the serum iodine changes are similar to the UI/Cr. The UIC results in our study are not corrected according to the GFR, which is the third limitation. The fourth and last limitation is the different number of participants in trimester and 5-week gestational groups which further reduces the real estimate of UIC.

CONCLUSIONS

We have demonstrated that the iodine status of pregnant women in our study cohort is generally sufficient by WHO recommendations. The median UIC decreased from the first to the third trimester during pregnancy, but not with statistical significance. The overall median UIC values and median UIC in each trimester did not deviate from the median reference values according to the WHO guidelines, also in any of the eight 5-week gestational age groups.Evident decrease of median UIC is observed in 5-week gestational age group during pregnancy, which is also statistically insignificant.

The most pronounced descending decline in the UIC trend curve registered in the section from 5 to 20-week interval and it's milder decrease to the end of pregnancy is in line with maternal and fetal physiology of iodine needs.

We found strong inversely dependency of GAB from maternal age, but not from UIC and BMI, and strong positive dependency of birth weight from maternal BMI, but not from UIC and maternal age. Because the reference interval for UIC to each trimester or 5-week interval of pregnancy is not established,it is difficult to make an appropriate assessment of correlation of the

UIC and birth outcomes. The median UIC has no significance in predicting birth outcome, but is of great importance for assessing iodine status in pregnant population, more for assessment of population iodine nutrition status, than for individual assessment for it. The validity of a single urine sample for the assessment of iodine status in pregnancy and its impact on birth outcomes warrants further research.

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SAŽETAK

KONCENTRACIJA JODA U MOKRAĆI: PREDSKAZATELJ PORODAJNE TEŽINE ILI BIOLOŠKI BILJEG ZA PROCJENU JODNOG STATUSA SAMO U ZDRAVIH TRUDNICA?

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Uvod: Ova je studija utvrdila koncentraciju joda u mokraći (UIC) tijekom trudnoće, procijenila prehrambeni status joda kod majke i povezala ga s gestacijskom dobi pri rođenju (GAB) i porođajnom težinom (BW). Mjerenje UIC-a omogućava najbolje pojedinačno mjerenje prehrambenog statusa joda u populaciji. ***Cilj:*** Određivanje UIC-a trudnicama u sjevernoj Makedoniji. ***Metode:*** Ova prospektivna studija procjenjivala je prehrambeni status joda tijekom trudnoće, pozivajući se na medijan UIC 364 zdrave trudnice u različitoj gestacijskoj dobi (u intervalima tromjesečja i 5 tjedana). ***Rezultati:*** Ukupna i prosječna UIC od 1. do 3. tromjesečja bila su: 183,7, 207, 189,75 i 169,28 [µg / L]. Srednji rezultati UIC (µg / L) prema intervalu od 5 tjedana u napredovanju trudnoće bili su: 232,34, 200,13, 152,81, 194,39, 181,28, 160,28, 169,41 i 175,24. Otkrili smo 5,22 % (19/364) i 74,72 % (272/364) s medijanom UIC <50 µg / L, odnosno UIC ≥ 100 µg / L. U višestrukoj regresiji, medijan UIC (β = 0,0000767, P = 0,929) nije imao statistički značajno predviđanje za GAB. Rezultati prevalencije bolesti za srednji UIC u otkrivanju BW nisu imali statističku značajnost: područje ispod krivulje (AUC) = 0,521, z-statistika (0,340), osjetljivost (45,83 %), specifičnost (66,27 %), prediktivna (6,59 %) i P vrijednost (0,734). ***Zaključak:*** Jodni status trudnica u našem istraživanju u pravilu je dovoljan prema preporukama Svjetske zdravstvene organizacije. Medijan UIC-a u svakom tromjesečju i intervalu od 5 tjedana statistički je beznačajno smanjen u skladu s napredovanjem trudnoće. Medijan UIC nema značenje u predviđanju GAB i BW.

Ključne riječi: trudnoća, koncentracija joda u mokraći, prehrambeni status joda, težina rođenja, gestacijska dob pri rođenju, metabolizam štitnjače

DENTAL STATUS OF NON-CONTACT SPORTS ATHLETES

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The relationship between dental status of athletes involved in non-contact power sports and their professional level was studied. Data on 60 young men were analyzed, divided into three groups: group 1 (n=20) included non-professional athletes, group 2 (n=20) professionals, and group 3 (control, n=20) men, not engaged in sports. The examination included interviewing and determining dental status, as follows: caries intensity (KPI index (h)), oral hygiene status (OHI-S scale), periodontal status (PBI, PMA, PI indices), microvasculature status (V.I. Kulazhenko test) and viscosity of mixed saliva (according to T.L. Redinova and A.R. Pozdeev). In professional athletes, compared with amateurs, more pronounced deviations of dental status were revealed, i.e. by the PMA index 1.7 times, by the bleeding index (PBI) 1.2 times, by the PI index 1.2 times, and by Kulazhenko sample 1.2 times ($p<0.05$); saliva viscosity after training was 1.3 times higher than that of non-professionals ($p<0.05$), which could be associated with intense physical and psycho-emotional stress and consequential impairment of the water-electrolyte metabolism. Non-contact sports athletes demonstrated low alertness regarding the occurrence of dental pathology, and there was a high degree of dental status disorders.

Key words: dental status, periodontal status, athletes, saliva viscosity, strength sports

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INTRODUCTION

The health of athletes plays an important role in the training process; it directly affects the body's response to physical activity, and athletic performance and results (1-3). Intense physical and psycho-emotional activities can cause the overtraining syndrome, affecting both the training process effectiveness and the health of the athlete (4-6). Significant physical and psycho-emotional activities deplete the body, affect the metabolism level, lead to an immunity decrease and contribute to suppression of the overall reactivity of the body. This may lead to the protein and electrolyte metabolism disorder, shifting the acid-base balance towards metabolic acidosis with respiratory alkalosis, the loss of calcium, phosphorus, potassium and fluorine. As a result, saliva acidity is increasing, and in combination with immunosuppression the microbial metabolism of the mouth is changing, creating conditions for demineralization of tooth enamel and reduced blood flow in the salivary glands (1,7-10).

There is a correlation between inflammatory periodontal diseases and functional disorders of athletes; moderate physical activity helps reduce the inflammatory periodontal diseases, while intensive activity serves as a factor for development of the disease (1,6). Those significant power loads lead to masticatory muscle hypertonicity, which causes temporomandibular joint problems and increases tooth abrasion. Psycho-emotional imbalance during the training period increases the bioelectrical activity of all masticatory muscles, especially of temporal lobe muscles, which is a poor prognostic factor for the longevity of restoration and leads to a growing number of abrasion teeth (1,5).

It is proved that intensive physical training changes the general immune state (increased interleukin-1 and

interleukin-8 deficiency) (11) and local oral immunity ⌈decreased levels of secretory immunoglobulin A (SIgA), lysozyme in saliva⌋ and electrolyte balance of salivary fluid, and as a result contributes to the development of inflammatory periodontal diseases (2). In addition, a number of studies have noted the effect of saliva viscosity on the state of oral cavity; its increase prevents the natural tooth cleaning and contributes to plaque deposition, while its decrease reduces the number of minerals and bicarbonates, thereby limiting the anti-caries activity of saliva (13). Not only excessive physical activity, but also various metabolites that accumulate in the body of athletes during the training process can inhibit the immune response (6,14).

In this context, it is interesting to study the correlation between the severity of dental system disorders and the professional level of athletes.

The purpose of this study was to assess dental status of athletes engaged in non-contact sports at different professional levels.

SUBJECTS AND METHODS

There were 60 young men aged 18 to 30 years in the survey. The study was designed according to ethical norms and laws of the Russian Federation and approved by the Department of Therapeutic Dentistry, Irkutsk State Medical University (head of the Department O. I. Tirskaya) by Protocol No. 7 of January 28, 2019. Before the study, the participants signed a voluntary informed consent for medical examination.

Exclusion criteria were acute inflammatory processes outside the oral cavity; severe cardiovascular, endocrine, and digestive system diseases; age (younger than 18 and older than 30); viral diseases in the oral cavity during the survey (acute and recurrent chronic herpetic infection) and refuse to participate in the study.

Depending on the athletic training level, the participants were divided into three groups. Group 1 (n=20) included non-professional athletes engaged in non-contact power sports for at least 5 years, using weights up to 100-150 kg up to one repeated maximum in a single exercise. Group 1 training was 1.5 hours 2 times a week. Their mean age was 25.8 years, median age 26 (min 23.75; max 27.25).

Group 2 (n=20) included professional athletes engaged in non-contact power sports for at least 5 years, using weights up to 100-150 kg up to one repeated maximum in a single exercise. Group 2 training was 1.5 hours 5 times a week. Their mean age was 25.5 years, median age 27 (min 24.0; max 27.0).

Group 3 (control group, n=20) included men who presented to the Department of Therapeutic Dentistry for treatment or professional hygiene. According to outpatient records, they did not have general somatic pathology and did not exercise regularly. Their mean age was 22.8 years, median age 20 (min 24.5; max 22.8).

Reproducible noninvasive, low-cost screening methods were selected for the survey. The study was based on a questionnaire about the interviewees' attitude to preventive examinations and the risks of developing dental pathology: do you believe that sports can have an undesirable effect on the teeth and/or gums condition; do you consult a dentist for preventive examination, and if so, how often; do you consult a dentist only for treatment in case of problems (yes/no); and what oral cavity problems you can relate directly to power sports.

All participants underwent comprehensive assessment of dental status, including caries intensity ⌈CPI (h) index⌋ and oral hygiene state (Green-Vermillion index, OHI-S). Periodontal status study included periodontal pocket depth assessment using a periodontal probe, pathological tooth mobility, degree of gum bleeding ⌈Muellemann-Saxer index (PBI)⌋, gum inflammation (PMA index), and degree of periodontal tissue destruction (periodontal index).

A modified vacuum sample of V.I. Kulazhenko helped assess the functional state of the microcirculatory bed and capillary reactivity. Using a portable AVLT-Gum device, after creating a negative pressure device in the system of 0.6-0.7 kg/cm^2, we applied an 8-mm diameter glass tip to the gum in the transitional fold area in the lower front teeth and recorded the time in which the hematoma appeared.

According to the method of T. L. Redinova and A. R. Pozdeyev, we evaluated the mixed saliva viscosity in dynamics in groups 1 and 2, before and after training (15). For this purpose, we collected 1-2 mL of oral fluid. The material was taken immediately before the study by spitting into sterile polypropylene tubes with a tightly closed lid. A calibrated pipette fixed in an upright position helped taking 1 mL of saliva and determine the saliva volume flowed from the micro-pipette in 5 seconds. Calculation of relative viscosity of mixed saliva (Ws) in relative units was performed using the formula:

$$Ws = Vв \times Wв/Vs,$$

where Vв is the volume of water (in mL), Wв is viscosity of water (equal to 1.0 Rel. units), and Vs is the volume of saliva (in mL).

Statistical processing was performed using Excel software (Microsoft Office 2010) in the Windows 7 operating system. The data obtained were processed using nonparametric methods of statistical analysis. The median and interquartile range (C25-C75 percentiles) were calculated. Intergroup differences on comparison of the two unrelated groups were evaluated using the Mann-Whitney U-test. The critical value of statistical significance level was at least 95% ($p<0.05$).

RESULTS

According to their history, only 25% of athletes (n=5) from group 1, 50% (n=10) from group 2 and 20% (n=6) from control group 3 had undergone preventive dentist examinations regularly. At the same time, a quarter of athletes from group 1 and 35% from group 2 did not exclude the possibility of dental system pathological processes due to intensive non-contact training background.

Dental status analysis of the participants revealed that non-contact sports professional athletes had the most pronounced disorders. Thus, caries intensity (according to the CPI index) was 9.0 (7.75-10.25). The indicators 'caries' and 'dental filling' were almost equal due to the high incidence of chipped restorations in this group of patients, which led to destruction of the filling permeability edge and therefore considered as the indicator 'caries'. For non-professional athletes (group 1), the CPI (h) was 8.5 (7.0-10.25), and the index structure was dominated by filled teeth. In the control group 3, the index was 8.0 (6.75-9.25), dominated by filled teeth.

Comparative analysis of periodontal status revealed the most pronounced changes in professional athletes (Table 1), where 11 (55%) participants had chronic catarrhal gingivitis, 8 (40%) had generalized early periodontitis and one (5%) had intact periodontal disease. The median value of the PMA index was 34.5% (29.5-45.25), which indicated the average severity of gingivitis in the majority of the group. More pronounced inflammatory phenomena were combined with a more significant decrease in capillary resistance indicators. Kulazhenko's sample in this group was 32.0 (18.8-40.0) seconds. The periodontal index (PI) corresponded to the moderate stage of the disease and amounted to 1.95 (1.6-5.13) points.

Table 1
Index and functional indicators of periodontal tissue condition (DI)

Parameter	Reference value	Group		
		Group 1 (n=20)	Group 2 (n=20)	Group 3 (control) (n=20)
Green-Vermillion, OHI-S (points)	0-0.6, good level of hygiene; 0.7-1.6, satisfactory 1.7-2.5, unsatisfactory ≥2.6, poor level of hygiene	1.2 (1.1-1.5)	1.3 (1.0-1.5)	1.2 (1.1-1.3)
Bleeding index (PBI) (points)	0 normal (no bleeding during probing) 1 spot bleeding 2 multiple spot or linear bleeding 3 interdental space is filled with blood	1.8 (1.6-2.4)[1]	2.2 (1.9-2.8)[1]	1.0 (1.0-1.13)
PMA (%)	0% normal ≤30%, low degree of gingivitis 30%-60%, average degree of gingivitis ≥60%, severe gingivitis	20.5 (18.8-27.0)[1,2]	34.5 (29.5-45.2)[1,2]	13 (0-20.3)
PI (points)	0 normal 0.1-1.5, initial and stage I of the disease 1.5-4.0, stage II 4.0-8.0, stage III	1.6 (1.4-2.6)	1.9 (1.6-5.1)[1]	1.1 (0-1.5)
Kulazhenko test (sec)	In the front teeth area, normal is 50-60 seconds	37.5 (27.5-42)	32 (18.8-40)[1]	39.5 (30.5-55.2)

1 = significant differences compared to control group ($p<0.05$); 2 = significant differences between group 1 and group 2 ($p<0.05$).

Periodontal examination of non-professional athletes (group 1) revealed chronic catarrhal gingivitis in 12 (60%), generalized periodontitis of mild severity in 5 (25%) and intact periodontitis in 3 (15%) subjects. The median value of the PMA index was 20.5 (18.8-27.0) and periodontal index (PI) showed a moderate stage of the disease – 1.6 (1.4-2.6) points; the Kulazhenko sample was 37.5 (27.5-42) seconds.

Periodontal status evaluation of the control group showed that 10 (50%) participants had signs of chronic generalized gingivitis, 3 (15%) had generalized early periodontitis, and 7 (35%) had healthy periodontal examination results. Inflammatory phenomena in periodontal tissues were less pronounced in this group; the PMA index at the time of examination was 13 (0-20.3)%, the bleeding index was 0.95 (0-1, 13), PI 1.15 (0-1, 5), and the Kulazhenko sample was 39.5 (30.5-55.25) seconds.

The hygiene index did not differ significantly among the three groups and corresponded to the average values reflecting a satisfactory level of oral hygiene.

Thus, comparative analysis of periodontal status revealed the changes to be most pronounced in professional athletes. Significant differences were recorded between group 1 and group 3. The PMA index was 2.6-fold (34.5 (29.5-45.25)% *vs*. 13 (0-20.3)%, respectively); bleeding index (PBI) 2.2-fold (2.25 (1.9-2.8) points *vs*. 1.0 (1-1, 13) points, respectively), and PI index 1.7-fold greater (1.95 (1.6-5.13) points *vs*. 1.15 (0-1.5) points, respectively), for the Kulazhenko sample – 1.2-fold greater (32 (18.8-40) sec *vs*. 37.5 (27.5-42) sec, respectively), $p<0.05$.

Assessment of saliva viscosity (Table 2) before training showed approximately the same values: 2.85 (2.58-3.25) c.u. for non-professionals and 3.0 (2.86-3.73) c.u. for professionals. After training, saliva viscosity increased 2.2 times in group 1 and 2.85 times in group 2, and the difference between the indicators was 1.3 times (6.35 (5.75-6.83) c.u. *vs*. 8.55 (8.05-9.33) c.u. ($p<0.05$).

Table 2
Viscosity indicators of mixed saliva before and after training (DI)

Parameter	Group 1 (n=20)	Group 2 (n=20))
Relative viscosity of saliva before training, c. u.	2.85 (2.58-3.25)	3.0 (2.86-3.73)
Relative viscosity of saliva after training, c. u.	6.35 (5.75-6.83)*	8.55 (8.05-9.33)*

*significant differences between group 1 and group 2 ($p<0.05$).

DISCUSSION

Recently, there is a growing interest in dental pathology prevention (4,7,16). The study results revealed that both professional and non-professional non-contact sports athletes were not really concerned about dental system pathological processes (2,4). The risk of acute maxillofacial injuries in these sports is much lower than in contact sports (hockey or wrestling), where, according to some data, it accounts for up to 25% of the total number of sports injuries (6).

Research results in recent years indicate a greater prevalence of major dental diseases in athletes than in people who do not engage in sports, which is associated with intense physical activities, psycho-emotional overstrain, suppressing both local oral immunity and overall body responses (5,6). Comparative analysis of dental profile revealed that despite the fact that the level of hygiene in all the subjects examined was the same and corresponded to the average (satisfactory) level, professional athletes had the highest values of the caries intensity index (CPI(z)). In addition, the indicators 'caries' and 'filling' were almost equal due to the high incidence of chipped restorations that lead to violation of marginal permeability of fillings. Non-professional athletes and subjects not engaged in sports (control group) had the index structure dominated by sealed teeth. The results obtained are consistent with other authors' data (6,9). Periodontal status also showed greatest deviations in professional athletes, i.e. gingivitis and moderate periodontitis signs (according to the PMA and PI indexes), pronounced bleeding disorders (PBI index), and a significant decrease in capillary resistance (Kulazhenko test). In addition, professional athletes had significantly higher saliva viscosity after training than non-professional athletes, which can be considered as an aggravating factor of imbalance in the oral cavity (13).

Thus, the results obtained made it possible to identify more significant dental status disorders in a professional group of athletes.

CONCLUSION

Non-contact sports athletes demonstrated low alertness regarding the occurrence of dental pathology; only 25% of non-professional athletes and 50% of professional athletes had regular dental examinations.

Examination of professional athletes showed a high degree of dental status disorders; more significant signs of gingivitis and periodontitis (according to the PMA and PI indexes), pronounced bleeding disorders (PBI index) and a significant decrease in capillary resistance (Kulazhenko test); saliva viscosity after training also increased more significantly than in non-professional athletes. The results obtained can be used in planning medical and preventive dental care for non-contact sports athletes.

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SAŽETAK

DENTALNI STATUS BESKONTAKTNIH SPORTAŠA

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Ispitivana je povezanost dentalnog statusa sportaša koji se bave beskontaktnim sportom i njihova profesionalna razina. Analizirani su podatci 60 mladih muškaraca podijeljenih u tri skupine: prva skupina (n=20) uključila je sportaše amatere, druga (n=20) profesionalne sportaše, a treća (n=20) je bila kontrolna skupina koju su činile osobe koje se ne bave sportom. U ispitivanju se koristio intervju i utvrđivanje dentalnog stastusa: intenzitet karijesa ⌈indeks KPI (h)⌋, higijena usne šupljine (ljestvica OHI-S), periodontalni status (ljestvice PMI, PMA, PI), stanje mikrovaskulature (test V. I. Kulaženka) i miješana slina (prema T. L. Redinovoj i A. R. Pozdeevu). Utvrđeno je da su profesionalni sportaši u usporedbi sa sportašima amaterima imali izraženija odstupanja dentalnog statusa: u indeksu PMA 1,7 puta, indeksu krvarenja (PBI) 1,2 puta, 1,2 puta u testu V. I. Kulaženka (p<0,05); viskozitet sline nakon treninga bio je 1,3 puta viši nego kod amatera (p<0,05), što se može povezati s intenzivnim fizičkim i psiho-emocionalnim stresom i posljedičnim poremećenjem metabolizma vode i elektrolita. Beskontaktni sportaši pokazivali su nisku svijest s obzirom na pojavu dentalne patologije, a postoji visok stupanj poremećaja dentalnog statusa.

Ključne riječi: dentalni status, periodontalni status, sportaši, viskozitet sline, sportovi snage

PROMJENA INHIBITORA VASKULARNOG ENDOTELNOG FAKTORA RASTA U LIJEČENJU VLAŽNOG OBLIKA SENILNE MAKULARNE DEGENERACIJE: META-ANALIZA I PREGLED LITERATURE

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Cilj: Provesti sustavni pregled i meta-analizu znanstvenih radova koji su analizirali ishod liječenja u bolesnika s eksudativnom degeneracijom makule povezane s dobi nakon terapijskog prelaska s bevacizumaba / ranibizumaba na aflibercept. ***Materijali i metode:*** Pretražene su proširene baze podataka *Pubmed (Medline) i Science Citation Index* u posljednjih 5 godina, uz kombinaciju ključnih riječi. Definirani su jasni kriteriji i istražene su najbolje korigirane oštrine vida, uz mjerenje središnje debljine makule pomoću koherencijske tomografije očiju prije i nakon promjene lijeka. ***Rasprava:*** U nedavno objavljenim publikacijama koje su analizirale rezultate liječenja rezistentne senilne degeneracije makule konverzijom na aflibercept objavljene su dvije meta-analize, sa sličnim kriterijima uključivanja, od kojih je najvažniji najmanje šestomjesečno praćenje bolesnika nakon terapijske konverzije. Prva meta-analiza uključivala je 7, a druga 28 studija, prospektivnih i retrospektivnih. Obje meta-analize pokazale su značajno poboljšanje središnje debljine makule nakon prelaska na aflibercept, dok je poboljšanje oštrine vida u jednoj skromno, a u drugoj nepromijenjeno. Tako je promjena lijeka značajno poboljšala anatomski ishod; međutim, nije primijećeno značajno poboljšanje vidne funkcije. Razlog je kronicitet bolesti i posljedično oštećenje, što podrazumijeva ograničenu mogućnost za oporavak vida. Naša analiza pokazala je, slično rezultatima prethodno spomenutih meta-analiza, da se promjenom terapije može postići poboljšanje anatomske strukture makule. U završnici je u meta-analizu uključeno jedanaest od dvadeset studija koje su istraživale ishod konverzije jednog lijeka protiv vaskularnog endotelnog faktora rasta na drugi lijek. Rezultati su pokazali statistički značajno smanjenje debljine makule nakon konverzije na aflibercept u svim studijama (ukupna razina značajnosti p <0,001). ***Zaključci:*** Provedena analiza pokazala je značajno poboljšan anatomski ishod, ali je skromno poboljšanje vida nađeno u samo nekoliko studija. Taj se rezultat vjerojatno može objasniti činjenicom da dugotrajna kronična bolest uzrokuje nepovratna oštećenja i sprečava značajan funkcionalni oporavak. Prospektivne studije s jednako definiranim ulaznim kriterijima omogućile bi bolju usporedbu rezultata liječenja dobivenih nakon promjene lijeka.

Ključne riječi: intravitrealne injekcije, makularna degeneracija, meta-analiza, vaskularni endotelni faktor rasta A

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UVOD

Senilna makularna degeneracija (SMD) već je odavno prepoznata kao najčešći uzrok oštećenja vidne funkcije iznad 50. godine života. Starenjem populacije raste rizik i broj oboljelih od ove bolesti, pa je senilna makularna degeneracija veliki medicinski i socioekonomski problem u svijetu. Smatra se da je makularna degeneracija uzrok stečene sljepoće kod starijih od 65 godina u 10 % do 13 % slučajeva, uz značajno smanjenje kva-

litete života oboljelih (1,2). Spoznajom glavnih patogenetskih osnova, otkrivanjem uloge VEGF u neovaskularnom obliku SMD (nSMD) te brzim razvojem i usavršavanjem novih dijagnostičkih metoda, započela je nova era u liječenju SMD. Relativno laganim pristupom blokadi aktivnosti VEGF-a putem intravitrealne primjene (IVT) anti-VEGF lijekova, zaustavljena je progresija bolesti, normalizirana struktura makule te značajno smanjeno oštećenje vidne funkcije kod velikog dijela oboljelih (3). Od 2004. kada je odobren prvi anti-VEGF pripravak za liječenje vlažnog oblika SMD do danas, imamo tri odobrena IVT lijeka koji blokiraju VEGF. To su pegaptanib, ranibizumab i aflibercept, te u masovnoj primjeni uspješni, ali neodobren za tu indikaciju, bevacizumab. Brojne studije su istraživale i pokazale učinkovitost ali i nuspojave navedenih lijekova te ukazale na činjenicu da terapija kod dijela pacijenata nema (ili ima manje) povoljan učinak. S obzirom na veliku razliku u cijeni koja ograničava dostupnost nekih od navedenih lijekova danas je prisutan varijabilan pristup u kliničkom liječenju oboljelih od SMD (4). No i u okolnostima kada su lijekovi dostupni i kod oboljelih je provođeno adekvatno liječenje, često se u realnoj kliničkoj praksi rezultati liječenja ne pokažu tako učinkovitima kao u istraživanjima. Zapaženo je da se kod dijela pacijenata ne dobije očekivani povoljni odgovor, pa u njih nakon povoljnog početnog odgovora bolest napreduje unatoč kontinuiranom liječenju (5). Razumijevanje razloga varijabilnosti odgovora na anti-VEGF terapiju omogućilo bi individualizirani pristup bolesniku, odabir povoljnijeg načina liječenja i optimalizaciju broja i rasporeda primjene intravitrealnih injekcija. Povoljni rezultati individualiziranog pristupa donose optimalni klinički rezultat, smanjenje rizika terapije, smanjenje broja pregleda i konačno troškova liječenja. Nekoliko temeljnih karakteristika bolesnika i bolesti, kao što su trajanje bolesti, dob pacijenata, najbolje korigirana vidna oštrina, karakteristike i veličina lezije, debljina makule i genetske karakteristike povezani su s varijabilnim odgovorom na anti-VEGF terapiju (6,7). Epidemiološki čimbenici kao što su starija dob pacijenta i duljina trajanja simptoma prije početka anti-VEGF terapije povezani su s lošijim ishodom liječenja (8). Lošija početna vidna oštrina prije liječenja anti-VEGF lijekom isto tako je statistički značajno povezana s lošijom prognozom (9). Morfološke karakteristike lezija zbog korioidalne neovaskularizacije (CNV lezije) kao što je veličina i tip, bitno utječu na ishod liječenja. Analizom veličine lezije i ishoda liječenja u studiji MARINA pokazano je da veličina lezije negativno utječe na ishod liječenja ranibizumabom (10). Loš odgovor na anti-VEGF intravitrealnu terapiju evidentan je i kod podtipa makularne degeneracije koji se zove polipoidna koroidalna vaskulopatija (PCV), te je fotodinamska terapija glavna metoda liječenja ove bolesti (11). Nekoliko studija istraživalo je utjecaj vitreomakularnog kontakta na liječenje anti-VEGF lijekovima, te većina radova potvrđuje negativan utjecaj vitreomakularne adhezije u smislu lošijeg odgovora na liječenje, a i većeg broja potrebnih injekcija, ali neke studije nisu potvrdile negativan utjecaj (12-14). Prve studije koje su istraživale ovisnost odgovora na intravitrealnu anti-VEGF terapiju s jednostrukim genskim polimorfizmima (SNPs) čvrsto povezanim s razvojem makularne degeneracije dokazale su povezanost alela CFH, ARMS2, HTRA1 i C3 s makularnom degeneracijom, ali ne i povezanost tih alela s odgovorom na anti-VEGF terapiju (15-17). Istraživanjem SNPs kod VEGF gena i njihovih receptora utvrđen je signifikantni utjecaj VEGFR2/KDR gena i VEGF haplotipa TGA na varijabilnost odgovora na anti-VEGF terapiju, što bi moglo pomoći u kliničkom radu (18,19). U dijagnostici i praćenju pacijenata sa senilnom makularnom degeneracijom koristimo stereoskopsku fundoskopiju na biomikroskopu s nekontaktnom lećom, ispitivanje najbolje korigirane vidne oštrine, dijagnostičke metode SD(SS) OCT, fluoresceinsku angiografiju i *„indocyanine green"* angiografiju. Svaki pacijent treba biti liječen i praćen s individualiziranim pristupom prilagođenim s obzirom na njegovu kliničku sliku. Zbog evidentne interindividualne razlike u odgovoru na intravitrealnu anti-VEGF terapiju postavlja se pitanje s kojim parametrima definirati taj odgovor. Većina kliničara i istraživača određuje aktivnost bolesti na osnovi najbolje korigirane vidne oštrine, pregleda fundusa gdje se vidi nazočnost krvarenja i eksudata, OCT analizom intraretinalne (IRF) i subretinalne tekućine (SRF), intraretinalnih cisti (IRC), središnje debljine makule (CRT), postojanja odljepljenja retinalnog pigmentnog epitela (PED), te slikama fluoresceinske angiografije kod klasične koroidalne neovaskularizacije (20). Odgovor bolesnih očiju na terapiju može biti promatran s funkcijske strane ali i morfološke strane. Taj odgovor možemo klasificirati kao dobar, djelomičan, loš i bez odgovora na terapiju. Amoaku i sur. (20) odgovor na anti-VEGF terapiju definiraju kao optimalan, djelomičan, loš i bez odgovora na liječenje. Optimalan odgovor: potpuna odsutnost SRF, IRF, IRC i redukcija CRT >75 % od početne, te poboljšanje najbolje korigirane vidne oštrine >5 slova po *Early Treatment Diabetic Retinopathy Study* (ETDRS) ili dosegnuta dobra početna vidna oštrina (≥70 slova po ETDRS). Djelomični odgovor: redukcija CRT 25-75 % od početnih vrijednosti, perzistiranje SRF, IRF, IRC ili pojava novog IRC, IRF, SRF, te promjena u vidnoj oštrini 1-5 slova po ETDRS. Loš odgovor: 0-25% redukcije od početne CRT s perzistentnim ili novim IRF, SRF, IRC, te promjena najbolje korigirane vidne oštrine 0-4 slova po ETDRS. Bez odgovora: bez promjene, ili pogoršanje CRT, IRF, SRF i IRC ili PED, s povećanjem hemoragija i eksudata u usporedbi s početnim stanjem, te gubitak >5 slova po ETDRS u usporedbi s početnom vidnom oštrinom. Funkcijski odgovor se

često ne poklapa s morfološkim odgovorom, tako da morfološki neuspjeh terapije često ne prati funkcijski neuspjeh i obratno. Nekoliko važnih studija također potvrđuju da nakon inicijacijske faze od 3 IVT terapije funkcijski rezultat ne prati uvijek morfološke promjene (21-23). Neuspjeh terapije se može verificirati mjesec dana nakon inicijacijske treće doze lijeka i tada ga se smatra primarnim neuspjehom. Kada se nakon faze uspješnog liječenja i poboljšanja morfoloških biomarkera bolesti učinak terapije kasnije smanji, ishod se smatra sekundarnim neuspjehom terapije. Uzroci neuspjeha intravitrealne anti-VEGF terapije su različiti. Uz veće spomenute čimbenike koji utječu na morfološki i funkcijski odgovor i uspjeh terapije, kao što su trajanje bolesti, dob pacijenata, najbolje korigirana vidna oštrina, karakteristike i veličina lezije, debljina makule i genetske karakteristike, treba svakako istaći tahifilaksiju, razvoj neutralizirajućih protutijela na lijek, kronicitet s pridruženom promjenom u citokinskom profilu bolesti, ali i nepravilno davanje lijeka uz refluks pa i neadekvatan raspored terapije (24-26). Identifikacija mogućeg uzroka nedovoljno dobrog odgovora nužna je za razumijevanje stanja te planiranje sljedećeg koraka u terapiji. Ako su dostupni svi lijekovi, racionalni sljedeći korak je promjena anti-VEGF lijeka, tzv."*switching*". S obzirom na različit način djelovanja logično je da se pri promjeni lijeka bira lijek koji nema sličan ili isti način blokade VEGF-a kao već primjenjivani. U recentnoj je literaturi objavljen niz članaka koji opisuju rezultate promjene IVT lijeka kod nSMD. Mali ih broj opisuje konverziju s ranibizumaba na bevacizumab (27-29), bevacizumaba na ranibizumab (30-32) i s aflibercepta na ranibizumab ili bevacizumab (33,34). Međutim, najviše radova, zbog nezadovoljavajućeg terapijskog odgovora, odnosno perzistiranja intraretinalne (IRF) i/ili subretinalne tekućine (SRF) na OCT-u, opisuje rezultate konverzije na aflibercept s bevacizumaba ili ranibizumaba. Stoga smo u ovom radu proveli meta-analizu članaka s rezultatima terapijske konverzije na aflibercept s bevacizumaba ili ranibizumaba.

CILJ RADA

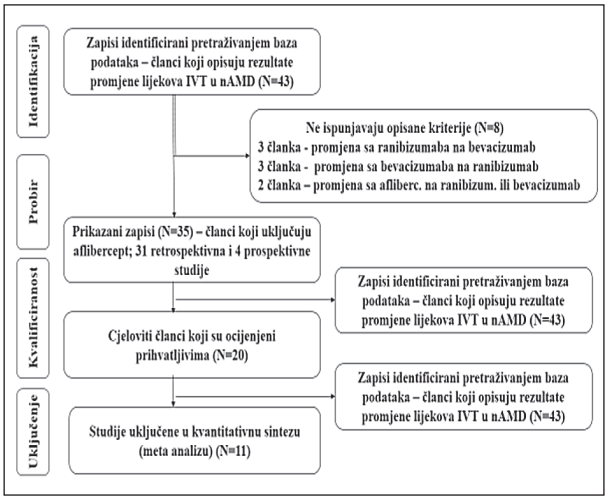
Meta-analiza znanstvenih radova koji su istraživali ishod liječenja u bolesnika sa senilnom neovaskularnom makularnom degeneracijom nakon prelaska s bevacizumaba/ranibizumaba na terapiju afliberceptom, uz. pregled literature.

METODE RADA

Pretraživanjem baza znanstvenih radova *Pubmed (Medline), SCI Expanded* posljednjih 5 godina, uz kombinaciju ključnih riječi: *macular degeneration, anti-VEGF treatment, resistant, nonresponders, bevacizumab, ranibizumab, aflibercept, switching, conversion* pronašli smo ukupno 43 studije koje prikazuju rezultate terapijske konverzije na aflibercept s bevacizumaba ili ranibizumaba. Studije su vodili različiti istraživači na uzorcima koje je teško homogenizirati s obzirom na različitu duljinu trajanja bolesti, nedostak podataka o podtipu makularne degeneracije, broju intravitrealnih terapijskih postupaka prije konverzije, pa i ritmu i duljini terapije afliberceptom nakon konverzije. Uključni kriteriji za meta-analizu ovih studija bili su: trajanje anti-VEGF terapije prije konverzije minimalno 4 mjeseca, te minimalno 3 IVT terapije afliberceptom nakon konverzije, evaluacija rezultata liječenja minimalno 4 mjeseca nakon konverzije, evaluacija najbolje korigirane vidne oštrine (*Best Corrected Visual Acuity*, BCVA) prije i nakon konverzije uz statističku značajnost promjene, evaluacija CRT-a na OCT prikazu, te statistička značajnost promjene.

REZULTATI

Pretraživanjem baza nađena su 43 članka među kojima je identificirano ukupno 20 originalnih studija relevantnih za našu analizu, 4 prospektivne i 16 retrospektivnih. Od toga je 9 imalo ili nedostatne statističke podatke ili dizajn koji nije bio usporediv s drugim studijama. Na kraju, 11 studija sa 787 očiju uključeno je u kvantitativnu analizu CRT-a (35-45). Shema tijeka isključivanja studija iz meta-analize prikazana je na sl. 1, a na tablici 1 prikazana je srednja životna dob bolesnika, broj očiju, vrijeme liječenja prije konverzije lijeka i vrijeme prospektivnog praćenja pacijenata u studijama uključenima u našu meta-analizu.



Sl. 1. *Shema tijeka isključivanja studija*

Tablica 1.
Popis studija uključenih u meta-analizu, uz prikaz srednje životne dobi bolesnika, broja očiju, vremena liječenja prije konverzije lijeka i vremena prospektivnog praćenja

Autor (god.)	Srednja životna dob (god.)	Broj očiju	Vrijeme prije konverzije (mj.)	Prospektivno praćenje (mj.)
Yonekawa (2013.)	79,6	102	30	4
Cho (2013.)	90,69	28	>6	6
Kumar (2013.)	79	34	>6	6
Bakall(2013.)	79	36	>6	6
Gharbiya (2014.)	70,1	31	41,3	6
Chan (2014.)	83,4	189	>6	6
Grewal (2014.)	80,7	21	>6	12
Messenger (2014.)	80	109	12	12
Eadie (2014.)	79,9	111	>4	>4
Fassnacht (2014.)	78,9	96	4	4
Hall (2014.)	80,4	30	>6	12

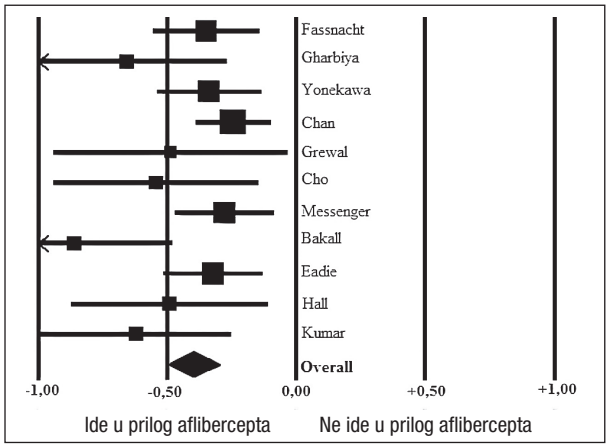
Prema prikazu u tablici 1, prosječna dob varira od 70 do 91 godine. Vrijeme liječenja proteklo prije konverzije bilo je najmanje 4 mjeseca, dok je trajanje praćenja bilo u rasponu od najmanje 4 mjeseca do najviše 12 mjeseci nakon prve injekcije aflibercepta. Najmanji broj očiju po studiji bio je 21, a najveći 189. Većina bolesnika uključenih u studije imala je dugotrajnu bolest i najdulje praćenje prije konverzije terapije bilo je 41,3 mj., a najkraće 4 mj. Nakon konverzije svi su pacijenti praćeni u kontinuitetu najmanje 4 mjeseca dobivši minimalno 3 mjesečne injekcije aflibercepta, a najviše 12 mjeseci.

Tablica 2.
Sveukupni učinak na centralnu debljinu retine nakon prelaska na liječenje afliberceptom

Autor (god.)	Standarna srednja razlika	Standardna pogreška	Donja granica	Gornja granica	P vrijednost	Relativno značenje studije
Yonekawa (2013.)	-0,336	0,102	-0,535	-0,136	<0,001	12,87
Cho (2013.)	-0,541	0,202	-0,938	-0,145	0,008	5,00
Kumar (2013.)	-0,619	0,187	-0,986	-0,252	<0,001	5,67
Bakall (2013.)	-0,859	0,195	-1,242	-0,477	<0,001	5,31
Gharbiya (2014.)	-0,655	0,198	-1,043	-0,267	<0,001	5,19
Chan(2014.)	-0,243	0,074	-0,388	-0,099	<0,001	17,20
Grewal(2014.)	-0,485	0,231	-0,937	-0,033	0,038	4,02
Messenger (2014.)	-0,277	0,098	-0,468	-0,085	0,005	13,44
Eadie(2014.)	-0,321	0,097	-0,512	-0,130	<0,001	13,48
Fassnacht (2014.)	-0,347	0,105	-0,553	-0,141	<0,001	12,43
Hall(2014.)	-0,489	0,193	-0,868	-0,111	0,012	5,39
Sveukupno	**-0,396**	**0,050**	**-0494**	**-0298**	**<0,001**	

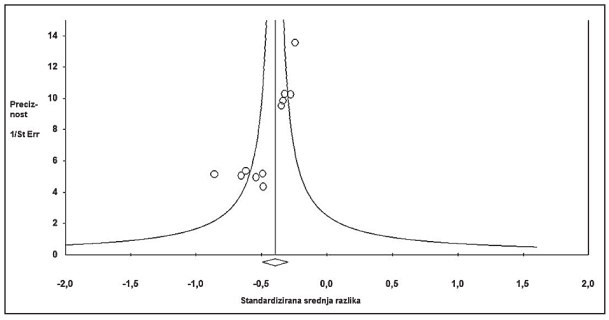
Kada analiziramo središnju debljinu makule na OCT prikazu (tablica 2, sl. 2), unatoč heterogenim skupinama ispitanika s obzirom na trajanje bolesti prije konverzije, različitu duljinu terapije, broju IVT injekcija, pa i broju injekcija aflibercepta nakon konverzije, vidljivo je da je svaka studija pokazala statistički značajnu redukciju CRT-a nakon prelaska na aflibercept (sveukupna značajnost p <0,001). Iz analize je vidljivo da su pacijenti imali značajno poboljšanje, tj smanjenje CRT-a (WMD -0,396, 95 % CI -0,50 do -0,30, p<0,001) u razdoblju od 4 do 12 mjeseci nakon prve injekcije aflibercepta. Analiza promjene vidne oštrine

u odnosu na nalaz prije početka liječenja pokazala je znatno lošije rezultate: u samo 4 studije nađeno je statistički značajno poboljšanje vidne oštrine.



Sl. 2. *Forrest plot za standardnu razliku aritmetičkih sredina i 95 % CI (interval pouzdanosti, gornja i donja granica) za 11 studija i ukupni učinak liječenja*

Na kraju je pomoću *funnel plot*-a (sl. 3) testiran *bias,* odnosno tendencija nakladnika/urednika da, ako rad sadrži mali broj ispitanika, mora imati jako velike razlike u razdoblju prije u odnosu na razdoblje poslije primjene nekog lijeka, odnosno, ako je uzorak jako velik, onda te razlike mogu biti izrazito male i bit će prihvatljive. Eggerov test se koristi kada imamo barem 10 studija u meta-analizi i kvantificira vrijednosti *funnel plot*-a. Drugim riječima, kada želimo eksplicitni statistički pokazatelj je li rad pod utjecajem pristranosti uglavnom se koristi Eggerov test. *Funnel plot* analiza pokazala je *bias*, što je potvrđeno Eggerovim testom (p<0,001).



Sl. 3. *Funnel plot - pretraživanje postojanja mogućeg bias-a među publikacijama (N = 11)*

RASPRAVA

U recentnoj su literaturi objavljene dvije meta-analize u kojima se analiziraju studije s rezultatima liječenja rezistentne senilne makularne degeneracije konverzijom na aflibercept (46,47), s međusobno sličnim uključnim kriterijima, od kojih je najvažniji onaj o minimalno šestomjesečnom praćenju pacijenata nakon konverzije terapije. U meta-analizi Seguin-Greinstein i sur. (46) uključeno je sedam studija od kojih su četiri retrospektivne i tri prospektivne. Ukupni rezultati meta-analize pokazali su malo, ali statistički značajno poboljšanje vidne oštrine šest mjeseci nakon prelaska na aflibercept (p=0,04), a učinak je bio značajniji u podatcima prikupljenima iz prospektivnih studija (p=0,038). Došlo je i do značajnog poboljšanja CRT-a nakon prelaska na aflibercept (p<0,0001). Navedena je meta-analiza pokazala da se nakon prelaska na aflibercept može značajno poboljšati CRT, sa stabilizacijom ili čak nekim poboljšanjem vidne oštrine. U meta-analizi Spoonera i suradnika (47) uključeno je 28 studija, 8 prospektivnih i 20 retrospektivnih. Rezultati su pokazali malo prosječno poboljšanje vidne oštrine 6 i 12 mjeseci nakon prelaska na aflibercept (p=0,17 i p=0,17). U srednjim vrijednostima CRT-a došlo je do značajnog poboljšanja p<0,001 i p<0,001 u intervalima od 6 i 12 mjeseci nakon prelaska na aflibercept. Analiza je pokazala znatno poboljšani anatomski ishod, ali vizualna funkcija je ostala stabilna, a rezultati očuvanja vida su učinka sličnog drugim anti-VEGF agensima. Problem je kronična bolest u tih bolesnika s ograničenim potencijalom za vizualni oporavak. Naša analiza pokazala je, slično rezultatima ranije spominjanih meta-analiza, da se kod nSMD koja ne reagira na višekratnu terapiju anti-VEGF lijekovima, primjenom lijeka koji se razlikuje po načinu djelovanja od prethodnog lijeka, može postići poboljšanje anatomske strukture makule. Važno je naglasiti da su u većini studija analizirani rezultati konverzije na bolesnicima koji su dulje vrijeme imali i liječili SMD. Dugotrajna nSMD zbog akumulirajućeg učinka CNV, fibroze i atrofije može objasniti nedovoljan funkcijski oporavak.

ZAKLJUČAK

Naša analiza pokazuje da se kod nSMD koja ne reagira na višekratnu terapiju anti-VEGF lijekovima primjenom lijeka koji se razlikuje prema načinu djelovanja od prethodnog lijeka može postići poboljšanje anatomske strukture makule. Velika većina studija nije pokazala statistički značajnu korist u poboljšanju vidne oštrine nakon konverzije, jer kao što znamo, morfološki uspjeh terapije ne prati nužno funkcijski uspjeh. Međutim, većina studija analizirala je rezultate konverzije na bolesnicima koji su dulje vrijeme imali i liječili SMD. Dugotrajna nSMD zbog akumulirajućeg efekta CNV, fibroze i atrofije može objasniti nedovoljan funkcijski oporavak. S obzirom na dominantan broj retrospektivnih studija, nameće se potreba novih prospektivnih kliničkih istraživanja. Pri tom je nužna homogenizaci-

ja ispitanika s obzirom na trajanje bolesti, podtip SMD, broj IVT injekcija i režim liječenja. Nakon terapijske konverzije primjena standardiziranog načina liječenja omogućila bi kvalitetniju usporedbu rezultata dobivenih liječenjem nakon promjene terapije.

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SUMMARY

CHANGE OF VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITOR IN THE TREATMENT OF WET FORM OF SENILE MACULAR DEGENERATION: META-ANALYSIS AND LITERATURE REVIEW

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The aim was to perform a systematic review and meta-analysis of scientific papers that analyzed treatment outcome in patients with exudative age-related macular degeneration after therapeutic switch from bevacizumab/ranibizumab to aflibercept. Pubmed (Medline) and Science Citation Index expanded databases were searched over the last 5 years, with a combination of keywords. Clear criteria were defined, and evaluation of the best corrected visual acuity, with measurement of the central macular thickness by ocular coherence tomography before and after drug conversion was performed. Two meta-analyses have been published in recent literature analyzing studies with the results of treatment of resistant senile macular degeneration by conversion to aflibercept, with somewhat similar inclusion criteria, the most important of which is the minimum six-month follow-up of patients after conversion therapy. The first meta-analysis included 7 and the second 28 studies, prospective and retrospective. Both meta-analyses showed a significant improvement in the central macular thickness after conversion to aflibercept, while the improvement in visual acuity was very modest in one and unchanged in the other. Thus, a change in drug significantly improved the anatomic outcome; however, no significant improvement in visual function was observed. The reason is chronic illness and impairment, which implies a limited potential for vision recovery. Similar to the results of the previously mentioned meta-analyses, our analysis showed that improvement in the anatomic structure of the macula can be achieved by changing therapy. Finally, eleven of twenty studies that investigated the outcome of conversion from one anti-vascular endothelial growth factor drug to another were included in meta-analysis. The results showed a statistically significant decrease in macular thickness after conversion to aflibercept in all studies (overall significance level $p<0.001$). The analysis performed showed a significantly improved anatomic outcome, but visual improvement was found to be modest in only a few studies. This result could probably be explained by the fact that a long-lasting chronic disease causes irreversible damage and prevents significant functional recovery. Prospective studies with uniformly defined input criteria would allow better comparison of the results obtained after change in the treatment.

Key words: intravitreal injections, macular degeneration, meta-analysis, vascular endothelial growth factor A

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DIJAGNOSTIČKO ZNAČENJE METODA NUKLEARNE MEDICINE U GASTROENTEROLOGIJI

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Dijagnostika gastroenteroloških bolesti temelji se, uz metode kliničkog pregleda i laboratorijsku dijagnostiku, u prvom redu na endoskopskoj, ultrazvučnoj i radiološkoj obradi. Ove metode osim značenja u dijagnostici osnova su za nekirurške intervencije kod gastroenteroloških bolesnika. U dijagnostičkom smislu, iako poprilično zapostavljene pa čak i zaboravljene, određenu ulogu imaju i nuklearnomedicinske metode koje svojom neinvazivnošću i visokom dijagnostičkom točnošću mogu doprinijeti donošenju konačne dijagnoze te će u ovom preglednom radu biti ukratko i na razumljiv način opisane.

Ključne riječi: nuklearna medicina, gastroenterologija, dijagnostika, endoskopija

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UVOD

Nuklearna medicina je grana medicine koja koristi radioaktivne izotope za slikovni prikaz funkcije i morfologije pojedinih organa ili organskih sustava. Iako je to relativno mlada specijalnost, koja svoje početke bilježi početkom prošlog stoljeća od konstrukcije ciklotrona i otkrića umjetne radioaktivnosti do konstrukcije prve gama kamere, eksponencijalni tehnologijski napredak omogućio joj je primjenu u gotovo svim područjima medicine (1). U ovom preglednom članku biti će opisane nuklearnomedicinske dijagnostičke metode u gastroenterologiji, isključujući oslikavanje tumora. Istaknuto je i u kojoj mjeri navedene pretrage koristimo u našem Kliničkom zavodu i kritički uspoređeno s navodima iz literature.

ULOGA NUKLEARNE MEDICINE U GASTROENTEROLOGIJI

S obzirom da se gastroenterologija vrlo brzo razvija i da tehnološke mogućnosti endoskopske dijagnostike i terapije rastu, jasno je da su te metode uz radiološke pretrage dominantne u dijagnostici gastroenterooloških bolesti. Ipak, komplementarno se mogu koristiti nuklearne metode, koje još uvijek imaju određeno mjesto u gastroenterološkoj dijagnostici. Pregled nuklearnomedicinskih dijagnostičkih metoda u gastroenterologiji prikazan je u tablici 1.

Tablica 1.
Pregled nuklearnomedicinskih dijagnostičkih metoda u gastroenterologiji (isključujući oslikavanje tumora)

Naziv nuklearnomedicinske metode	Radiofarmak (najčešće primjenjivani)	Doza radiofarmaka	Uobičajeni način snimanja
Scintigrafska ispitivanja jednjaka	^{99m}Tc-koloid	18,5-37 MBq	Dinamička scintigrafija; 10min
Scintigrafija gastroezofagealnog refluksa	^{99m}Tc-koloid	18,5-180 MBq	Dinamička scintigrafija; 30-45 min
Scintigrafija pražnjenja želuca	^{99m}Tc-koloid	18,5-37 MBq	Dinamička scintigrafija; 60 min do 4h
Scintigrafija tranzita kroz tanko i/ili debelo crijevo.	^{111}In-DTPA[a] i ^{99m}Tc-perteh. ob. celuloza ili čestice smole	3,7-37MBq/kg 18,5-37 MBq/kg	Dinamička scintigrafija uz dodatne statičke scintigrame
Scintigrafija heterotopične želučane sluznice	^{99m}Tc-pertehnetat	185-370 MBq	Dinamička scintigrafija; 45 min.
Scintigrafija za detekciju gubitka bjelančevina u crijevima	^{99m}Tc-albumin	370 MBq	Dinamička scintigrafija uz statičke scintigrame 8-10h i 24h pi.[d]
Ispitivanje gubitka bjelančevina crijevima	^{51}Cr-klorid	1,85 MBq	-
Scintigrafija za detekciju gastrointestinalnog krvarenja	^{99m}Tc-koloid ili vl.E[b] ob. ^{99m}Tc-pertehnetatom	370 MBq	Dinamička scintigrafija uz statičke scintigrame do 24h pi.
Scintigrafija vaskularnih prostora jetre (hemangiomi)	vl. E ob. ^{99m}Tc-pertehnetatom.	740 MBq	Brza dinamička studija, statike 10 min i 2h pi.; SPECT/CT
Scintigrafija jetre i žučnih vodova (hepatobilijarna scintigrafija)	^{99m}Tc-HIDA[e], ^{99m}Tc-DISIDA[f], ^{99m}Tc-BRIDA[g] i drugi	111-185 MBq	Dinamička scintigrafija, potom po potrebi odgođeni statički scintigrami
Scintigrafija s obilježenim leukocitima	^{99m}Tc-HMPAO [h] ob. L[c]	370 MBq	Statički scintigrami 30min, 1h, 2h, 4h i 24h pi.
Koloidna scintigrafija jetre i slezene	^{99m}Tc- koloid	111-185 MBq	Statički sintigrami 10-15 min pi.; SPECT, SPECT/CT

Gastroezofagusna funkcijska ispitivanja

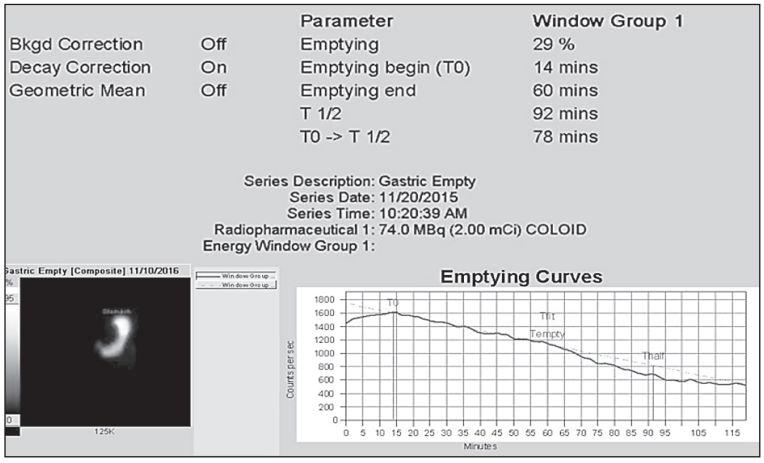
Scintigrafska ispitivanja jednjaka. Scintigrafija jednjaka je metoda kojom se snima prolazak obroka obilježenog ^{99m}Tc-koloidom, a služi za procjenu funkcije i morfologije jednjaka. Pacijent popije vodu pomiješanu s ^{99m}Tc-koloidom te se snima prolazak vode u jednjaku pri čemu se vizualno ocjenjuje njegova morfologija, a potom iscrtavanjem krivulja aktivnosti nad jednjakom ocjenjuje i njegova funkcija, u smislu izračunavanja vremena prolaska aktivnosti u jednjaku koje u zdravih osoba iznosi 5-11 sekundi. Indikacije za scintigrafiju jednjaka su procjena motiliteta jednjaka kod difuznog spazma ili hipertoničnog jednjaka i ahalazije te kod sekundarnih poremećaja motorike u pacijenta sa sklerodermijom, sistemskim eritematoznim lupusom (SLE), mišićnom distrofijom i sl. (2,3).

Scintigrafija gastroezofagusnog refluksa. Nastavkom scintigrafije jednjaka može se otkriti i kvantificirati gastroezofagusni refluks (GER) na način da se pacijentu nakon standardnog dijela pretrage ponudi još 300 mL vode kako bi se isprala aktivnost iz jednjaka i ispunio želudac. Potom se snima eventualni povrat aktivnosti iz želuca u jednjak te se taj povrat može kvantificirati u obliku indeksa refluksa koji normalno iznosi do 4 %. Osjetljivost ove metode je 84-90 %, a specifičnost 73-93 %, čime je ona najosjetljivija neinvazivna metoda za otkrivanje gastroezofagusne refluksne bolesti (GERB) (4,5).

Komplementarne endoskopske i radiološke metode za procjenu motiliteta i morfologije jednjaka te GERB-a su 24-satna ph-metrija te manometrija jednjaka, ezofagogastroduodenoskopija (EGDS) kao zlatni standardi te ezofagogram s barijem. Iako se u Kliničkom zavodu za nuklearnu medicinu Kliničkog bolničkog centra Rijeka (KZNM) ne izvode scintigrafska ispitivanja jednjaka, kao ni scintigrafija gastroezofagusnog refluksa u prvom redu zbog izostanka upita za te metode, u svijetu se i dalje koriste u različitim istraživanjima, ali i rutinskoj primjeni. Tako su Burton i sur. (6) analizirali doprinos scintigrafije GER-a u procjeni ezofagusnih i ekstraezofagusnih manifestacija GERB-a u usporedbi s ph-metrijom i manometrijom jednjaka te su zaključili kako je scintigrafija GER-a dobra alternativna dijagnostička metoda uz veliku prednost istovremenog otkrivanja ekstraezofagusnih manifestacija, kao npr. aspiracije regurgitata u pluća uz mogućnost njegovog predviđanja temeljem određenih scintigrafskih parametara. Nadalje, Jeon i sur. (7) analizirali su kliničke parametre, nalaze radioloških i endoskopskih metoda te scintigrafije jednjaka, u pacijenata s ahalazijom te su zaključili da u pacijenata koji se prezentiraju simptomima GERB-a, a koja je rezistentna na terapiju treba posumnjati na ahalaziju, koja se može dijagnosticirati različitim metodama, između ostalog i scintigrafijom jednjaka.

Scintigrafija pražnjenja želuca. Scintigrafija pražnjenja želuca je dijagnostička metoda kojom se snima prolazak radiofarmakom obilježenog krutog ili tekućeg obroka za ocjenu motoričke funkcije želuca u pacijenata kojima se simptomi javljaju nakon jela (mučnina, povraćanje, bolovi u trbuhu, osjećaj rane sitosti), kao znakove usporenog pražnjenja želuca. Najčešće se javlja

u dijabetičara, kao odraz dijabetičke gastropareze. Kao kruti obrok se koristi ^{99m}Tc-koloid pomiješan s bjelanjcima, kruhom i pekmezom od jagode (standardizirani obrok), dok se kao tekući obrok koristi ^{99m}Tc-koloid pomiješan s vodom ili sokom. Nakon što pacijent popije ili pojede obilježeni obrok započinje snimanje gornjeg dijela abdomena u trajanju od 60 min do 4 h, potom se iscrtaju krivulje aktivnosti nad čitavim želucem te zasebno nad njegovim aboralnim i antralnim dijelom. Dobiveni rezultat se izražava kao postotak aktivnosti koji se isprazni do isteka 60 min, koji normalno iznosi 60 % za kruti te 80 % za tekući obrok (sl. 1) (3,4).



Sl. 1. *Scintigrafija pražnjenja želuca s obilježenim tekućim obrokom u pacijentice s dijabetičkom gastroparezom. Nakon 60. min ispraznilo se samo oko 30 % sadržaja što upućuje na usporeno pražnjenje tekućeg obroka.*

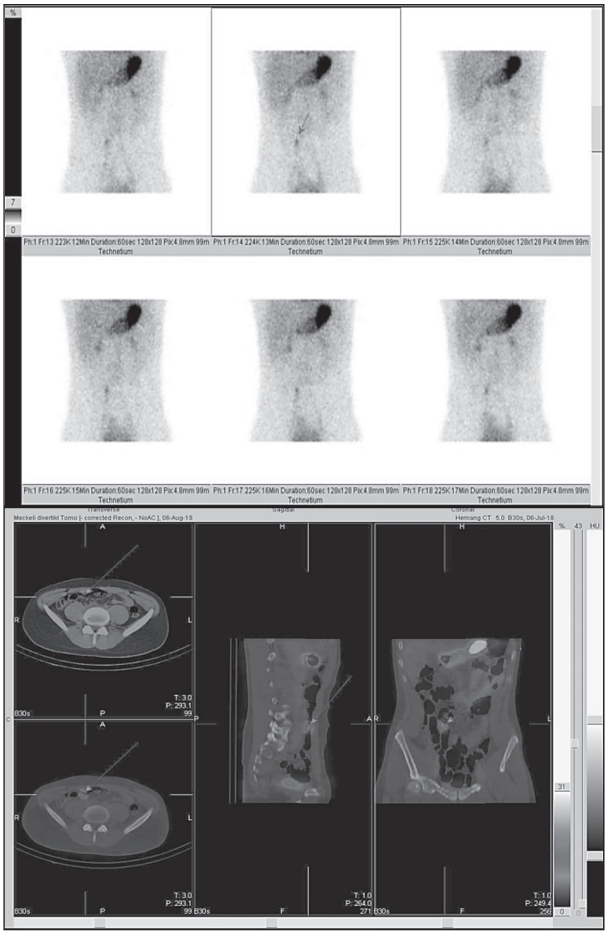
Scintigrafija pražnjenja želuca je zlatni standard za procjenu motoričke funkcije želuca, a kao komplementarne metode mogu se koristiti i izdisajni test za procjenu pražnjenja želuca s ugljikom C-13, endoskopija videokapsulom i EGDS, gastroduodenomanometrija te elektrogastrografija. U našem Kliničkom zavodu za nuklearnu medicinu scintigrafija pražnjenja želuca se zadnjih godina izvodi nekoliko puta mjesečno te se bilježi pozitivan trend u potražnji ove pretrage, a unazad 9 godina učinjeno je sveukupno 60-tak studija. Spomenut ćemo nekoliko svjetskih istraživanja. Orthey i sur. (8) u svojem su istraživanju naglasili važnost vizualne procjene raspodjele obilježenog obroka u želucu tijekom samog snimanja, uz kvantitativnu analizu scintigrafskih parametara, čime se dobivaju dodatni podatci o motilitetu želuca, a kojima se može dodatno objasniti uzrok simptoma u pacijenata.Zikos i sur.(9) analizirali su povezanost poremećaja motiliteta jednjaka i želuca koristeći se manometrijom jednjaka i scintigrafijom želuca te su ustvrdili da postoji mogućnost zajedničkog patofiziološkog mehanizma nastajanja ovih poremećaja i posljedično moguće jedinstvene terapije te kod postojanja jednog poremećaja motiliteta treba posumnjati i na postojanje drugog.

Scintigrafija prolaza kroz tanko i/ili debelo crijevo. U pojedinih je pacijenata teško razlučiti jesu li gastrointestinalni simptomi posljedica poremećaja motiliteta gornjeg ili donjeg dijela probavnog sustava, stoga se za tu procjenu između ostalog može koristiti i scintigrafija prolaza kroz crijeva sa celulozom obilježenom ^{111}In, ^{131}I ili^{99m} Tc-pertehnetatom, česticama ugljena ili smole, a može se procijeniti čitav gastrointestinalni trakt računajući vrijeme prolaska kroz njegove pojedine dijelove (npr. gastrocekalni prolaz) (5,10).

Za procjenu prolaza kroz tanko i/ili debelo crijevo danas se najčešće koristi endoskopija videokapsulom, a mogu se koristiti još i manometrija debelog crijeva, anorektalna manometrija te RTG abdomena s biljezima i anorektalna defekografija. U našem Kliničkom zavodu ova scintigrafija se ne izvodi, no u svijetu se i dalje koristi, bez obzira što na prvi spomen zvuči pomalo kao opsoletna metoda. Spomenut ćemo istraživanje Liu i sur. (11) objavljeno 2018. godine, koji su ustvrdili uz pomoć scintigrafije prolaza kroz tanko crijevo i genskog sekvencioniranja crijevne mikroflore, da težina mikrobiotske disbioze ovisi više o prolazu kroz tanko crijevo nego o Child-Pugh kategoriji u pacijenata s cirozom jetre. Nadalje, iste godine Vijayvargiya i sur. (12) analizirali su utjecaj povišenih primarnih žučnih kiselina u stolici na masu stolice i vrijeme prolaska kroz debelo crijevo u pacijenata s iritabilnim kolonom i proljevima koristeći se scintigrafijom prolaza kroz debelo crijevo.

Scintigrafija heterotopične želučane sluznice. Meckelov divertikul je najčešća prirođena anomalija probavnog sustava, a predstavlja heterotopičnu sluznicu želuca smještenu najčešće u tankom crijevu, obično ileumu. Za njegov slikovni prikaz intravenski primijenimo ^{99m}Tc-pertehnetat, potom snimamo regiju abdomena, a istovremeni prikaz sluznice želuca i divertikla oko 30. minute nakon injiciranja nalaz je koji potvrđuje dijagnozu (sl. 2) (13).

Komplementarne metode za otkrivanje Meckelovog divertikla koje se najčešće koriste jesu kolonoskopija, endoskopija kapsulom i CT. U našem se Zavodu, iako rijetko budući da se radi o rijetkom kliničkom entitetu, i danas izvodi scintigrafija heterotopične želučane sluznice te je unazad 10 godina snimljeno 15 studija. U literaturi se spominju brojni prikazi slučajeva u kojima je upravo scintigrafija pridonijela postavljanju dijagnoze Meckelovog divertikla. Tako su Zhu i sur. (14) opisali rijedak slučaj spontane perforacije i intraabdominalnog apscesa zbog Meckelovog divertikla, a Xue i Tang (15) krvarenje i sekundarnu opstrukciju crijeva također zbog ove rijetke prirođene anomalije.



Sl. 2. *Scintigrafija heterotopične želučane sluznice s ^{99m}Tc-pertehnetatom; a) planarni scintigram, b) jednofotonska emisijska tomografija uz „low dose" kompjuteriziranu tomografiju (SPECT/CT). Fokalno nakupljanje aktivnosti u srednjem dijelu abdomena istovremeno s pojavom aktivnosti u želucu odgovara Meckelovom divertiklu u tankom crijevu.*

Scintigrafija za otkrivanje gubitka bjelančevina u crijevima i ispitivanje gubitka bjelančevina crijevima. Scintigrafija za otkrivanje gubitka bjelančevina u crijevima je dijagnostička metoda koja omogućava vizualizaciju gubitka bjelančevina u crijevima, a izvodi se pomoću intravenski primijenjenih ^{99m}Tc-albumina, a snima se tijekom 24 h, u određenim vremenskim intervalima. Vidljiva aktivnost u crijevima upućuje na pozitivan nalaz i potvrđuje dijagnozu (16).

Ispitivanje gubitka bjelančevina crijevima nije scintigrafija u pravom smislu riječi, u smislu slikovnog prikaza, no služi za točnu i preciznu kvantifikaciju gubitka proteina probavnim sustavom. Nakon intravenske primjene ^{51}Cr-klorida, koji se veže za proteine plazme, idućih 4-5 dana pacijent sakuplja stolicu te se u njoj mjeri aktivnost. Zdrave osobe izluče manje od 2 % dane doze krom klorida. Ovom metodom se može diferencijalno dijagnostički razlikovati gubitak proteina crijevima od drugih uzroka hipoproteinemije (5,17).

Ovaj povijesni zlatni standard prema Waldmannu i sur. (18) danas je zamijenjen jednostavnijom metodom ispitivanja gubitka bjelančevina crijevima, a to je laboratorijska pretraga krvi u smislu mjerenja klirensa α_1-antitripsina, iako ta metoda ne može nadmašiti osjetljivost i negativnu prediktivnu vrijednost metode s radioaktivnim kromom ^{51}Cr.

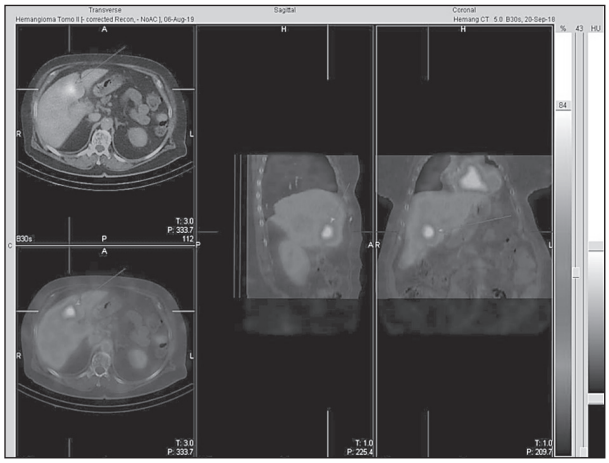
Scintigrafija za detekciju gubitka bjelančevina u crijevima uz pomoć obilježenih albumina, prema preglednom članku Levitt i sur.(19), postaje sve popularnija pretraga za dijagnozu i lokalizaciju enteropatije s gubitkom proteina (engl. *protein loosing enteropathy,* PLE), na temelju njezine jedinstvene prednosti upravo u otkrivanju mjesta „curenja" proteina te visoke osjetljivosti od 87 % i specifičnosti od 62 %, kao što su ustvrdili Khalesi i sur.(20) u svojoj meta-analizi. Nakaya i sur. (21) opisali su slučaj pacijentice koja je razvila akutni kolageni kolitis i PLE, a potonja je scintigrafski dijagnosticirana. Sličan prikaz slučaja prikazali su i Ozeki i sur. (22).

Scintigrafija za otkrivanje gastrointestinalnog krvarenja. To je metoda za otkrivanje i lociranje mjesta krvarenja u lumen tankog ili debelog crijeva pomoću ^{99m}Tc-koloida ili vlastitih eritrocita obilježenih ^{99m}Tc-pertehnetatom. Scintigrafija može otkriti krvarenja vrlo male brzine; 0,1 mL/min kod ^{99m}Tc-koloida, odnosno 0,2-0,4 mL/min kod vlastitih eritrocita ob. ^{99m}Tc-pertehnetatom te kao takva ima ujedno i prognostičko značenje. Ako se ne vidi znakove krvarenja 90-120 min nakon intravenskog injiciranja radiofarmaka, ne radi se o životno ugrožavajućem krvarenju. Prednosti ove metode su da ne zahtijeva pripremu pacijenta, neinvazivna je i niskog rizika, detektira i vensko krvarenje te može ukazati i na višestruka krvarenja (5,23).

Već sama klinička prezentacija, tj. simptomi krvarenja u probavnom sustavu, u većini slučajeva upućuje na lokalizaciju krvarenja pa se shodno tome primjenjuje odgovarajuća dijagnostička metoda, u prvom redu endoskopska. Na raspolaganju su EGDS, kolonoskopija, endoskopija s videokapsulom, duboka enteroskopija, enteroskopija asistirana balonom te od radioloških arteriografija i CT angiografija. Ako su endoskopija i CT angiografija negativne, primjenjuje se scintigrafska metoda za otkrivanje gastrointestinalnog krvarenja. Farhat i sur. (24) u svom su istraživanju opisali prediktivnu vrijednost analize perfuzijske faze scintigrafije s obilježenim eritrocitima uz pomoć regija interesa, u određivanju koji će od pacijenata s krvarenjem iz donjeg dijela gastrointestinalnog sustava imati koristi od konvencionalne angiografije. Slično istraživanje objavili su i Gurajala i sur. (25). Nadalje, 2018. godine Otomi i sur. (26) usporedili su dijagnostičku točnost planarne scintigrafije, jednofotonske emisijske tomografije (engl. *single-photon emission computed tomography,* SPECT) i

hibridnog oslikavanja SPECT uz „*low dose*“ kompjuteriziranu tomografiju (engl. *single-photon emission computed tomography/computed tomography,* SPECT/CT) koristeći se endoskopijom ili endoskopijom videokapsulom kao referentnim metodama te su ustvrdili kako sve tri metode imaju vrlo visoku osjetljivost, specifičnost i dijagnostičku točnost, a SPECT/CT je najbolja metoda za lokalizaciju mjesta krvarenja.

Scintigrafija krvnih prostora jetre (hemangiomi). Ova metoda nam koristi za slikovni prikaz lezija jetre suspektnih na hemangiom, a zbog razlikovanja hemangioma od tumorskih lezija odnosno jetrenih metastaza. Izvodi se pomoću radiofarmaka koji se zadržavaju u krvnim prostorima, npr. vlastitim eritrocitima obilježenim ^{99m}Tc-pertehnetatom (sl. 3) (27).



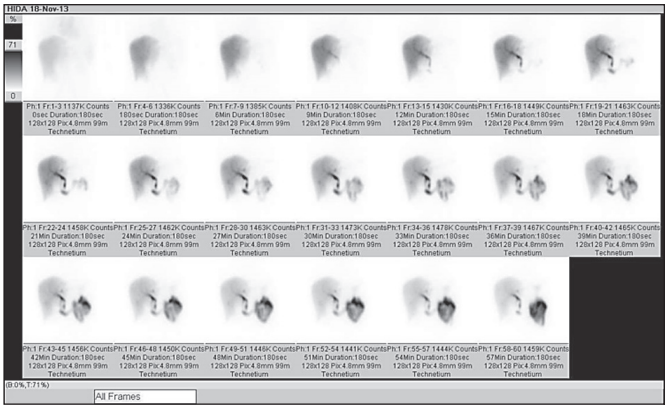
Sl. 3. *Scintigrafija vaskularnih prostora jetre pomoću vlastitih eritrocita obilježenih ^{99m}Tc-pertehnetatom (SPECT/CT). U desnom režnju jetre vidi se okruglasto područje pojačanog nakupljanja aktivnosti koje odgovara hemangiomu.*

Iako je glavna metoda za dijagnosticiranje hemangioma ultrazvuk, a mogu se još koristiti i CT, MR te angiografija, ponekad upravo scintigrafija može riješiti dvojbene slučajeve pa su tako Guan i sur. (28) prikazali slučaj pacijentice sa splenozom i hemangiomom u fundusu želuca koji su imitirali gastrointestinalni stromalni tumor te time postali prvi u svijetu koji su opisali takav slučaj.

Od svih nuklearnomedicinskih metoda u gastroenterologiji, ova scintigrafija se najčešće izvodi te je unazad 9 godina u našem zavodu snimljeno stotinjak scintigrafija.

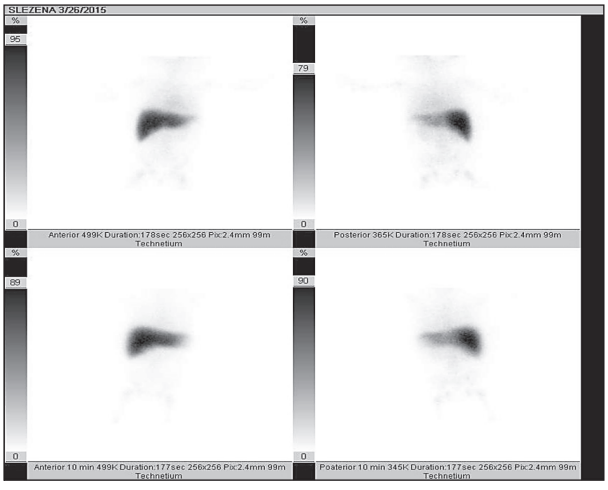
Scintigrafija jetre i žučnih vodova (hepatobilijarna scintigrafija). Hepatobilijarna scintigrafija je metoda kojom se procjenjuju funkcija i morfologija jetre i žučnog sustava pomoću radiofarmaka koji se izlučuju u žuč, a to su tehnecijem obilježeni derivati iminodioctene kiseline (npr. ^{99m}Tc-HIDA, ^{99m}Tc-DISIDA, ^{99m}Tc-BRIDA itd.). Nakon intravenske aplikacije, radiofarmak iz krvi ekstrahiraju hepatociti, potom ga izlučuju u žuč koja slijedi svoj fiziološki put izlučivanja u tanko crijevo i žučni mjehur u određenim vremenskim intervalima (sl. 4). Indikacije za hepatobilijarnu scintigrafiju su akutni i kronični kolecistitis, diferencijalna dijagnoza žutice (hepatocelularna vrs. opstruktivna), otkrivanje patoloških komunikacija bilijarnog stabla i „bijega“ žuči (engl. *biliar leak*) nakon operacije ili traume, upale i tumori jetre, fokalna nodularna hiperplazija, žučne fistule i perforacije, disfunkcija Oddijevog sfinktera, procjena prohodnosti bilijarnog stenta, stanje nakon transplantacije jetre (29). Funkcija hepatobilijarnog sustava danas se uglavnom procjenjuje laboratorijski, dok se morfološki prikazuje i procjenjuje ultrazvukom (s elastografijom ili bez nje), CT-om, MR kolangiopankreatografijom, endoskopskom retrogradnom kolangiopankreatografijom (ERCP) te perkutanom transhepatičnom kolangiografijom. U našem Kliničkom zavodu za nuklearnu medicinu učinjeno je svega nekoliko scintigrafija, iako se u svijetu i dalje koristi. Tako su Choi i sur. (30) javno objavili istraživanje u kojem su ustvrdili kako nakon brzog punjenja žučnog mjehura, a bez prikaza prolaza radiofarmaka u tanko crijevo, ne treba primijeniti kolecistokinin ili odgoditi snimanje, jer je vjerojatnost klinički značajne opstrukcije zajedničkog žučnog voda jednaka nuli. Rassam i sur. (31) proveli su istraživanje o stres testu funkcije jetre, dok su Vélez-Gutierrez i sur. (32) analizirali ulogu scintigrafije hepatobilijarnog sustava u pacijenata nakon transplantacije jetre i procjeni ranih bilijarnih komplikacija.

Scintigrafija s obilježenim leukocitima. Endoskopija je zlatni standard za postavljanje dijagnoze upalne bolesti u crijeva, no u praćenju ovih pacijenta, osobito onih koji nisu pogodni za endoskopiju, može se koristiti neinvazivna scintigrafija s ^{99m}Tc-HMPAO obilježenim leukocitima koja ima svojih prednosti pred drugim modalitetima praćenja: nije potrebna posebna priprema pacijenata, neinvazivnost, vizualizacija aktivnosti bolesti u čitavom probavnom traktu u jednom pregledu, malo radijacijsko opterećenje, nije kontraindicirana u pacijenta s akutnom fazom bolesti, nema rizika od komplikacija (npr. perforacija crijeva, krvarenje i slično), procjena učinka terapije te može razlikovati stenozu uzrokovanu fibrozom od stenoze u aktivnoj upali koja nastaje zbog edema stijenke crijeva. Osjetljivost ove pretrage je vrlo visoka i iznosi 95-100 %, uz specifičnost od 85-100 % zbog čega se može koristiti kao alternativa konvencionalnim metodama u praćenju i procjeni pacijenata s upalnom bolesti crijeva (33). Rispo i sur. (34) na temelju rezultata svojeg istraživanja preporučuju ovu metodu u kombinaciji s UZV tankog crijeva, kao rani i neinvazivni dijagnostički pristup pacijentima u kojih se sumnja na upalnu bolest crijeva, za selekciju onih koji će nastaviti endoskopsku obradu.



Sl. 4. *Hepatobilijarna scintigrafija s ^{99m}Tc-BRIDA. Izostanak prikaza funkcionalnog parenhima lijevog režnja jetre i žučnjaka uz uredan prikaz desnog režnja i žučnih vodova te prijelaza radiofarmaka u tanko crijevo (afunkcija lijevog režnja jetre kao posljedica sekundarne bilijarne ciroze zbog dugotrajne opstrukcije lijevog duktusa hepatikusa kamencem).*

Koloidna scintigrafija jetre i slezene. To je dijagnostički postupak za prikaz morfologije, funkcije i eventualnih lezija jetre i slezene koristeći se sposobnošću retikuloendotelnog sustava (RES; Kupferove stanice u jetri i monocitno-makrofagni sustav slezene) da fagocitira obilježene koloidne čestice. Nakon intravenske primjene ^{99m}Tc-koloid se veže za bjelančevine plazme (opsonin) čineći tako kompleks koji fagocitira RES. Potom se snima regija abdomena i analizira raspodjela aktivnosti u ciljnim organima (sl. 5). Iako su značenje ove pretrage potisnuli UZV, CT i MR, scintigrafija ima prednost u procjeni funkcionalnog stanja jetre i slezene, kao npr. u obradi tvorbe u gornjem dijelu abdomena za koju je potrebno isključiti ili potvrditi povezanost s jetrom i slezenom ili u dijagnostici ruptura ovih parenhimnih organa. U našem Kliničkom zavodu ova se pretraga vrlo rijetko izvodi pa ih je unazad 5 godina učinjeno svega nekoliko (sl. 5).



Sl. 5. *Koloidna scintigrafija jetre i slezene s ^{99m}Tc-koloidom. Uredan prikaz jetrenog parenhima, bez prikaza funkcionalnog parenhima slezene (funkcionalna asplenija).*

Matesan i sur. (35) su u svojem istraživanju ustvrdili povezanost pojedinih scintigrafskih parametara s parametrima funkcije jetre u pacijenata s difuznom bolešću jetre.

U tablici 2. prikazana je primjenjivost pojedinih nuklearnomedicinskih pretraga ovisno o zahtjevnosti pripreme radiofarmaka, trajanju i načinu snimanja.

Tablica 2.
Primjenjivost nuklearnomedicinskih pretraga ovisno o zahtjevnosti pripreme radiofarmaka, trajanju i načinu snimanja.

Naziv nuklearnomedicinske metode	Zahtjevnost pripreme radiofarmaka	Trajanje i način snimanja
Scintigrafska ispitivanja jednjaka	+[1]	+
Scintigrafija gastroezofagealnog refluksa	+	+
Scintigrafija pražnjenja želuca	++[2]	++
Scintigrafija tranzita kroz tanko i/ili debelo crijevo	+++[3]	+++
Scintigrafija heterotopične želučane sluznice	+	+
Scintigrafija za detekciju gubitka bjelančevina u crijevima	++	+++
Ispitivanje gubitka bjelančevina crijevima	++	-
Scintigrafija za detekciju gastrointestinalnog krvarenja	+++	+++
Scintigrafija vaskularnih prostora jetre (hemangiomi)	+++	+
Scintigrafija jetre i žučnih vodova (hepatobilijarna scintigrafija	+	+
Scintigrafija s obilježenim leukocitima	+++	+++
Koloidna scintigrafija jetre i slezene	+	+

[1]+ jednostavna priprema radiofarmaka odnosno kratko trajanje studije
[2]++ složenija priprema radiofarmaka odnosno srednje dugo trajanje studije
[3]+++ zahtjevna priprema radiofarmaka odnosno dugo trajanje studije

ZAKLJUČAK

Nuklearna medicina je područje medicine koje svojim metodama istovremeno objedinjuje dijagnostičku informaciju o funkciji i morfologiji organa čineći je time posebnom u odnosu na druge grane medicine i čime se ujedno osigurava njezina sveprisutnost u mnogim dijagnostičkim algoritmima. Većina dijagnostike bolesti ili stanja u gastroenterologiji obavlja se uz pomoć različitih endoskopskih i/ili radioloških metoda od kojih su neke danas gotovo u potpunosti zamijenile određene nuklearnomedicinske postupke koji su zbog toga i zbog slabog kliničkog interesa pali u zaborav. Međutim, u dvojbenim situacijama kada se iscrpe sve druge dijagnostičke mogućnosti, treba imati na umu postojanje i ovih metoda koje ponajprije svojom neinvazivnošću i viso-

kom dijagnostičkom točnošću mogu doprinijeti kako postavljanju konačne dijagnoze tako i krojenju daljnjeg terapijskog plana za pacijenta. Navedena svjetska istraživanja u ovom članku, samo su neka od mnogih koja su objavljena unazad nekoliko godina te pokazuju kako nuklearna medicina i dalje ima svoje mjesto u gastroenterologiji, u dijagnostici i praćenju terapijskog učinka istovremeno dajući svoj doprinos i razumijevanju složenih patofizioloških mehanizama pojedinih stanja i bolesti čime se otvaraju nove mogućnosti njihova liječenja. Neka stoga ovaj pregledni članak bude podsjetnik kliničarima na ove dijagnostičke metode koje su se nekad znatno više koristile, a danas polako i neopravdano ulaze u povijest nuklearne medicine zbog tek sporadičnog, iznimno rijetkog interesa za njihovo izvođenje.

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SUMMARY

DIAGNOSTIC RELEVANCE OF NUCLEAR MEDICINE IN GASTROENTEROLOGY

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Diagnostics in gastroenterology is based on endoscopy, ultrasound and radiological imaging, in addition to physical examination and laboratory testing. Besides being used as valuable diagnostic tools, these methods also represent the foundation for non-surgical interventions in gastroenterological patients. In the field of diagnostic imaging, a specific role is attributed to nuclear medicine methods. Although rarely used, the latter may contribute to definitive diagnosis of diseases in such patients, as they are noninvasive and accurate. This review article provides a brief and comprehensible summary of nuclear medicine methods in gastroenterology.

Key words: nuclear medicine, gastroenterology

JOHN CUNNINGHAM VIRUS-ASSOCIATED NEPHROPATHY IN A KIDNEY TRANSPLANT RECIPIENT

MARKO BANIĆ[1,3], MARIJANA ĆORIĆ[2,3], VESNA FURIĆ-ČUNKO[1], MISLAV MOKOS[3], IVANA JURIĆ[1], NIKOLINA BAŠIĆ-JUKIĆ[1,3]

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John Cunningham (JC) virus is a well-known cause of progressive multifocal encephalopathy. Only a few cases of polyomavirus-associated nephropathy due to JC virus have been reported so far. We report one such case in a kidney transplant recipient who presented with proteinuria and increased serum creatinine. Allograft biopsy revealed polyoma virus-associated nephropathy. Real-time polymerase chain reaction revealed negative result for BK and JC virus in the blood, negative for BK virus and positive for JC virus in the urine, and finally, when performed on the biopsy sample it detected more than 10^6 copies of JC virus DNA, which allowed us to establish JC virus-associated nephropathy as a definitive diagnosis. The patient was treated with intravenous immunoglobulins and reduction of immunosuppression. Serum creatinine returned to initial levels with decrease of proteinuria. This case documents that JC virus may cause significant changes in renal allograft and should be included in the differential diagnosis of allograft dysfunction.

Key words: immunosuppression, kidney transplantation, JC virus, JC virus nephropathy

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INTRODUCTION

While BK virus presents a well-known cause of renal allograft dysfunction, far fewer cases describing John Cunningham (JC) virus as a culprit have been reported. Both of the viruses, along with several others described, belong to the same group of species-specific polyomaviruses (1). These viruses are ubiquitous with seroprevalence in humans ranging from 65% to 90% for BK virus and 44%-92% for JC virus (2). JC virus primary infection usually occurs during the first years of life and is most commonly asymptomatic. After primary viremia, JC virus latently infects kidney epithelial cells and may be found in the urine (3,4). Some authors suggest that JC virus may develop persistent infection in kidneys and lymphoid organs (5). The virus is also neurotropic and may cause progressive multifocal leukoencephalopathy (5,6). While BK virus-associated nephropathy (BKVAN) is relatively common, manifested in up to 10% of renal transplant recipients (1), JC virus-associated nephropathy (JCVAN) is seen far less often; a review from 2016 (7) has reported only 20 cases described in the English-language literature with the first one in 2003 (8).

CASE REPORT

A 68-year-old male with a history of alcoholism and essential hypertension was diagnosed with focal segmental glomerulosclerosis and IgG kappa monoclonal gammopathy of unknown significance in 2008. He was started on hemodialysis in 2015 and received a kidney transplant from a deceased donor in July 2017. He received basiliximab for induction and tacrolimus, mycophenolate mofetil and steroids for maintenance. The post-transplantation period was complicated with urinary tract infections and spontaneous vertebral fractures, which were treated with denosumab. Addition-

ally, he had leukopenia, which demanded decreased doses of mycophenolate. In August 2018, serum creatinine increased from the baseline value of 150 μmol/L with proteinuria of 0.6 g/day to creatinine 209 μmol/L and proteinuria of 4 g/day, so renal biopsy was performed. Donor specific antibodies were negative. The patient's blood and urine samples were analyzed employing the real-time polymerase chain reaction (RT-PCR) by the LightMix Kit for detection of Polyomaviruses. The blood samples were negative for both BK virus and JC virus DNA, but in urine >10^6copies of JC virus DNA were detected with negative BK virus DNA.

The biopsy specimen showed pathological findings that were described as a Banff score class III polyomavirus-associated nephropathy (pvl1, ci3) along with findings described as chronic parenchymal changes, which may have been the consequences of previous bacterial infections. Also, epithelial polymorphy with nuclear hyperchromasia and intranuclear viral inclusions was visible in some tubules, which also displayed positive immunohistochemical reaction to SV40 antigen (Figures 1 and 2), common to both JC and BK viruses. In order to prove JC virus as a pathogen, RT-PCR analysis of the biopsy sample was performed. It detected >10^6 copies of JC virus *per* mL with negative BK virus DNA. The diagnosis of JCVAN was established.

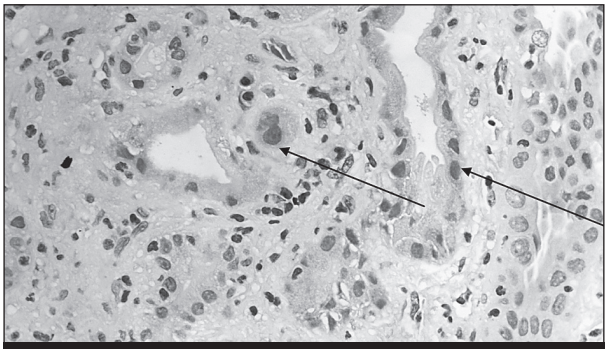

Fig. 1. *Micrograph of the biopsy sample showing papyloma virus-associated nephropathy pathology.*

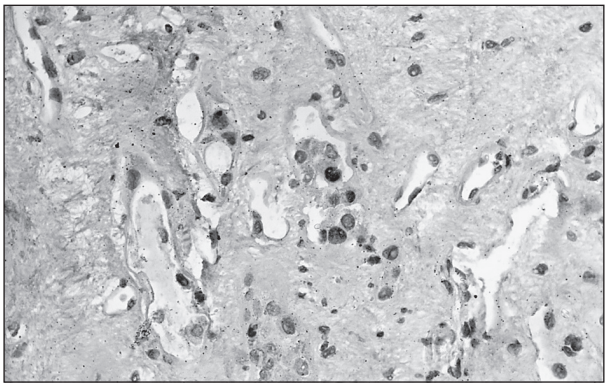

Fig. 2. *Positive SV40+ staining.*

At the time, his immunosuppressive therapy included tacrolimus monohydrate at a dose of 1.75 mg (through level 4.8 ng/mL), mycophenolate mofetil 2x500 mg and 10 mg of prednisone. After the diagnosis, immunosuppressive therapy remained the same but was lowered to 1 mg/2x500 mg/5 mg, respectively. Intravenous immunoglobulins (IvIg) (2 g/kg) were also applied, divided over four days. After IvIg therapy, his renal parameters began to fall towards the earlier values. He was released home on day 22 of his hospital stay.

Not a month after discharge from the hospital, he suffered yet another urosepsis but recovered quickly. His current kidney function is steady with serum creatinine levels of 145 μmol/L, proteinuria 1.5 g/day and immunosuppressive therapy consisting of tacrolimus (target through level around 3-4 ng/mL) and prednisone 5 mg.

DISCUSSION

John Cunningham virus is a well-known cause of progressive multifocal leukoencephalopathy in immunocompromised patients, such as HIV-infected with low CD4+ count (5). It is far less common for JC virus to cause polyomavirus-associated nephropathy. In a prospective cohort study by Drachenberg *et al.*, 0.9% of kidney transplant patients were diagnosed with JCVAN, while studies on BK virus report on 1%-10% incidence of BKVAN in kidney transplant population (1,8-12).

The most prominent problems with JCVAN are diagnosis and screening. Although Drachenberg *et al.* displayed a strong association between JC viremia and JCVAN, it was not present in all of the patients as 2 out of 6 patients were not proven to have JC viremia at the time of the study (10). Other cases of JCVAN without PCR-proven JC-viremia have also been noted (13). John Cunningham viremia may yet prove to be useful in diagnosing JCVAN, as a vast number of patients with JC viremia do develop JCVAN (4,10). Some authors suggest that JC viruria is not a helpful screening tool for detection of JCVAN, as its incidence is not significantly increased in kidney-transplant patients; the more so, it does not appear to be increasing at all in immunosuppressed patients, unlike the BKV viruria (14). Regarding the viral quantitative load, it is still unclear whether it does increase in the immunosuppressed patients (4).

The most common immunosuppression used in our institution for kidney transplant patients is a combination of tacrolimus, mycophenolate mofetil and prednisone. Querido *et al.* proposed some risk factors for

development of JCVAN in kidney transplant patients including the use of mycophenolate mofetil and tacrolimus as immunosuppressive agents (15). Besides immunosuppression, additional risk factors found in our patient were male gender and deceased donor transplantation. He neither received anti-thymocyte globulin induction therapy nor had acute rejection episodes.

We reversed the course of JCVAN successfully with high doses of intravenous immunoglobulins and reduction of immunosuppressive therapy. Some cases of JCVAN have been reported to improve after conversion from tacrolimus to everolimus (15), which was not possible in our patient due to proteinuria. Attempts to improve glomerular filtration rate with tacrolimus to cyclosporine have also been made, as well as some antiviral agents and adding leflunomide to therapy (11,13).

CONCLUSION

Available data on the diagnosis and treatment of JCVAN are scarce. Our case demonstrated that due to biology similarities of JC virus and BK virus, experiences and methods used in the treatment of BKVAN may be employed in the treatment of JCVAN.

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SAŽETAK

NEFROPATIJA POVEZANA S VIRUSOM JOHN CUNNINGHAM U PRIMATELJA TRANSPLANTATA BUBREGA

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Dok je John Cunningham (JC) virus dobro poznati uzročnik progresivne multifokalne encefalopatije, dosad je opisan kao uzročnik nefropatije u tek nekoliko slučajeva. Prikazujemo bolesnika s transplantiranim bubregom koji se prezentirao proteinurijom i porastom serumskog kreatinina. Biopsijom presatka je dokazana poliomavirusna nefropatija. Uporabom lančane reakcije polimeraze BK virus i JC virus su bili negativni u krvi, u mokraći je BK virus bio negativan, a JC virus pozitivan, dok je iz bioptata dokazano više od 106 kopija DNA JC virusa, čime smo potvrdili dijagnozu nefropatije presatka uzrokovane JV virusom. Bolesnik je liječen intravenskim imunoglobulinima uz smanjivanje intenziteta imunosupresije. Ovaj bolesnik potvrđuje da JC virus može uzrokovati značajne promjene u bubrežnom presatku i da ga treba uključiti u diferencijalnu dijagnozu pogoršanja funkcije presatka.

Ključne riječi: **imunosupresija, transplantacija bubrega, JC virus, JC virusna nefropatija**

PLASTIČNI BRONHITIS – JE LI RIJEČ O SINDROMNOJ BOLESTI?

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Plastični ili odljevni bronhitis izrazito je rijetka i teška bolest koju se sve češće prikazuje kao kasnu komplikaciju kod djece nakon uspostave Fontanove cirkulacije. Ovdje prikazujemo 11-godišnjeg dječaka s inicijalnom dijagnozom sindroma hipoplastičnog lijevog srca (HLHS) kod kojeg se u dobi od 11 godina razvila slika plastičnog bronhitisa s tipičnim kliničkim, makroskopskim i mikroskopskim nalazom. Razmatraju se mogući etiološki čimbenici u nastanku bolesti, od nekih graničnih izvornih kriterija (hipoplazija velikih plućnih krvnih žila) do brojnih kirurških i interventnih postupaka. Neovisno o činjenici da ne postoji jedinstven etiološki čimbenik, u pozadini bolesti nalazi se poremećaj limfne drenaže. U radu se razmatraju mogući etiološki čimbenici s opsežnom analizom mogućeg poremećaja limfne drenaže u kardiopulmonalnom odnosu kod Fontanove cirkulacije. Kratko se opisuju i druge kasne komplikacije kod Fontanove cirkulacije, ali i opsežan i uspješan terapijski pristup sindromu odljevnog bronhitisa.

Ključne riječi: **Fontanova cirkulacija, kasne komplikacije, plastični bronhitis, djeca, etiologija, liječenje**

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UVOD

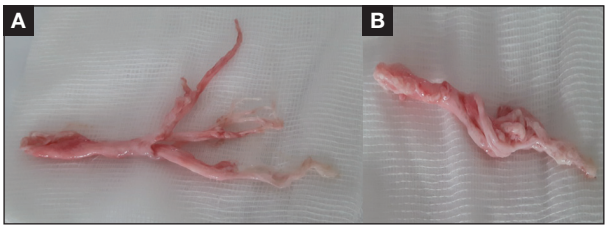
Plastični ili odljevni bronhitis je vrlo rijetko, potencijalno smrtonosno stanje koje se očituje iskašljavanjem dijelova odljeva traheobronhalnog stabla i uzrokuje različit stupanj respiracijskog distresa (1-5). Javlja se u raznim plućnim bolestima (2,3), a sve se češće opisuje u djece sa složenim prirođenim srčanim grješkama (PSG) s jedinstvenom (zajedničkom) klijetkom otkako se one sa sve većim uspjehom palijativno liječe operacijom po Fontanu, odnosno njenim modifikacijama. Javlja se kao kasna komplikacija ovih operacija (6-12). Jedini prikaz plastičnog bronhitisa u našoj literaturi potječe iz 2007. godine, a odnosi se na dijete s primarnom patologijom dišnog trakta. Riječ je o petogodišnjoj djevojčici kod koje je odljevni bronhitis izazvao teški respiracijski distres, ali se brzo klinički oporavila nakon bronhoskopskog uklanjanja odljeva (12).

Ovdje želimo prikazati pojavu plastičnog bronhitisa u 11-godišnjeg dječaka s inicijalnom dijagnozom hipoplastičnog lijevog srca (HLHS) (engl. *hypoplastic left heart syndrome),* a nastao je jamačno kao kasna komplikacija modificirane operacije po Fontanu. Također u raspravi dajemo uvide u dosadašnja saznanja o etiologiji i patogenezi ovoga stanja te mogućnostima njegovog liječenja.

PRIKAZ BOLESNIKA

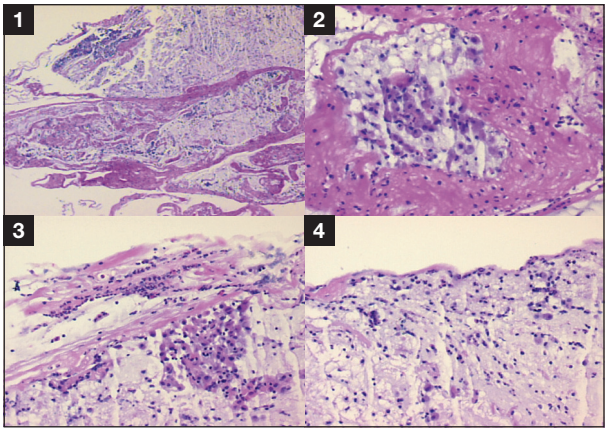
Riječ je o dječaku u dobi od 11 godina rođenom sa HLHS-om, kojem su prethodno učinjene sve tri palijacijske operacije; 1. Norwood I s mBT anastomozom neposredno nakon poroda (mBT – modificirana Blalock-Taussigina anastomoza), 2. PCPC anastomoza u dobi od 4 mjeseca (PCPC – parcijalna kavopulmonal-

na konekcija, engl., *partial cavopulmonary connection*)), 3. TCPC anastomoza s fenestracijom u dobi od 3 godine (TCPC – potpuna kavopulmonalna konekcija, engl. *total cavopulmonary connection*). Slijedom toga, u dobi od 10 god. i 10 mj. zatvorena je fenestracija PFO okluderom (PFO – *persistent foramen ovale*). Tri mjeseca potom (sredinom 2016. godine) primljen je u Zavod za pedijatrijsku kardiologiju zbog iskašljavanja odljeva bronha, što je prepoznato kao kasna komplikacija operacije po Fontanu s nazivom plastični bronhitis (sl. 1. A i B). Osim nativnog iskašljaja prikazan je i makroskopski nalaz dobiven bronhoskopski. Dijagnoza je potvrđena i patohistološkom analizom kako slijedi: trakasti, razgranati uzorci ukupnog promjera 2 i 3 cm, histološki građeni pretežno od fibrina i sluzi s nešto upalnih stanica i tračaka odljuštenog epitela, što histološki odgovara plastičnom bronhitisu.



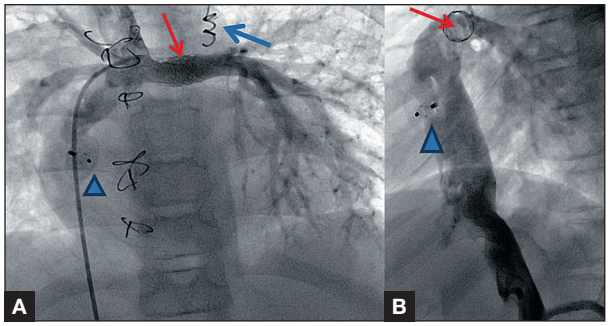
Sl. 1. *Prikaz iskašljaja kod odljevnog bronhitisa:* A. Makroskopski nalaz nakon spontanog iskašljaja. B. Odljev bronha uklonjen bronhoskopski.

Mikrobiološkom obradom iskašljaja nađeni su saprofitna *Neisseria*, *Staphycoloccus aureus, Candida albicans, Penicillium sp., Streptococcus sp.(viridans*)(sl. 2. - 1,2,3,4**).** Dijagnoza PSG, točnije HLHS-a postavljena je u 24-tom tjednu gestacije fetalnom ehokardiografijom, a potvrđena je nakon porođaja koji je uslijedio spontano u 37-om tjednu trudnoće u tercijarnom opstetričkom centru. Odmah poslije porođaja premješten je u Referentni centar za pedijatrijsku kardiologiju s infuzijom prostaglandina (PGE1) zbog održavanja otvorenog arterijskog duktusa (desno-lijevi pretok). U dobi od 9 dana učinjena je operacija Norwood I sa Sano *shuntom* (provodnik od desne klijetke do plućne arterije) koji je zbog teške stenoze u dobi od 4 mjeseca zamijenjen novim. U dobi od 6 mjeseci učinjena je operacija po Glennu, odnosno PCPC anastomoza (anastomoza gornje šuplje vene s desnom granom plućne arterije). Zbog hipoplastične lijeve plućne arterije (LPA) istovremeno je u nju ugrađena i potpornica (stent). U dobi od godine dana je zbog daljnje stenoze pulmonalnih ogranaka učinjena redilatacija stenta u LPA i dilatacija desne grane plućne arterije (RPA), ali i embolizacija aortopulmonalnih kolaterala zavojnicama (*coils*) te dilatacija istmične stenoze s gradijentom višim od 20 mm Hg (kriterij za koarktaciju). U dobi od 4,5 godine učinjena je TCPC anastomoza uz kiruršku rekonstrukciju luka aorte.

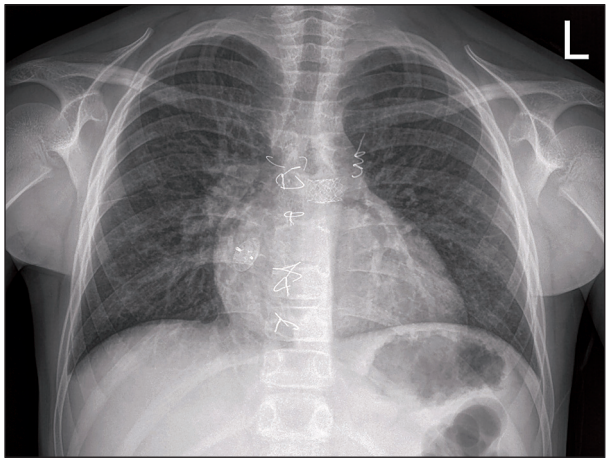


Sl. 2. *Trakasti, razgranati uzorci ukupnog promjera 2 i 3 cm, histološki građeni pretežno od fibrina i sluzi s nešto upalnih stanica i tračaka odljuštenog epitela, što histološki odgovara acelularnom plastičnom bronhitisu (tip 2).*

Prethodno mu je tijekom preoperacijske kateterizacije zbog okluzije venskog sustava od vene femoralis prema donjoj šupljoj veni s desne strane, u lijevu zajedničku i vanjsku ilijakalnu venu ugrađena potpornica kako bi se održao pristup od lijeve femoralne vene prema donjoj šupljoj veni. U dobi od 6 god. i 4 mj. učinjena je redilatacija stenta LPA (12 mm), dilatacija Glenn-ove anastomoze (zbog razvoja stenoze) i dilatacija RPA (ogranak za gornji režanj), a potom slijedi transkatetersko zatvaranje fenestracije Amplatzerovim kišobranom (PFO okluder). Nakon zatvaranja došlo je do očekivanog porasta periferne sistemne saturacije kisikom, pa je postupno ukinuta antikoagulacijska terapija (warfarin) i započinje antiagregacijska terapija (acetilsalicilna kiselina) (sl. 3)**.** Razlozi za ugradnju stentova u pritočne krvne žile iz kardinalnog venskog sustav a kaudalno te potreba za dilatacijom Glennove anastomoze, ne mogu se dokučiti bez dodatne sumnje na koagulacijske probleme u kardinalnom venskom sustavu, neovisno o urednoj antikoagulacijskoj i antiagregacijskoj terapiji i neovisno o neprestano urednim rutinskim laboratorijskim kontrolama koagulacije. Tri mjeseca nakon zatvaranja fenestracije dijete počinje sve učestalije produktivno kašljati uz iskašljavanje guste sluzi, a povremeno i bijelog, žilavog sekreta u debelim nitima koji poprimaju oblik odljeva bronhalnog stabla (sl. 1) (kompletan makroskopski i mikroskopski opis naprijed, sl. 2).



Sl. 3. A. *Prikaz LPA; A. S potpornicom koja je dilatirana(crvena strjelica), prikaz zavojnice u aortopulmonalnoj kolaterali (plava strjelica) i prikaz PFO okludera na mjestu prethodne fenestracije TCPC anastomoze (vrh strjelice).* B. *Lateralna projekcija*



Sl. 4. *Rendgenska slika u djeteta s plastičnim bronhitisom; zastojne promjene u plućima s krupnijim vaskularnim hilusima, bez infiltrata ili izljeva.*

S vremena na vrijeme vidljivi su i tračci svježe krvi. Na rendgenogramu pluća vidljiv je zastojni plućni crtež s krupnijim vaskularnim hilusima, bez prisutnosti infiltrata i izljeva (sl. 4). Uz kardiotonike i diuretike (enalapril, furosemid, spironolakton), uvedena je inhalacija acetil-cisteinom i hipertoničnom otopinom natrijeva klorida. Unatoč tome ima sve učestalije napadaje kašlja te izraženiju hipoksiju s dispnoičkim krizama i produktivan kašalj uz distenziju vratnih vena. Javljaju se i aritmogene epizode atrijske tahikardije do 150/min s pojedinačnim ventrikularnim ekstrasistolama. Nad trikuspidalnim ušćem nalazi se sistolički šum II/6 zbog trikuspidalne insuficijencije. Jetra se palpira 3 cm pod DRL, slezena nije palpabilna. Pulsacije perifernih arterija su uredne, edema nema. Upalni parametri su normalni (SE 12 mm/3,6 ks, CRP 8,6 mg/L) kao i biokemijski (ionogram, GUK, koagulogram, antitrombin, hepatogram, ureja, kreatinin, troponin T, CK, proteinogram i elektroforeza proteina) te urin. Ima umjerenu poliglobuliju (E 5,60 10^{12}/L, Hb 165..161g/L, Hct 0,497 L/L). Plinska analiza krvi pokazuje normalan parcijalni tlak kisika (pO_2 9,4 kPa) bez popratne acidoze i/ili hiperkapnije. EKG pokazuje takozvani infantilni tip; hiperdevijacija el. osi udesno(+140°), AV blok I (PQ 0,24 s), QRS 0,08 s, QTc 0,42 s, nepotpun (Wilsonov) blok desne grane (obrazac rSR'), znakovi opterećenja desne klijetke uz negativne T valove V1-V3. Na ponovljenom rendgenogramu srca i pluća nešto je naglašeniji zastojni plućni crtež uz stacionaran ostali intratorakalni nalaz. U testovima plućne funkcije nalazi se teška opstrukcijsko-restrikcijska slika (oko 50 % plućne funkcije), bez reakcije na Ventolin. Uz spomenutu kardiotoničku terapiju i kisik (2 L/min.) nastavlja se simptomatska terapija; dostatna hidracija, sekretolitici (acetilcistein, bromheksin) uz inhalacije 3-5 % otopine NaCl-a te intenzivna respiracijska fizikalna kineziterapija uz primjenu vibrirajuće torakalne drenaže kojom je znatno olakšano iskašljavanje bronhalnog odljeva. Kratkotrajno prima i sistemske glukokortikoide te je uvedena inhalacijska terapija potiscima flutikazona. Dodatno se u terapiju uvodi sildenafil te antagonist receptora endotelina-1 bosentan s ciljem smanjivanja plućnog vaskularnog otpora. Već od drugog tjedna boravka došlo je do značajnog smanjenja učestalosti i intenziteta kašlja, pa se pacijenta uskoro u dobrom hemodinamskom stanju otpušta u kućnu njegu. U međuvremenu je prebolio infektivnu mononukleozu i desnostranu parakardijalnu bronhopneumoniju uz manju količinu desnostranog pleuralnog izljeva, a liječen je ceftriaksonom i azitromicinom. Redovito se kontrolirao u kardiološkoj ambulanti uz nepromijenjene nalaze EKG-a i UZV srca. Uz opisanu simptomatsku terapiju kontinuirano prima sljedeće lijekove: sotalol 2 x 20 mg p.o., Enap 1 x 2.5 mg p.o., Lasix 2 x 10 mg p.o., Aldactone 1 x 12,5 mg p.o., Aspirin 1 x 50 mg p.o., sildenafil 3 x10 mg.p.o., Stayveer 1 x 62,5 mg.p.o. I dalje je povremeno kašljao uz iskašljavanje manjih komadića čvrstog bronhalnog odljeva no uz simptomatsku terapiju inhalacijama hipertonične otopine natrijeva klorida i sekretolitika takve epizode postupno prestaju. Simptomi i klinički znaci mogućeg recidiva trajali su godinu dana. Sredinom 2017. god. je zbog potrebe revizije stanja učinjena rekateterizacija srca i CT angiografija toraksa, abdomena i zdjelice. Prikazano je zadovoljavajuće stanje i hemodinamika Fontanove cirkulacije (srednji tlak u PA 17 mm Hg, PVR 2,5 j/m^2, Nakata indeks ispod 300 mm^2/m^2) na osnovi čega je u daljnjem postupanju u obzir došla samo rekonstrukcija Fontanove operacije s mogućim otvaranjem rasteretnog otvora. No kako je u sljedećem razdoblju došlo do spontanog prestanka svih simptoma plastičnog bronhitisa navedeno nije učinjeno. Dječak je već gotovo četiri godine godine nakon inicijalnog nalaza plastičnog bronhitisa u redovitim ambulantnim kardiološkim kontrolama, uz gore navedenu terapiju, dobrog općeg i kliničkog stanja, nepromijenjenog nalaza ultrazvuka srca, zadovoljavajućih kontrolnih laboratorijskih biokemijskih parametara, za sada bez naznake za razvijanje neke druge kasne komplikacije.

RASPRAVA

Plastični bronhitis je vrlo rijetko, ozbiljno, potencijalno smrtonosno stanje koje se očituje stvaranjem dugačkih, blijedoružičastih, gumastih, rastegljivih i razgranatih fibromukoznih čepova unutar velikih i malih dišnih putova. Opisani sadržaj opstruira dišne putove i ponaša se kao svojevrsno „strano tijelo" pa se očituje učestalim napadajima kašlja tijekom različitog razdoblja i s različitim stupnjem zaduhe i respiracijskog distresa (dispneja, cijanoza, sipnja, hemoptiza). Može nastati i gušenje s posljedičnim kardiorespiracijskim zatajenjem i smrtnim ishodom (1-4). Dijagnoza se postavlja na osnovi kliničke slike i tijeka bolesti, te nakon iskašljavanja gore navedenog „odljeva" traheobronhalnog stabla po kojem je dijagnoza slikovito i dobila ime - plastični bronhitis (4-7). Dijagnoza se rjeđe postavlja nakon ekstrakcije odljeva pomoću bronhoskopa što je često vrlo teško jer sluzavi čepovi čvrsto prijanjaju uz zid bronha u kojem nastaju i lomljivi su (13). Dijagnozu je moguće postaviti ili potvrditi i na osnovi histološkog nalaza (1,3). U našeg je bolesnika sumnja na plastični bronhitis postavljena na osnovi kliničke slike, a potvrđena kako tipičnim makroskopskim nalazom odljevnog bronhitisa (sl. 1A i 1B), tako i na osnovi histološke analize osobitog iskašljaja (sl. 2 - 1,2,3,4,). Prvi opisi ovog stanja sežu još od Galena, a vrlo je neuobičajen u djece. Javlja se kod bronhopulmonalnih upalnih i alergijskih bolesti (pneumonija, kronični bronhitis, astma, respiracijske infekcije, bronhiektazije, tuberkuloza), kao i kod cistične fibroze, reumatoidnog artritisa, amiloidoze, abnormalnosti limfne drenaže i kod bolesti srpolikih stanica (2,3,14,15).

Sve se češće opisuje u djece sa složenim prirođenim srčanim grješkama, osobito u onih palijativno kirurški liječenih uspostavom Fontanove cirkulacije. Javlja se kao kasna komplikacija te operacije, s procijenjenom učestalošću od 1 do 4 %, uz stopu smrtnosti u akutnoj fazi 29 %, a prema nekim izvorima petogodišnji je mortalitet čak i do 50 %. Oko 40 % djece s Fontanovom cirkulacijom razvija kod plastičnog bronhitisa simptome životne ugroženosti (2,16). Fontanova je cirkulacija postupan palijativni kardiokirurški pristup kojim se postiže fiziološka korekcija brojnih prirođenih srčanih grješaka s anatomskim ili funkcionalnim univentrikularnim srcem, tj. jednom (zajedničkom) funkcionalnom klijetkom (SV) (engl. *single ventricle-SV)*. U osnovi se teži prema tome da se ukupni sistemski venski povrat krvi iz kardinalnog venskog sustava preusmjerava izravno u plućno arterijsko stablo bez prisutnosti pogonske „pumpne" subpulmonalne klijetke, dok jedinstvena (zajednička) klijetka vrši „pumpnu" funkciju sistemne cirkulacije i time funkcionalno postaje isključivo sistemska klijetka, neovisno o morfologiji (lijeva, desna, nedeterminirana). Time se odvaja plućni i sistemni optjecaj krvi koji su iz patološkog paralelnog spojeni u fiziološki, serijski položaj. Na taj se način postiže bolja oksigenacija i rasterećenje sistemne klijetke uz porast minutnog volumena i smanjenje rizika od paradoksne embolije, ali na uštrb povišenog centralnog venskog tlaka. Ipak, minutni volumen ovako korigirane grješke nikada ne iznosi više od 70-80 % minutnog volumena zdravog srca.Važno je naglasiti da u takozvanoj „Fontanovoj" cirkulaciji (neovisno o modifikaciji) srčani minutni volumen ovisi isključivo o plućnom protoku odnosno o zadovoljavajućem transpulmonalnom gradijentu tlaka, tj. razlici centralnog venskog tlaka i srednjeg tlaka lijeve pretklijetke te je plućni optjecaj "ključna i slaba karika" o kojoj ovisi uspješnost ishoda ove cirkulacije. Fontanova operacija i modifikacije sa svim kriterijima do sada su opsežno opisane u literaturi (8,17-19).

Od izvornih kriterija iz 1972. godine („*ten commandements*", Choussat, Fontan) koji su smatrani nužnima za uspjeh operacije atrezije trikuspidalne valvule, proširenjem spektra prirođenih srčanih grješaka s funkcionalno samo jednom klijetkom, uključujući i HLHS, iznjedreni su neki novi rizični čimbenici, ali sva iskustva pokazuju da je plućni optjecaj „najslabija karika" u fiziologiji „Fontanove" cirkulacije. Među najvažnijim rizičnim čimbenicima ostali su povišen plućni žilni otpor (PVR), povišen srednji tlak u plućnoj arteriji i relativna hipoplazija plućnih arterija. Trajno se zahtijevaju kriteriji po kojima srednji tlak plućne arterije ne smije biti viši od 17 mm Hg (takozvani podtlak), PVR mora biti ispod 2,5 Wood jedinica, a veličina plućnih krvnih žila više od 350 mm^2/m^2 (indeks Nakata). Kod našeg bolesnika imali smo zadovoljene kriterije srednjeg tlaka i izračunat kriterij niske PVR, ali smo ispočetka imali hipoplaziju krvnih žila koju smo pokušali sanirati opisanim dilatacijama ili implantacijom potpornica. Pacijent je ispunjavao i kriterije sistoličke i dijastoličke funkcije sistemne (ovdje desne) klijetke (EF > 55 % i end-dijastolički tlak manje od 8 mm Hg). Ista je otklonjena prilikom treće operacije rekonstrukcijom istmusa aorte. Čini se da razvoj opstrukcijskih lezija na lijevoj strani (koarktacija aorte) ima manju ulogu, ali ga također treba otkloniti na vrijeme. Postoji, dakle niz čimbenika koji su tijekom vremena do posljednje faze (TCPC anastomoza) mogli remetiti funkciju plućnog krvnog žilja kao što su; maldistribucija protoka kroz plućno vaskularno korito, hipoplazija plućnih arterija, mehanička opstrukcija tijekom abnormalnih kirurških anastomoza, stenoza, distorzija, kirurških ožiljaka i vanjskih kompresija, dugotrajno smanjen protok, desaturacija, povećan kolateralni protok, manjak pulsatilnog protoka koji dovodi do endotelne disfunkcije sa smanjenim lučenjem NO iz endotela koji je fiziološki moćni vazodilatator, odsutnost razdoblja ubrzanog i tlačno visokog protoka kroz pluća s regrutacijom novih plućnih arterija kao i znatno oslabljenom plućnom vaskularnom reaktivnošću

tijekom tjelesne aktivnosti. Iako smo se držali preporučenog vremenskog razmaka od palijacije do palijacije, u međuvremenu su kod našeg pacijenta učinjeni neki interventni zahvati. Poznato je da s vremenom i u zaista optimalnim slučajevima dolazi do postupnog povišenja PVR-a i centralne venske kongestije te do rane i kasne dijastoličke, a potom i sistoličke disfunkcije sistemne klijetke (17,18).

Plastični bronhitis pripada kasnim komplikacijama Fontan-Kreutzerove operacije u koje se još među ostalima ubrajaju i aritmije, tromboembolijske komplikacije, plućne arteriovenske malformacije (fistule), venovenske fistule i enteropatija s gubitkom bjelančevina (8-10). Iako uzrok i mehanizam nastanka ovog stanja još uvijek nisu u potpunosti razjašnjeni, na osnovi opisanih prikaza slučajeva u literaturi se pretpostavlja da abnormalnosti hemodinamike, limfnog sustava i imunološkog odgovora imaju odlučujuću ulogu u njegovu nastanku. Oni su opet u međusobnom čvrstom, no nedovoljno razjašnjenom suodnosu. Vrlo uzak raspon hemodinamike (osobito u njenom plućnom optoku) pridonosi ovom stanju, pa možemo reći da je ono manifestacija suboptimalne prilagodbe na direktnu kavopulmonalnu cirkulaciju, odnosno pojavljuje se u bolesnika koji su iskusili značajne perioperativne komplikacije tijekom njezinog postupnog izvođenja. Tome u prilog govore i iskustveno iznjedreni rizični čimbenici za pojavnost ove komplikacije, a oni su: prolongirano vrijeme drenaže prsnog koša nakon 2. i 3. koraka Fontanove operacije, ascites i značajne aorto-pulmonalne kolaterale koje su zahtijevale zatvaranje zavojnicom (*coil*-om) postupkom interventne kateterizacije i pojava hilotoraksa u bilo kojoj fazi ove operacije. Rekonstrukcija luka aorte tijekom 1. faze ove operacije smatra se graničnim rizičnim čimbenikom. Primijećena je i poveznica ranijeg razvoja plastičnog bronhitisa s dugotrajnijom drenažom prsnog koša, a raniji nastup ove komplikacije (osobito unutar godine dana nakon dovršenja operacije po Fontanu) je pak povezan s povećanom smrtnošću (20). Da je ona čvrsto povezana s poremećajima hemodinamike Fontanove cirkulacije govori i činjenica da se ona povremeno povlači nakon medikamentnih, interventnih kateterizacijskih, kirurških i inih pokušaja liječenja kojima se ona nastoji nanovo optimizirati, a u potpunosti nestaje nakon uspješne presadbe srca. U nekih bolesnika poremećaji limfnog sustava imaju osobito značenje, a detaljan prikaz njene abnormalne anatomije i obrazac limfnog protoka mogu se prikazati limfoscintigrafijom i/ili dinamičkom kontrastnom magnetnorezonantnom limfangiografijom (21,22). Kod našeg bolesnika ovu je pretragu u našim uvjetima bilo nemoguće učiniti, ali i u globalnim razmjerima su dijagnostičke metode za definiranje limfne drenaže oskudne. U posljednje se vrijeme sve češće razmatraju stanja koja su kod složenih PSG vezana uz mogući poremećaj limfne drenaže (14,21,22,23,24). Zna se da sistemna venska hipertenzija u donjoj šupljoj veni dovodi do povećane produkcije limfe i stvaranja limfedema, a u gornjoj šupljoj veni do otežane drenaže limfe zbog povišenja njenog intratorakalnog tlaka. To dovodi do staze limfe i abnormalnog retrogradnog protoka limfe od torakalnog duktusa prema plućnom hilusu s posljedičnim strukturalnim promjenama u vidu dilatacije peribronhalne limfne mreže, nastankom limfangiektazija i abnormalnih limfnih kolaterala. Vremenom zbog vjerojatno upalom potaknutog oštećenja bronhalne sluznice i njene povećane propusnosti (permeabilnosti) dolazi do stvaranja limfo-bronhalnih, tj. limfo-alveolarnih fistula i prodora hilusnog sadržaja u traheobronhalno stablo s formiranjem hilusnih odljeva. Takvo je zbivanje prvi put patohistološki prikazala Hug sa suradnicima u četverogodišnjeg dječaka sa složenom PSG (15). U tim će slučajevima kirurško podvezivanje torakalnog duktusa ili perkutana selektivna embolizacija torakalnog duktusa i patoloških limfnih žila (kolaterala i dilatirane peribronhalne limfne mreže) moguće dovesti do poboljšanja stanja, a u nekim slučajevima i do trajnog izlječenja od ove komplikacije. Da u etiologiji i patogenezi ovog stanja važnu ulogu zauzima i abnormalan imunološki odgovor pokazao je i nalaz stanične imunofenotipizacije i profila proteina i citokina u uzorku bronhalnog odljeva bolesnika podvrgnutih Fontanovoj operaciji. Naime, prvu histološku klasifikaciju učinili su Seear i sur., koji su je podijelili na dva tipa: tip 1, odnosno upalni tip, sastavljen je uglavnom od fibrina s gustim infiltratom eozinofila, a tip 2, tzv. acelularni tip, uglavnom od mucina (sluzi) s vrlo malo (ili gotovo ništa) celularnog infiltrata, kakav je opisan i u našeg dječaka. Onaj prvi vidljiv je u plućnim upalnim bolestima i dobro reagira na protuupalno liječenje inhalatornim steroidima, a potonji u oboljelih od složenih srčanih grješaka i zahtjevniji je u terapijskom smislu riječi (1). Smatra se da je on posljedica neobičnog odgovora plućnog epitela na povišen venski tlak koji se očituje hipersekrecijom sluzi. No, gore navedeno istraživanje Racza i suradnika pokazalo je da je profil citokina u njemu proupalan i da je zapravo riječ o složenom biološkom procesu u kojem se događa vrhunac upalne „savršene oluje“ s abnormalnim imunološkim odgovorom na istu (20). U literaturi se nalaze i podatci da je restrikcijski foramen ovale i odlaganje balonske atrioseptostomije kod HLHS-a češće vezano uz kasniju pojavu plastičnog bronhitisa, a zbog posljedičnog razvoja takozvanog „*nutmeg lung*“ („pluća muškatnog oraščića“) zbog razvoja sekundarne pulmonalne limfangiektazije. Iako pretjerano rana atrioseptostomija i stvaranje širokog ASD-a može dovesti do akutne srčane insuficijencije u djeteta s HLHS-om, čini se da kasna atrioseptostomija kod restriktivnog PFO može biti razlogom spomenutog oštećenja plućne mikrovaskulature (26,27). Zato je glavni zadatak fetalnog kardiologa utvrditi težinu

restrikcije na osnovi doplerskog obrasca pulmonalnih vena i indicirati atrioseptostomiju (septektomiju) neposredno nakon porođaja. Tromboembolijska plućna hipertenzija (28) i drugi mogući rijetki poremećaji koagulacije mogu biti razlogom odlaganja trombotičkih partikala na stijenke plućnih krvnih žila, sužavati ih i razvijati mehanizam za razvoj već opisanog plastičnog bronhitisa. Zato svako takvo dijete po našem mišljenju zahtijeva dodatne i osobite koagulacijke testove, uključujući i antifosfolipidni sindrom kao potencijalno rijetki reumatološki entitet, a ne treba zaboraviti ni na srpastu anemiju (15). To znači da je na terenu vulnerabilne Fontanove cirkulacije moguća i pojava plastičnog bronhitisa drugačije, nekardiološke etiologije.

Liječenje ove komplikacije je vrlo teško i u potpunosti individualno, prilagođeno svakom bolesniku posebno. Temelji se na medikamentima koji djeluju na pojedine komponente bronhalnog odljeva, omekšavaju ga i pomažu lakšem iskašljavanju kao što su mukolitici i fibrinolitici (inhalacije aerosoliziranim acetil-cisteinom, aktivatorom tkivnog plasminogena, heparinom, urokinazom, rekombinantnom alfa dornazom) (29-31), inhalacijama hipertonične otopine natrijeva klorida, salbutamola, kortikosteroida te drugim mjerama kao što su fizikalna respiratorna terapija i posturalna drenaža, a povremeno je ključno mehaničko odstranjenje odljeva te opetovana toaleta dišnih putova bronhoskopski. Također se u cilju smanjenja PVR-a i centralnog venskog tlaka koriste plućni vazodilatatori kao što su sildenafil i bosentan (32), a pokušana je i kontinuirana parenteralna terapija prostaciklinskim preparatima (epoprostenol). Od farmakološkog liječenja koristi se i antikoagulacijska terapija, diuretici i azitromicin koji je pokazao snažno protuupalno i imunomodulatorno djelovanje (33,34). Sukladno gore navedenoj etiologiji i patogenezi potrebna je pomna i temeljita analiza, tj. revizija hemodinamike „Fontanove" cirkulacije koja uključuje traženje opstrukcije uzrokovane stenozom ili trombozom i druge hemodinamske poremećaje kao što su perikardijski izljev, atrioventrikularna nesinkroniziranost (RCT – resinhronizacijska kardijalna terapija) (35) i drugi te njezine optimizacije djelovanjem na sve reverzibilne uzroke kirurškim i/ili interventnim kateterizacijskim postupcima (36-39). Sve su ove mjere primijenjene u našeg bolesnika uspješno, tako da već nekoliko godina nema recidiva. Povremeno je od koristi traženje abnormalnosti limfnog sustava s prikazom detaljne anatomije i patološke cirkulacije te gore opisanim kirurškim ili interventnim kateterizacijskim djelovanjem na istu. Ako su iscrpljene sve medikamentne i kirurške mogućnosti liječenja u obzir dolazi i transplantacija srca koja je krajnja, no učinkovita opcija i čini se jedina dovodi do trajnog izlječenja od plastičnog bronhitisa (40).

ZAKLJUČAK

Prikazali smo 11-godišnjeg dječaka s izvornom dijagnozom HLHS-a, u kojeg se nakon zatvaranja fenestre razvila slika plastičnog (odljevnog) bronhitisa kao rijetke kasne komplikacije Fontan-Kreutzerove cirkulacije. Kompliciran tijek bolesti, granične vrijednosti nekih ključnih kriterija za Fontanovu cirkulaciju i brojne interventne i kirurške metode vjerojatni su razlozi pojave plastičnog bronhitisa. Iako je jedinstven etiološki čimbenik ostao nepoznat i ne postoje jedinstvene smjernice za liječenje, teoretsko poznavanje mogućih etioloških čimbenika i terapijskih metoda omogućili su nam uspješno liječenje plastičnog bronhitisa kod ovog djeteta.

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SUMMARY

PLASTIC BRONCHITIS - IS IT A SYNDROMIC DISEASE?

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Plastic or cast bronchitis is a very rare and severe condition that occurs as a late complication with increasing frequency in children after the establishment of the Fontan's circulation. The case study presents an 11-year-old boy with an initial diagnosis of hypoplastic left heart syndrome (HLHS) who developed plastic bronchitis features with typical clinical, macroscopic and microscopic findings. Possible etiological factors are considered in the disease pathogenesis, from some of the borderline original criteria (hypoplasia of large pulmonary blood vessels) to numerous operating and interventional procedures. Regardless of the fact that there is no unique etiological factor, the disease is marked by an underlying disorder in the lymphatic drainage. Possible etiological factors are evaluated in the paper, with extensive analysis of a possible lymphatic flow disorder in cardiopulmonary relationship with Fontan's circulation. Furthermore, other possible late complications with Fontan's circulation are presented, as well as a comprehensive and successful therapeutic approach to the plastic bronchitis syndrome.

Key words: **Fontan's circulation, late complications, plastic bronchitis, children, etiology, treatment**

WHEN PUSH COMES TO SHOVE: ORGANIZING HEALTHCARE DURING CORONAVIRUS PANDEMIC 2020 – THE MODEL OF ZABOK GENERAL HOSPITAL AND CROATIAN VETERANS' HOSPITAL

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The coronavirus pandemic, starting in 2019, penetrated almost all aspects of modern civilization. Governments and organizations worldwide have imposed rules and regulations in order to control the spread of the virus, thereby introducing tremendous changes to everyday life. As the pandemic and the number of the infected around the world increased, so did the need for adequate medical care. Many uncertainties and unknowns regarding the virus and disease have made the task of organizing healthcare a day-to-day battle. The data presented were acquired from February 12 until March 15, 2020, during which time 2638 individuals were tested for SARS-CoV 2 infection. One hundred and forty among them were confirmed positive, with 25 requiring hospital treatment, among which two, unfortunately, passed away. One hundred and thirty individuals under age 18 were tested, infection was confirmed in 10 subjects and none were hospitalized. The mean age of individuals infected was 49.9 years. Our goal was to present and share the experience and challenges during the coronavirus pandemic, which affected us during 2020 in the Zabok General Hospital and Croatian Veterans' Hospital in the Krapina-Zagorje County, which was one of the major pandemic hotspots in Croatia.

Key words: COVID-19, coronavirus, healthcare management, hospital organization, pandemic

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INTRODUCTION

The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV 2) epidemic, from its origins in Wuhan, Hubei Province, PR of China, spread in a matter of weeks across the globe, putting our civilization in an unprecedented position. With the illness, dubbed coronavirus disease (COVID-19), presenting itself with a wide variety of symptoms, as well as due to the fact that a significant amount of the infected had no clinical manifestations, the organization of healthcare has become an arduous task.

In order to cope with the newly established situation, the isolation of patients presenting with symptoms of coronavirus infection, in order to reduce the possibility of them infecting both other 'non-corona' patients, as well as healthcare workers, has become a priority. The answers to the question 'how to treat them' came easier, in a way, than 'where to treat them'. In an optimal setting, the patients could be treated in so-called 'corona-negative' and 'corona-positive' facilities with the 'positive' and 'negative' pertaining to verified infection or suspicion of infection with coronavirus in the said patients (1) Examples from PR of China and Italy, which were overflown with patients, show that such organization of healthcare plays a significant role in macro-management of the infection. However, such organization is only possible if the number of medical facilities in a specific area allows for it, together with the necessary manpower, which would allow that all patients, infected or not, would receive the highest level of medical care.

While such organization looks perfect on paper and shows promise, what if the infrastructural and logistic setting does not allow for such organization? In this case, a medical facility is supposed to organize its work on three fronts, the first being the care for COVID-19 patients, the second regarding patients who were suspicious of coronavirus infection (until arrival of their swab analysis) but whose general condition did not allow hospital discharge, and the third, which has to cope with 'normal' or uninfected patients presenting with cases unrelated to coronavirus (2) such as Ebola, Nipah and Zika, it is important that such facilities are kept ready during the inter-epidemic period for training of health professionals and for managing cases of multi-drug resistant and difficult-To-Treat pathogens. While endemic potential of such critically ill patients is not yet known, the health system should have surge capacity for such critical care units and preferably each tertiary government hospital should have at least one such facility. This article describes elements of design of such unit (e.g., space, infection control, waste disposal, safety of healthcare workers, partners to be involved in design and plan. The newly found situation becomes a daily struggle, with the daily-changing regulations and guidelines imposed by the government demanding that the organization of work and manpower is able to adapt to it. An unprecedented situation to say at least.

LEADERSHIP IN THE PANDEMIC

As the news regarding SARS-CoV 2 pandemic began to emerge in Europe and the proximity of Croatia (the grim scenario of Italy having the most significant outreach), the country began to prepare itself for a similar situation. The need for a governing body led to the establishment of the national Civil Protection Directorate. While the National Directorate was at the top of the chain of command, it did not give out orders *per se*, only recommendations to hospitals and other healthcare institutions. County Directorates were, in turn, founded in order to govern the situation at the local level and had total autonomy during the pandemic. The Hospital established its own Crisis Directorate, which included the Hospital director, consultant infectologist, head nurse of the Emergency Department, and head nurse for hospital infections, who organized procurement and distribution of the necessary equipment. Rules of conduct were also established by the Hospital Directorate, which were regularly updated according to the instructions of the National Directorate.

INFRASTRUCTURE AND SETTING

Zabok General Hospital and Croatian Veterans' Hospital is, as of 2020, the youngest hospital in Croatia. Built in 2009, it covers an area of over 23,000 square meters. It lies near the Croatian-Slovenian border, which will become an essential factor in dealing with the coronavirus epidemic in Croatia, and it is the only hospital in Krapina-Zagorje County, which has a population of over 130,000 spread across 7 towns and 25 districts. The hospital has 12 departments, 222 beds, including surgical, neurological, pediatric, obstetric and gynecologic, and internal medicine wards and covers the majority of healthcare-related needs of the County catchment population.

Following the rise of patients presenting themselves with the symptoms of coronavirus infection, the facility underwent a set of organizational changes. In order to accommodate patients potentially infected with the coronavirus, part of the Hospital had to be 'transformed'. Initial planning for reorganization and repurposing of the Emergency Department began in February 2020. The only available option at the time was part of the Emergency Department, which has a separate entrance, colloquially dubbed 'the Isolation Ward'. The Isolation Ward was initially sealed off from the rest of the hospital on February 12, 2020, when the first patient suspected of COVID-19 infection was admitted. The area initially contained 4 separate patient rooms, each covering about 20 square meters. The area has a separate entrance and exit for patients and medical personnel attending them, not to come in contact with other patients and healthcare workers and potentially infect them. Following the steep increase in the number of cases, 4 more rooms were included in the emergency room quarantine.

As the Isolation Ward was initially planned only for isolation of the suspected of COVID-19 until arrival of their swab analysis, the ward was outfitted with only a limited amount of medications and equipment, taking into account the fact that the patients presenting in the early days of the pandemic in Croatia all had only mild symptoms of the COVID-19 infection. As the number of potentially infected individuals grew, the Ward, with its initial capacity and resources, could not cope with the ever-increasing patient numbers, so additional measures had to be taken. Following suspension of all non-essential medical procedures and outpatient clinics, the Department of Physical Medicine and Rehabilitation was repurposed for treating patients with severe COVID-19 (a COVID ward). After removing all unnecessary furniture and equipment, the area was thoroughly disinfected and outfitted. Eighteen bed units were set up, with the necessary equipment for ventilation and invasive monitoring. The Department

of Physical Medicine is the sole department located in the hospital subterranean level and also has its own separate entrance, factors which greatly help organize healthcare and attendance of such patients. A 24-hour video surveillance was also introduced to all isolation units, and a healthcare worker was continually attending to the video material. The follow-up measurement of vital parameters was conducted at least twice daily. Additionally, on March 30, 2020, 2 pediatric isolation units were established and furnished adequately to meet the needs of this particular age group within the pediatric ward. Until then, children were examined in the Isolation Ward.

As a way of proving that an individual is infected with coronavirus is by analysis of the naso- and oropharyngeal swabs, it was necessary to organize swabbing of those potentially infected in such a way that the risk of infection for healthcare workers and other patients was reduced to minimum. For this purpose, a specially modified container was set up in the proximity of the hospital. Those potentially infected would have their swabs taken and their vital parameters inspected. With the increase in the number of swabs taken daily, a 'drive-in' swab station was also organized. Those with suspicion of coronavirus infection would have their vital parameters and swabs taken while sitting in their vehicles, after which, if their parameters were within the reference values, they would drive home. The drive-in station helped immensely in speeding up the process while simultaneously upholding safety regulations regarding contact between patients and healthcare workers.

Because of the potential risk of having to operate on a patient infected with SARS-CoV 2, a surgical theater was prepared and outfitted with all necessary surgical and protective equipment. Gynecologic operations and childbirths were also to be conducted in this theater if the need had arisen.

HUMAN RESOURCES

On February 12, the first patient in the Zabok County Hospital and Croatia was isolated because of the suspected coronavirus infection. Until the end of March 2020, all patients suspected of SARS-CoV 2 infection were attended by a consultant infectologist and the Emergency Department head nurse. Afterwards, Emergency Department nurses and junior doctors were performing swab sampling in non-hospitalized patients suspected of COVID-19. They conducted swabbing of patients and attended mostly to the ones hospitalized, as those patients presented with mostly mild symptoms or were asymptomatic and isolated because of epidemiological reasons. They also maintained and managed all documentation regarding the patients (history of illness, reporting forms for national and local epidemiology departments).

With the number of patients, the severity and diversity of clinical presentations increased, and the need for more organized work structure became apparent. As the Krapina-Zagorje County was one of the 'hot spots' of coronavirus disease in Croatia (alongside the City of Zagreb and Split-Dalmatia County), a solid and steadfast solution was needed. On March 25, 2020, a 'corona team' workforce was organized and established. The workforce was made up of various specialists (infectology, internal medicine, neurology, anesthesiology), as well as residents or junior doctors and nurses. Teams worked in 14-day shifts followed by 14 days of self-isolation. Before returning to work, all members of the corona team were tested for SARS-CoV 2 to minimize any chance for intrahospital transmission of the virus. The physicians and nurses attended and monitored patients, and managed other respective comorbidities such as arterial hypertension, diabetes, and chronic obstructive pulmonary disease. Because of the shift in workload, nurses from outpatient clinics, as well as other departments such as surgery and internal medicine, were redeployed to the corona team. Physicians and nurses not assigned to the corona workgroup continued working in their designated departments, although in reduced numbers as they only covered emergency patients.

FLOWCHART OF HEALTHCARE ORGANIZATION IN SUSPECTED OR 'CORONA-POSITIVE' PATIENTS

The bulk of the work and management regarding coronavirus was handled in and around the Zabok County Hospital Emergency Department with daily communication and support of the local public health and epidemiological services of the Krapina-Zagorje County. Healthcare workers working in family medicine practices in the County were outsourced to the Hospital to fill the evident lack of personnel.

The Croatian Institute of Public Health (CIPH) established guidelines for patient triage regarding SARS-CoV 2 infection. Guidelines have been updated several times due to rapid changes in epidemiological dynamics regarding the spread of the virus. Case definition was established, and the daily number of suspected and confirmed cases was documented, which were later forwarded to relevant institutions (local public health service, Civil Protection Directorate of the country, and County likewise). At the beginning of the epidemic, both epidemiological and clinical criteria had to be met for an individual to be suspected

of SARS-CoV 2 infection (3). As of March 13, 2020, epidemiological criteria ceased to be included in the guidelines as the local transmission of the virus in Croatia had been confirmed (Fig. 1.A-B (4).

A	B
CLINICAL CRITERIA 1) a patient with acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, sore throat, shortness of breath) **AND** **EPIDEMIOLOGICAL CRITERIA** 2) a patient with any acute respiratory illness AND having been in close contact with a confirmed OR probable COVID-19 case in the last 14 days prior to onset of symptoms **OR** 3) a patient with a history of travel or residence in a country/area reporting local or community transmission* during the 14 days prior to symptom onset (China, South Chorea, Italy Venetto and Lombardia regions) * according to WHO classification, see respective daily updated Coronavirus disease (COVID-2019) situation reports at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/	1) a patient with acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath) AND with no other aetiology that fully explains the clinical presentation AND with a history of travel or residence in a country/area reporting local or community transmission* during the 14 days prior to symptom onset; **OR** 2) a patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, fever, shortness breath) AND requiring hospitalisation (SARI) AND with no other aetiology that fully explains the clinical presentation.

Fig. 1. *Criteria for recognizing an individual potentially infected with SARS-CoV 2; initial (A) and modified (B)*

Those who were suspicious of coronavirus infection were instructed first to contact one of the three epidemiological stations in the County by telephone upon which they would describe their case. Upon verification of suspicion, the potentially infected were instructed to contact the Emergency Department of the Hospital. The individual would then get reassessed based on a questionnaire that would be filled out by a nurse or junior doctor. The questionnaire contained detailed questions about occupation, lifestyle, recent travels, symptoms, and epidemiological parameters. After filling out the questionnaire, the individual was invited for swabbing at a specific time, in most cases, the day after initially contacting the Hospital. Also, those with suspicion were instructed not to leave their homes. As the pandemic progressed and the number of those suspicious of infection grew, the potentially infected were instead instructed to initially contact their attending general practitioner who would reassess their symptoms and, based on the outcome, indicate if swab analysis of the particular individual is needed.

Upon arrival for their scheduled swabbing, individuals would have their vital parameters (body temperature, blood pressure, heart rate, respiration frequency, and oxygen saturation) checked, as well as their naso- and oropharyngeal swabs taken (blood serum samples were taken at first alongside swabs, but the practice was discontinued as of the end of March). If the vital parameters were within the normal range, the patient had no significant comorbidities, and if the clinical presentation was mild, people were instructed to head to their homes after leaving their contact information directly; the result of the swab analysis would be conveyed to them *via* telephone. If the test came back positive, the individual was placed in self-isolation for 14 days, upon which they would have their swabs retaken. If the follow-up swab came back negative and the individual reported no symptoms, they were declared cured. This was the case until March 23, 2020; after this point, only healthcare workers and symptomatic individuals would be retested after the 14-day isolation; asymptomatic individuals would be declared cured. The CIPH defined this workflow.

Those patients presenting for swab diagnostics with pathological values of vital parameters or who had severe clinical presentation indicative of acute respiratory failure would be immediately hospitalized and isolated upon swabbing into the Isolation or COVID ward, depending on the severity of their presentation. The patients were constantly attended by at least two nurses and two physicians regarding their current but also concomitant medical conditions if they had any.

The ones whose swab analysis came back negative but still required medical treatment were taken out of the Isolation Ward and transferred to the pulmonary department of the Hospital for further treatment. The area they occupied while in the Isolation Ward would then be thoroughly cleaned and disinfected to allow for the potential new patients to be introduced.

Patients presenting with symptoms of acute respiratory failure and need for mechanical ventilation were directly admitted to our Isolation Ward, where they would be stabilized and connected to an artificial ventilation unit if there was an indication to do so. Upon stabilization of the patient, they would be transferred to the Respiratory Centre of Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb.

As stated before, the proximity to the Slovenian border was a contributing factor in the management of the coronavirus epidemic in Croatia. Most travelers

entering Croatia *via* Slovenia do so at the Macelj border crossing, which is the biggest one between the two countries, with the nearest hospital being the one in Zabok. In the early days of the pandemic, individuals returning from areas deemed high-risk of coronavirus infection were placed in self-isolation for 14 days; SARS-CoV 2 swabs would be taken at the beginning, as well as the end of the isolation period. When the local transmission of the virus was confirmed, this practice was discontinued with only the clinical criteria defining the need for isolation (5) 30 January 2020, World Health Organization declared Coronavirus disease-2019 (COVID-2019).

The residents of various nursing homes were another issue. The County has at least 17 private or state-run nursing homes that are home to more than 1500 people, each according to their capacity. As the residents of such institutions are, in most cases, elderly and have their own underlying comorbidities, they became an ideal spreading point for coronavirus. The fact that residents spend most of their time indoors with little to no social distancing only made the situation more complicated. As seen in countries such as Spain, this issue was widespread on a global scale (6).

DISCHARGING A CORONA-PATIENT

While the CIPH clearly defined criteria by which an individual is to be hospitalized if suspected of SARS-CoV 2 infection, the discharge criteria of the same patients upon curing them were not clearly established, at least in the first days of the pandemic. The Hospital established a practice of swabbing patients until their results came back negative. Afterwards, the CIPH defined the criteria as follows: cessation of clinical presentation of infection for at least 3 days together with 2 negative swab analyses in the last 72 hours.

Looking at the first like solid criteria, asymptomatic patients with positive swab tests began to emerge. Additionally, patients with prolonged (more than 30 days) symptoms whose swab tests were negative were also a clinical and logistic problem. After a period of ever-changing directives and recommendation, the CIPH finally established non-test based discharge criteria for these patients on April 2, 2020, as follows: patients were deemed 'corona-free' 28 days after the first clinical presentation for those with negative swab tests and 28 days after the first positive swab analysis for asymptomatic patients. An exception was made for healthcare workers and individuals who were infected, but their symptoms ceased within 28 days of the first presentation; 2 negative swab tests within a minimum period of 24 hours would deem them corona free. An asymptomatic patient could have his swabs taken at least 72 hours after withdrawal of symptoms, 7 days after first presenting with symptoms or 7 days after a first positive swab analysis result.

'CORONA-FREE' HEALTHCARE

While the organization of healthcare for coronavirus patients did take the world by storm, the world itself did not stop, and as such, patients came to the Hospital because of corona-unrelated reasons. Being the only general hospital in the County, Zabok Hospital could not cease to treat patients, although certain changes and regulations had to be implemented.

All non-essential diagnostic and curative procedures were postponed indefinitely. Patient visits were prohibited in all wards except for the pediatric ward. All medical personnel and patients had their body temperature measured upon entering and exiting the facility. In addition, a questionnaire regarding clinical and epidemiological parameters had to be filled out at the time. All personnel were required to wear surgical masks during working hours, with a new mask being used after every 3 hours of wearing one. Patients coming to the Emergency Department would be triaged with a quick questionnaire regarding symptoms, recent travels, and contacts with the potentially infected; their body temperature would be measured to define if they could be potentially infected with SARS-CoV 2. If the patient was afebrile and had no symptoms indicative of coronavirus, they would be declared 'corona non-suspected'. They would be allowed to enter the emergency department with a surgical mask as well, where they would receive appropriate medical care and treatment regarding their initial reason for arrival.

The ones who had symptoms, epidemiological evidence (before March 13, 2020) and/or elevated body temperature would be triaged according to the severity of their symptoms. Their underlying reason for coming to the emergency room would be reassessed. If they were vitally endangered, immediate diagnostics and treatment of the patient would start with them being treated as infected with coronavirus. Those whose condition allowed them to wait until the results of the swab analysis came would be isolated, the course of their treatment being based and planned upon swab results.

SPECIMEN TRANSPORT

The analysis of swab specimens, i.e. naso- and oropharyngeal swabs, as well as blood serum (only during the first 30 days of the pandemic) was performed by

real-time polymerase chain reaction (RT-PCR). Since our Hospital does not have its own RT-PCR device, all samples were transported to Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb and Varaždin County General Hospital. Both of these institutions have the necessary devices, as well as engineers who could operate them in order to analyze the specimens, and it only takes 30 minutes by automobile to reach them. The Hospital deployed a paramedic vehicle and its designated driver in order to transport the specimens for analysis regularly. The transport would be organized at least twice daily. Swab samples were transported inside iced boxes within zip-lock bags alongside all the needed documentation.

COMPARING APPROACHES

A major stepping stone that the Zabok General Hospital faced, together with other healthcare institutions in Croatia and worldwide, was the unprecedented character of the situation. In the light of the lack of knowledge about the pathogen, as well as low amounts of scientific evidence, guidelines were often made up 'on-the-go' and were often subjected to change. The overwhelming mass media interest in the pandemic, although praiseworthy, produced, at times, contradictory content and statements regarding the situation, which in turn affected the general public (7,8). In a way, the global availability of information in today's age helped healthcare institutions and workers organize themselves because it indirectly connected all of them; through interviews, news articles, and social media posts (9). Although the data are still scarce, comparing approaches of different institutions leads to a conclusion that our approach to the COVID-19 pandemic did not differ significantly from the strategies of bigger and more specialized institutions, although on a smaller scale, of course (10,11). While several institutions suffered under a shortage of personnel and equipment, the same could not be said for this case; throughout the pandemic, a lack of resources or manpower has never been reported. All of the activities were carefully documented for both on-site and future referencing (Table 1 A-B).

Table 1A.
Overview of data on COVID-19 pandemic collected at Zabok General Hospital

First patient suspected of SARS-CoV 2 infection	February 12, 2020
First patient with confirmed infection with SARS-CoV 2	March 15, 2020
Total number of the tested for SARS-CoV 2 (as of May 21, 2020)	2638
Total number of confirmed cases of SARS-CoV 2 infections	134+8 cases of patients not from the County
Total number of patients hospitalized with SARS-CoV 2 infection	25; 5 transferred to Dr. Fran Mihaljević University Hospital for Infectious Diseases
Total number of patients who passed away while hospitalized with SARS-CoV 2 infection	2
Total number of individuals under age 18 tested (as of May 21, 2020)	130
Total number of confirmed cases of SARS-CoV 2 in those tested under age 18	10
Total number of patients hospitalized under age 18 with SARS-CoV 2 infection	0
Mean age of individuals infected with SARS-CoV 2 tested in Zabok General Hospital	49.9

Table 1B.
Overview of SARS-CoV 2 tested versus infected individuals on a monthly basis

	February 2020	March 2020	April 2020	May 2020
Number of individuals tested	3	246	1132	1117
Number of positive results	0	69	88	6

CONCLUSION

The COVID-19 pandemic has introduced tectonic changes in today's society but simultaneously provided a setting from which new experience and knowledge could and have been drawn. In order to fight the virus, novel medical protocols have been tested and established. Consultants from different medical fields and nurses from various wards were included in the treatment and management of those infected with SARS-CoV 2, erasing the barriers between those fields and establishing a truly multidisciplinary team that was critical for the appropriate care of patients. Junior doctors of the Zabok General Hospital, most of whom had only recently graduated, improved their skills and knowledge exponentially in a 'baptism by fire' scenario. The National Civil Protection Directorate complimented the Hospital on more than one occasion for their efforts and results.

The ever-changing dynamics of the pandemic, combined with regulations and restrictions imposed by the National Directorate, meant that the system had to be flexible and susceptible to changes on a daily basis.

Hospitals and other healthcare institutions were mostly left to fend for themselves in this newfound situation, trying to provide the best healthcare with the personnel and resources they had at their disposal (12) Piedmont, Veneto, Friuli, Trentino, Emilia Romagna Regions.

With the world seemingly starting to recover from the pandemic and the restrictions imposed by various governments starting to loosen, a number of questions remain: will the coronavirus pandemic become a seasonal occurrence, or is this the last we have seen from it? Will the vaccines that are currently being developed prove effective, and if yes, when will it become available? Will the world be forced to adapt to the presence of the virus and, with facemasks on and increased sanitary regulations at all times? May more questions arise, with the answers still somewhat hidden and unclear. With adaptability and perseverance, the current situation has been brought under control. If hoping to be up to the task in the near and far future, sharing discoveries and achievements, failures, and mistakes, is the way by which new labors could and can be bested, with healthcare taking the helm. High-quality fundamentals have already been set if the need arises.

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SAŽETAK

STJERANI DO ZIDA: ORGANIZACIJA ZDRAVSTVENE SKRBI TIJEKOM PANDEMIJE KORONAVIRUSA 2020. – MODEL OPĆE BOLNICE ZABOK I BOLNICE HRVATSKIH VETERANA

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Pandemija koronavirusa, počevši krajem 2019., prožela je gotovo sve aspekte modernog društva. Pravila i zakoni uvedeni od vladajućih struktura i organizacija širom svijeta uveli su iznimne promjene u svakodnevicu. Sa širenjem pandemije i porastom broja zaraženih pojavila se i potreba za odgovarajućom zdravstvenom skrbi oboljelih. Nesigurnosti i nepoznanice vezane za virus pretvorile su rad s bolesnicima u svakodnevnu bitku. Prikazani podatci prikupljeni su u razdoblju od 12. veljače do 15. svibnja 2020. U navedenom razdoblju 2638 pojedinaca je bilo testirano na infekciju SARS-CoV 2 od kojih je 140 imalo pozitivan nalaz, 25 ih je zahtijevalo bolničko liječenje te su dvije osobe preminule. Testirano je i 130 pojedinaca mlađih od 18 godina od kojih je 10 bilo pozitivno na infekciju SARS-CoV 2, a nijedna osoba nije hospitalizirana. Cilj naše publikacije je prikazati i podijeliti iskustva koja smo stekli tijekom pandemije virusa tijekom 2020. u Općoj bolnici Zabok i Bolnici hrvatskih veterana u Krapinsko-zagorskoj županiji koja je bila jedna od većih žarišta pandemije u Republici Hrvatskoj.

Ključne riječi: **COVID-19, koronavirus, organizacija zdravstva, organizacija bolnica, pandemija**

LIJEČENJE MULTIPLE SKLEROZE LIJEKOM OKRELIZUMAB – RETROSPEKTIVNA 1,5-GODIŠNJA ANALIZA U KLINICI ZA NEUROLOGIJU KLINIČKOG BOLNIČKOG CENTRA SESTRE MILOSRDNICE U ZAGREBU

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U odnosu na važnost T limfocita u patogenezi multiple skleroze (MS) sve se više otkriva i značenje B limfocita u samoj patogenezi bolesti. Okrelizumab (Ocrevus®, Roche, Njemačka) je monoklonsko protutijelo koje ciljano djeluje na B stanice koje sadrže CD20 antigen. Brojna ispitivanja pokazala su djelotvornost okrelizumaba u liječenju relapsno remitentne multiple skleroze (RRMS) i primarno progresivne multiple skleroze (PPMS). Ranija klinička ispitivanja su pokazala da primjena okrelizumaba suprimira relapse, progresiju bolesti te supkliničku aktivnost bolesti utvrđenu magnetskom rezonancom (MR). Na Klinici za neurologiju Kliničkog bolničkog centra Sestre milosrdnice retrospektivno smo analizirali bolesnike kod kojih je bilo indicirano liječenje okrelizumabom. Ukupno je lijek primijenjen kod 36 bolesnika s RRMS-om i 13 bolesnika s PPMS-om. Cilj je bio prikazati populaciju bolesnika kod kojih je primijenjen lijek, njihove nuspojave te klinički ishod nakon primjene lijeka uz usporedbu navedenih podataka s dosadašnjim saznanjima o lijeku. Našom analizom u skupini s RRMS-om kod 47 % bolesnika primijenjen je drugi ciklus liječenja, a kod 8 % bolesnika i treći ciklus liječenja. Od navedenih bolesnika 94 % nije pokazalo kliničku progresiju bolesti. Što se nuspojava tiče u skupini bolesnika s RRMS-om 11 % je imalo nuspojave, a u skupini bolesnika s PPMS-om 23 % . Najčešće nuspojave bile su reakcija na infuziju i smanjenje broja limfocita (za sada još uvijek na granici s donjom graničnom vrijednosti). Analizom naših bolesnika potvrđeni su prethodni zaključci kliničkih ispitivanja. Lijek se pokazao sigurnim za primjenu uz malu učestalost nuspojava. Ipak, potreban je veći broj bolesnika za daljnju analizu što planiramo učiniti u budućim analizama.

Ključne riječi: multipla skleroza, okrelizumab, liječenje, iskustva

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UVOD

Iako se dugo u nastanku multiple skleroze isticala uloga T limfocita vremenom je utvrđeno da B limfociti imaju važnu ulogu u patogenezi multiple skleroze pridonoseći različitim mehanizmima nastanku demijelinizacije i neurodegeneracije (1). Okrelizumab (Ocrevus®, Roche, Njemačka) je lijek indiciran za liječenje bolesnika s relapsno remitentnom multiplom sklerozom (RRMS) koji imaju aktivnu bolest definiranu kliničkim značajkama ili značajkama vidljivima slikovnim pretragama. Također, lijek je indiciran i u liječenju bolesnika s primarno progresivnom multiplom sklerozom (PPMS) u smislu trajanja bolesti i razine onesposobljenosti te sa značajkama karakterističnima za upalnu aktivnost vidljivu slikovnim pretragama. Okrelizumab je monoklonsko protutijelo koje ciljano djeluje na B stanice koje izražavaju CD20

antigen. Točan mehanizam djelovanja lijeka nije u potpunosti razjašnjen, ali se pretpostavlja da lijek djeluje putem imunomodulacijskog odgovora na način da dovodi do smanjenja broja i funkcije B stanica koje izražavaju CD20 antigen.

Djelotvornost i sigurnost lijeka ocijenjivale su se u dvama randomiziranim, dvostruko slijepim, dvostruko maskiranim kliničkim ispitivanjima (ispitivanje OPERA I i OPERA II) kontroliranima aktivnim usporednim lijekom (interferon beta-1a). Rezultati ovih ispitivanja pokazali su da je okrelizumab značajno smanjio relapse, supkliničku aktivnost bolesti utvrđenu magnetskom rezonancom (MR) te je smanjio progresiju bolesti u odnosu na skupinu bolesnika koja je liječena interferonom beta-1a (1,2). Djelotvornost i sigurnost lijeka okrelizumab ocjenjivale su se i u randomiziranom, dvostruko slijepom, placebom kontroliranom kliničkom ispitivanju u bolesnika s primarno progresivnom multiplom sklerozom (ispitivanje ORATORIO). Rezultati ovog ispitivanja pokazuju da lijek značajno odgađa progresiju bolesti i smanjuje progresiju bolesti verificiranu klinički i slikovnom metodom MR-a (2,3). Od nuspojava u kliničkim ispitivanjima najčešće su opisivane reakcije na infuziju. Također se često mogu pojaviti reakcije na infuziju zbog čega je važno primijeniti premedikaciju.

Lijek okrelizumab odobren je početkom 2018. g. od Europske komisije za lijekove, a iste je godine započeta i njegova primjena u Republici Hrvatskoj. Nedugo za tim je i Hrvatsko neurološko društvo donijelo smjernice za liječenje multiple skleoroze koje uključuju i okrelizumab (tablica 1) (4).

Tablica 1.
Kriteriji za početak imunomodulacijske terapije druge linije kod bolesnika s RRMS prema smjernicama Hrvatskog neurološkog društva.

Indikacije za početak liječenja drugom linijom terapije (natalizumabom /fingolimodom / alemtuzumabom / kladribinom / okrelizumabom) bolesnika s relapsno-remitirajućom multiplom sklerozom:
1. Bolesnici kod kojih je bolest aktivna unatoč prvoj liniji terapije: a. ≥4 nove T2 lezije na MR-u nakon početka liječenja lijekovima prve linije ili b. ≥2 relapsa nakon početka liječenja lijekovima prve linije 2. EDSS ≤ 7,0 3. Odsutnost trudnoće 4. Odobrenje bolničkog povjerenstva za lijekove
Jedan lijek druge linije terapije u drugi lijek druge linije terapije (natalizumab / fingolimod / alemtuzumab / kladribin / okrelizumab) u bolesnika s relapsno-remitirajućom multiplom sklerozom može se promijeniti na indikaciju nadležnog neurologa, a u slučaju:
1. ≥1 relapsa nakon početka liječenja lijekovima druge linije 2. Nepodnošljivih nuspojava liječenja 3. U bolesnika liječenih natalizumabom u slučaju visokog titra anti JCV protutijela te povišenog rizika razvoja progresivne multifokalne leukoencefalopatije (PML)

(Preuzeto i modificirano prema: Smjernice Hrvatskog neurološkog društva za liječenje multiple skleroze. Dostupno na: https://neuro-hr.org/Content/Documents/Kriteriji-za-lijecenje-RRMS-a-2018-002.pdf).

CILJ RADA

Cilj ovog rada je retrospektivno (unatrag 1,5 godinu) prikazati populaciju bolesnika s RRMS-om i PPMS-om Klinike za neurologiju Kliničkog bolničkog centra Sestre milosrdnice kod kojih je odlučeno provesti liječenje okrelizumabom. Također, cilj je bio prikazati klinički ishod nakon primjene lijeka, moguće nuspojave i reakcije na lijek te usporediti navedene podatke s dosadašnjim saznanjima o lijeku iz prethodnh kliničkih ispitivanja.

METODE

Na Klinici za neurologiju Kliničkog bolničkog centra Sestre milosrdnice okrelizumab je prvi put primijenjen u rujnu 2018. godine. Obrada prije primjena lijeka uključivala je laboratorijske pretrage: kompletna krvna slika (KKS), diferencijalna krvna slike (DKS), enzimi jetrene funkcije, biljezi hepatitisa B i C, sediment urina, Quantiferonski test, test na John Cunningham virus (JCV), test na Varicella zoster virus (VZV). Slikovna obrada uključivala je MR mozga i vratne kralježnice. Nakon provedene obrade i mogućnosti primjene lijek je primijenjen prema pravilu sheme primjene okrelizumaba uz prethodnu premedikaciju. Za premedikaciju su korišteni: metilprednizolon 100 mg (intravenski, približno 30 minuta prije svake infuzije lijeka), antihistaminik (približno 30-60 minuta prije svake infuzije lijeka), antipiretik (paracetamol, približno 30-60 minuta prije svake infuzije lijeka). Početna doza od 600 mg primijenjena je u dvije zasebne intravenske infuzije. Najprije je primijenjena jedna infuzija od 300 mg, a dva tjedna kasnije druga infuzija od 300 mg. Nakon toga lijek se primjenjivao u obliku jedne intravenske infuzije od 600 mg svakih 6 mjeseci. Pokazatelji koje smo pratili kod bolesnika s RRMS-om su: dob, spol, vrijeme od početka simptoma, prethodna primjena imunomodulatorne terapije, trajanje prethodne primjene imunomodulatorne terapije, razina invalidnosti mjerena ljestvicom EDSS (*Extended disability status scale*) na početku liječenja, broj relapsa u prethodnoj godini, broj gadolinije imbibirajućih lezija u prethodnoj godini, broj novih i/ili progresija postojećih lezija. Također praćen je klinički ishod nakon početne primjene lijeka (pogoršanje ili stacionarno stanje/poboljšanje), reakcije na infuziju, početan broj limfocita prije liječenja, prosječan broj CD19+ limfocita prije liječenja, prosječan broj limfocita i CD19+ limfocita nakon svake infuzije.

Pokazatelji koje smo pratili kod bolesnika s PPMS-om su: dob, spol, vrijeme od početka simptoma, prethodna primjena imunomodulatorne terapije, trajanje prethodne primjene imunomodulatorne terapije, EDSS na po-

četku liječenja, broj relapsa u prethodnoj godini dana, broj gadolinij imbibirajućih lezija u prethodnoj godini, broj novih i/ili progresija postojećih lezija, klinički ishod nakon prvog ciklusa, nuspojave, reakcije na infuziju te broj limfocita i CD19+ limfocita prije liječenja.

REZULTATI

Od rujna 2018. godine kraja ožujka 2020. lijek je primijenjen kod 36 bolesnika s RRMS-om i 13 bolesnika s PPMS-om. Kod bolesnika s RRMS-om srednja dob bila je 40 godina. Od toga je bilo 52 % žena. Prosječno vrijeme od početka simptoma bilo je 7,94 godina. Prethodno je imunomodulatorna terapija primijenjena kod 80 % bolesnika, a prosjek trajanja prethodne primjene imunomodulatorne terapije bio je 28,15 mjeseci. Prosječan EDSS na početku liječenja bio je 3,6. Prosječan broj relapsa u prethodnoj godini dana bio je 1,9. Kod 44 % bolesnika bile su prisutne gadolinijem imbibirajuće lezije, a prosječan broj novih lezija ili progresije postojećih lezija na prethodnoj MR snimci bio je 3,22 lezije. Nakon primjene prvog ciklusa kod 94 % bolesnika stanje je bilo stacionarno ili poboljšano. Kod 47% bolesnika primijenjen je drugi ciklus liječenja, a kod 8 % i treći ciklus liječenja (tablica 2).

Od nuspojava najčešće su bile prisutne reakcije na infuziju (11 %) u obliku glavobolje i svrbeža te sniženje broja limfocita u odnosu na početnu vrijednost uz očekivanu sniženu vrijednost CD19+ limfocita (tablica 3).

Tablica 2.

Pokazatelji praćeni kod bolesnika s relapsno remitentnom multiplom sklerozom kod kojih je primijenjen okrelizumab

Indikacije za početak liječenja bolesnika s brzo napredujućom multiplom sklerozom (natalizumabom / fingolimodom / alemtuzumabom / kladribinom / okrelizumabom)

1. Bolesnici s teškom brzo napredujućom relapsno-remitirajućom multiplom sklerozom definiranom s 2 ili više onesposobljavajućih relapsa (motorički relaps, ataksija, moždano deblo) u trajanju manje od jedne godine neovisno o trajanju bolesti i prethodnoj terapiji
2. EDSS ≤ 7,0
3. Odsutnost trudnoće
4. Odobrenje bolničkog povjerenstva za lijekove

Indikacije za početak liječenja bolesnika s primarno progresivnom multiplom sklerozom okrelizumabom

1. Zadovoljeni revidirani McDonaldovi dijagnostički kriteriji iz 2017. za PPMS*
2. EDSS < 7,0
3. Odsutnost trudnoće
4. Odobrenje bolničkog povjerenstva za lijekove

**Kriteriji uključuju zadovoljen kriterij od 1 godine progresije onesposobljenosti (retrospektivno ili prospektivno) neovisno o kliničkim relapsima te zadovoljena dva od sljedećih triju kriterija: jedna ili dvije T2 hiperintenzivne lezije u karakterističnim mjestima za multiplu sklerozu (periventrikularno, kortikalno, jukstakortikalno ili infratentorijski), dvije ili više T2 hiperintenzivnih lezija u leđnoj moždini, prisutnost specifičnih oligoklonalnih vrpci u likvoru (5).*

⌈Rezultati su izraženi brojem (n), postotcima (%) i/ili standardnom devijacijom (±)⌋.

Tablica 3.

Nuspojave bolesnikas relapsno-remitentnom multiplom sklerozom liječenih okrelizumabom.

Nuspojave Reakcija na infuziju (n, %)	4/36 (11)
• Glavobolja	3 (8)
• Svrbež	1 (2)
• PRES (n, %)	1 (2)
• Prosječan broj limfocita prije primjene prvog ciklusa (10^9/L)	1,6 (±0,6)
• Prosječan broj CD19 limfocita prije primjene prvog ciklusa	8,3 (±3,9)
• Prosječan broj limfocita prije primjene drugog ciklusa (10^9/L) • Prosječan broj CD19 limfocita prije primjene drugog ciklusa	1,3 (±0,4) < 1

⌈Rezultati su izraženi izraženi brojem (n), postotcima (%) i standardnom devijacijom (±)⌋.

Kod bolesnika sa PPMS-om srednja dob bila je 52,15 godine. Ukupno je okrelizumabom liječeno 76 % žena. Prosječno vrijeme od pojave simptoma bolesti bilo je 10,92 godine. Prethodno je imunomodulatorna terapija primijenjena kod 38 % bolesnika, a prosječno vrijeme trajanja primjene imunomodulatorne terapije bilo je 24,9 mjeseci. Prosječan postotak bolesnika s gadolinijem imbibirajućim lezijama bio je 30 %, dok je prosječan broj gadolinijem imibibirajućih lezija bio 1,15, a broj novih lezija/progresije ranijih lezija 4,23. Kod jednog bolesnika primijenjen je drugi ciklus liječenja, a klinički ishod je bilo stacionarno stanje bolesti (tablica 4). Prosječan broj nuspojava bio je 23 %, od čega je najviše bilo reakcija na infuziju u obliku glavobolje i vrtoglavice (tablica 5).

Tablica 4.

Pokazatelji praćeni kod bolesnika s primarno progresivnom multiplom sklerozom

Pokazatelj	**Bolesnici s PPMS, n = 13**
Dob	52,15 (±11,9)
Spol (n, %) • Muškarci	10 (76) 3 (23)
Vrijeme od početka simptoma (godine)	10,92 (±8,63)
Prethodna imunomodulacijska terapija (n, %) • Interferon • Dimetil fumarat • Alemtuzumab	8/13 (61) 3/13 (23) 1/13 (7) 1/13 (7)
Prosjek trajanja prethodne imunomodulacijske terapije (mjeseci)	24,9 (±24,08)
Broj bolesnika bez prethodne imunomodulacijske terapije (n, %)	8/13 (61)
Prosječan EDSS	5,7 (±0,4)
Prosječan broj relapsa u prethodnoj godini	1,46 (±0,5)
Prosječan broj bolesnika s gadolinij inbirajućim lezijama u prethodnoj godini (n, %)	4/13 (30)
Prosječan broj gadolinij pozitivnih lezija u prethodnoj godini (n, %)	1,15 (±2,03)
Prosječan broj novih lezija/progresija ranijih lezija	4,23 (3,56)
Ishod nakon prvog ciklusa: kliničko poboljšanje/stacionano stanje (n, %)	1,13 (7)
Ishod nakon prvog ciklusa: kliničko pogoršanje	0
Broj bolesnika kojima je primijenjen drugi ciklus (n, %)	1/13 (7)

⌈Rezultati su su izraženi izraženi brojem (n), postotcima (%) i standardnom devijacijom (±)⌋

Tablica 5.
Nuspojave bolesnika s primarno progresivnom multiplom sklerozom liječenih okrelizumabom

Nuspojave (n, %)	
Reakcija na infuziju • glavobolja • vrtoglavica	3/13 (23) 2/13 (15) 1 (7)
Prosječan broj limfocita prije primjene prvog ciklusa (10^9/L)	2,1 (±1,6)
• Prosječan broj CD19+ limfocita prije primjene prvog ciklusa	11 (±6,1)

⌈Rezultati su su izraženi izraženi brojem (n), postotcima (%) i standardnom devijacijom (±)⌋

RASPRAVA

Što se tiče raspodjele po spolu u obje skupine veći broj bolesnika su žene što je u skladu s činjenicom da od multiple skleroze češće obolijevaju žene. Također, navedeno je prisutno i u kliničkim ispitivanjima (OPERA I i OPERA II). Što se tiče skupine bolesnika s PPMS-om naši rezultati u odnosu na ispitivanje ORATORIO se ponešto razlikuju. U našoj skupini bolesnika s PPMS-om bilo je 76 % žena, dok je u ispitivanju ORATORIO bilo 48,6 % žena. Navedeno možemo pripisati, za sada, malom uzorku naših bolesnika s PPMS-om. Kod bolesnika s RRMS-om u našoj skupini bolesnika prosječno vrijeme od početka simptoma bilo je 7,94 godine. U ranije navedenim ispitivanjima navedeni broj godina bio je 6,74 godine u ispitivanju OPERA I te 6,72 u OPERA II. Također, kod bolesnika s PPMS-om prosječan broj godina bio je 10,9 godina dok je u ispitivanju ORATORIO bio 6 godina. Iz navedenog je vidljivo da je u obje skupine naših bolesnika prošlo dulje vrijeme od pojave simptoma do primjene lijeka okrelizumab. Važno je istaknuti da je jedan dio bolesnika, posebno iz skupine s PPMS-om, određeni broj godina nije bio na kontrolama neurologa, a također do primjene okrelizumaba nije bilo specifičnog lijeka za liječenje PPMS-a. Što se tiče primjene prethodne imunomodulatorne terapije u našoj skupini bolesnika s RRMS-om, 80 % bolesnika liječeno je prethodno imunomodulatornom terapijom, a od toga je najčešće terapija prvog izbora bila terapija interferonom (47 %). Važno je istaknuti da su kod četiri bolesnika prethodno primijenjena dva lijeka prve linije, a kod jednog bolesnika došlo je do promjene lijeka s prve linije (glatiramer acetat) na drugu liniju (fingolimod) te je zbog daljnje progresije bolesti odlučeno primijeniti okrelizumab. Prethodno je imunomodulatornom terapijom liječeno 26,2 % bolesnika u ispitivanju OPERA I te 27,1 % u ispitivanju OPERA II. U ispitivanju ORATORIO 88 % bolesnika prethodno nije bilo liječeno imunomodulatornom terapijom, dok je u našoj skupini bolesnika 38 % prethodno bilo liječeno imunomodulatornom terapijom. Također, u ispitivanju OPERA I I OPERA II kategorija prethodne imunomodulatorne terapije uključivala je imunomodulatornu terapiju unatrag dvije godine, a u našem slučaju je primjena imunomodulatorne terapije analizirana od početka liječenja bolesti. U usporedbi s našom skupinom bolesnika rezultati bolesnika s RRMS-om su zadovoljavajući, ali je potrebno bolje analizirati razloge o smanjenoj upotrebi prethodne imunomodulatorne terapije bolesnika s PPMS-om. Prosječan EDSS kod bolesnika s RRMS-om bio je 3,6 u našoj skupini bolesnika što je nešto veća vrijednost u odnosu na ispitivanje OPERA I i II (prosječan EDSS=2,86 u OPERA I te prosječan EDSS=2,78 u OPERA II). Prosječan EDSS bolesnika s PPMS-om je 5,7, što je nešto veća vrijednost u odnosu na ispitivanje ORATORIO (prosječan EDSS=4,7). U skupini bolesnika s RRMS-om prosječan broj relapsa u prethodnoj godini dana bio je 1,94, a u OPERA I i OPERA II ispitivanju prosječan broj relapsa bio je nešto niži (prosječno 1,3 relaps u OPERA I te 1,32 u OPERA II ispitivanju). Što se tiče kliničkog ishoda nakon primjene prvog ciklusa u skupini bolesnika s RRMS-om kod 94 % bolesnika stanje je bilo stacionarno ili poboljšano. U ispitivanju OPERA I je u 7,6 % bolesnika došlo do pogoršanja, a u OPERA II kod 10,6 % tako da naše rezultate smatramo zadovoljavajućima. U skupini bolesnika s PPMS-om kod jednog bolesnika koji je primio drugi ciklus stanje je stacionarno te je za sada teško usporediti ostatak ove skupine u odnosu na ispitivanje ORATORIO. Što se nuspojava tiče, u obje s skupine najčešće bile reakcije na lijek. Kod jedne je bolesnice nakon odgođenog vremena došlo do pojave sindroma reverzibilne posteriorne encefalopatije (PRES), no nejasno je je li navedeni slučaj povezan direktno s primjenom lijeka. Također, praćena je početna vrijednost limfocita i CD19+ limfocita i broj limfocita prije svake sljedeće primjene da bi se kasnije moglo pratiti samo djelovanje lijeka te razina eventualne limfopenije. Ovi podatci će biti naknadno prikupljeni te ćemo imati veći broj sudionika da bi se rezultati mogli lakše usporediti. Važno je napomenuti da ćemo ubuduće pokušati povećasti suradljivost bolesnika sa ciljem da nas obavijeste o eventualnim nuspojavama u obliku infekcija. Osim navedenog očekujemo nove kontrolne MR snimke da bismo mogli usporediti i radiološku aktivnost bolesti.

ZAKLJUČAK

Za sada možemo reći da je naše iskustvo u primjeni lijeka okrelizumab kod bolesnika s RRMS-om i PPMS –om zadovoljavajuće i u skladu s odgovarajućim ispitivanjima. Veliki dio bolesnika s RRMS-om nakon prve infuzije nije imao relapsa što je u skladu s činjenicom da okrelizumab reducira godišnju stopu relapsa. Naša analiza nije pokazala veliki broj komplikacija i nuspo-

java pri primjeni okrelizumaba. Temeljem ove analize uočili smo još određene pokazatelje koje bi bilo dobro pratiti (IgM, IgA, biljege limfocita, elektroforezu proteina, kontrolni MR mozga i vratne kralježnice) te navedeno planiramo dalje umetnuti u praćenje ovih bolesnika.

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SUMMARY

TREATMENT OF MULTIPLE SCLEROSIS WITH OCRELIZUMAB − A RETROSPECTIVE 1.5-YEAR ANALYSIS AT DEPARTMENT OF NEUROLOGY, SESTRE MILOSRDNICE UNIVERSITY HOSPITAL CENTRE IN ZAGREB

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Considering importance of T lymphocytes in the pathogenesis of multiple sclerosis, the importance of B lymphocytes in the pathogenesis of the disease is increasingly revealed. Ocrelizumab (Ocrevus®, Roche, Germany) is a monoclonal antibody that targets B cells expressing CD20 antigen. Numerous studies have demonstrated the efficacy of ocrelizumab in the treatment of relapsing-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS). Previous clinical trials have shown that ocrelizumab administration suppresses relapses, disease progression and subclinical disease activity as determined by the method of magnetic resonance imaging. We retrospectively analyzed patients at the Department of Neurology, Sestre milosrdnice University Hospital Centre. Ocrelizumab was administered to 36 patients with RRMS and 13 patients with PPMS. The aim was to present the population of patients administered the drug, their side effects and clinical outcome after administration of the drug, comparing the above data with current knowledge on the drug. In our RRMS group analysis, 47% of patients were administered second treatment cycle and 8% were administered third cycle; 94% of these patients showed no clinical progression of the disease. In the groups of RRMS and PPMS patients, adverse events were recorded in 11% and 23% of patients, respectively. The most common side effects were response to infusion and decrease in lymphocyte count (still at the border of the lower reference value). The analysis of our patients confirmed previous findings of clinical studies. The drug has been proven to be safe to administer with a low incidence of side effects. Nevertheless, more patients are needed for further and detailed analysis, motivating us for further monitoring and publication of a new analysis in the future.

Key words: multiple sclerosis, ocrelizumab, treatment, experience

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PREDIKTIVNE JEDNADŽBE U PROCJENI DNEVNOG UNOSA KUHINJSKE SOLI

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Opće je prihvaćeno da je prekomjeran unos kuhinjske soli glavna odrednica koja pridonosi povećanju hipertenzije u populaciji, no veliki izazov predstavlja procjena dnevnog unosa kuhinjske soli. Prilikom određivanja dnevnog unosa soli koristi se „zlatni standard", odnosno procjenjuje se unos kuhinjske soli u organizam iz 24–satnog urina. Metoda 24–satnog prikupljanja urina nerijetko opterećuje pojedince uključene u istraživanja, što dovodi do nepotpunih podataka i posljedično do isključivanja ispitanika iz istraživanja te se kao alternativa koristi analiza tzv. slučajnog uzorka urina. Iako je u člancima, analiziranim u ovom radu, predloženo nekoliko prediktivnih jednadžbi, rezultati sugeriraju da se vrijednosti natrija iz prediktivnih jednadžbi značajno razlikuju od izmjerenih 24–satnih vrijednosti te pouzdanost navedenih jednadžbi nije zadovoljavajuća. Zaključno, s obzirom na kontinuiran porast prevalencije kardiovaskularnih oboljenja, sve je veća potreba razvijanja adekvatne metode procjene 24–satnog urina u svrhu procjene dnevnog unosa kuhinjske soli u populaciji.

Ključne riječi: hipertenzija, unos soli, 24–satni urin, prediktivne jednadžbe, natrij

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UVOD

Povišen arterijski tlak (arterijska hipertenzija) glavni je čimbenik rizika za razvoj kardiovaskularnih bolesti u svijetu, koje često mogu biti spriječene primjenom zdravog životnog stila (1-3). U svrhu smanjenja pobola i smrtnosti od kardiovaskularnih bolesti važno je održavati preporučene granične vrijednosti arterijskog tlaka ≤ 130/80 mm Hg (3). Od procijenjenih 1,13 milijardi ljudi s hipertenzijom, manje od 1 na 5 ima vrijednosti arterijskog tlaka unutar preporučenih graničnih vrijednosti (4). Ukupna prevalencija hipertenzije u Europi kod odraslih osoba iznosi 30–45 % (u Hrvatskoj 37,5 %) a starenjem populacije, povećanjem tjelesne težine i sjedilačkim načinom života očekuje se da će se učestalost hipertenzije u svijetu nastaviti povećavati (5,6). U posljednjih nekoliko desetljeća brojne studije pokazale su da je unos kuhinjske soli pozitivno povezan s ranim razvojem čimbenika kardiovaskularnog rizika (7-9). Istraživači iz studije INTERSALT provedene 1988. godine na 10 079 ispitanika utvrdili su povezanost povećanog 24-satnog izlučivanja natrija i povišenih vrijednosti arterijskog tlaka (10). Najviše natrija u organizam unosimo upravo konzumacijom kuhinjske soli (NaCl), putem gotovih ili polugotovih proizvoda te dosoljavanjem obroka (11). U brojnim je istraživanjima, provedenim nakon studije INTERSALT, zaključeno da smanjenje unosa kuhinjske soli doprinosi prevenciji arterijske hipertenzije te posljedično smanjenju smrtnosti od koronarnih bolesti (12-15). Svjetska zdravstvena organizacija (SZO) je 2010. godine smanjenje unosa kuhinjske soli preporučila kao isplativu aktivnost koju je nužno provoditi s ciljem prevencije bolesti i smanjenja troškova zdravstvene skrbi (16).

S obzirom na provedena istraživanja uočeno je da Hrvati dnevno unose trostruko više soli nego je potrebno (12 – 16 g), dok SZO preporuča dnevni unos soli do 5 g te isti navodi dostatnim za normalno funkcioniranje organizma odraslih osoba (17). Preporuke za smanjenje

unosa soli na 5-6 g/dan imat će veliki utjecaj na smanjenje krvnog tlaka, ali daljnje smanjenje unosa soli na 3 g/dan imat će značajniji učinak i dugoročno bi trebalo postati ciljana vrijednost za dnevni unos soli stanovništva (18). Jedan od devet globalnih ciljeva SZO upravo je smanjenje unosa soli za 30 % do 2025. godine (19). S obzirom na utvrđenu povezanost s krvnim tlakom, prehrana s nižim unosom soli jedna je od intervencija s ciljem smanjenja broja oboljelih od kardiovaskularnih bolesti (KVB) (20). U Hrvatskoj je u tijeku nacionalno istraživanje, nastavak projekta iz 2005. godine, pod nazivom *Epidemiologija hipertenzije i unos kuhinjske soli u Hrvatskoj (EH – UH 2)*, čiji je osnovni cilj odrediti prevalenciju, svjesnost, liječenje i kontrolu hipertoničara te odrediti unos kuhinjske soli mjerenjem 24-satne natrijurije (21). Postoji nekoliko metoda za procjenu dnevnog unosa soli, od kojih se prikupljanje 24-satnog urina smatra pouzdanom metodom jer se najveći dio natrija koji osoba unosi izlučuje upravo urinom (22,23). Prikupljanje 24–satnog urina naziva se „zlatnim standardom" za dnevnu procjenu unosa kuhinjske soli (24,25). Nedostatak ove metode jest taj što ispitanike može opteretiti 24–satno prikupljanje urina te zbog neadekvatnog prikupljenog urina dovesti do neispravnih uzoraka. Kao alternativna metoda za određivanje unosa natrija koristi se slučajan uzorak urina (engl. *spot urine sample*), koji se smatra vrijednom mjerom za procjenu dnevnog unosa soli prethodnog dana, iz kojeg se na temelju nekoliko postojećih prediktivnih jednadžbi određuje dnevni unos soli (26,27).

U radu je dan prikaz uporabe prediktivnih jednadžbi u procjeni dnevnog unosa kuhinjske soli na temelju triju istraživanja, s područja Kine, Južnoafričke Republike i Brazila, navedenih u tablici 1.

Tablica 1.
Članci odabrani za usporedbu prediktivnih jednadžbi u procjeni dnevnog unosa kuhinjske soli

Članak	Autori	Godina	Časopis	Metode
Validation of spot urine in predicting 24-h sodium excretion at the individual level	Long Zhou i sur. (1)	2017.	Am J Clin Nutr	Procjena dnevnog unosa soli na temelju tri prediktivne jednadžbe (Kawasaki, INTERSALT i Tanaka)
Prediction of 24-hour sodium excretion from spot urine samples in South African adults: a comparison of four equations	Karen Charlton i sur. (30)	2020.	J Hum Hypertens	Procjena dnevnog unosa soli na temelju četiri prediktivne jednadžbe (Kawasaki, INTERSALT, Tanaka i Mage)
Validation study of the Tanaka and Kawasaki equations to estimate the daily sodium excretion by a spot urine sample	José Geraldo Mill i sur. (32)	2015.	Rev Bras Epidemiol	Usporedba izmjerenih dnevnih vrijednosti unosa soli i dnevnih vrijednosti soli procijenjenih jednadžbama Tanaka i Kawasaki

PREDIKTIVNE JEDNADŽBE ZA PROCJENU DNEVNOG UNOSA KUHINJSKE SOLI

U istraživanju provedenom na kineskoj populaciji ispitanici su odabrani unutar programa smanjenja soli provedenog u gradu Dexing u provinciji Jiangxi. Kriteriji za uključivanje u istraživanje bili su sljedeći: 1) stanovnici zajednice koji rade s punim radnim vremenom, 2) stanovnici u dobi od 18 do 65 godina i 3) stanovnici koji redovito pripremaju obroke u svojim domovima. Isključni kriteriji bili su: 1) ispitanici s nefropatijom, 2) trudnice i 3) osobe koje su jele manje od 10 obroka tjedno u vlastitim domovima. Također, ispitanici su bili naknadno isključeni iz istraživanja ako nisu pravilno prikupili 24–satni urin ili je količina prikupljenog urina bila < 500 mL (1). U navedenom članku ukupno je bio 141 ispitanik od čega su žene činile 94,3 %, prosjek godina uključenih ispitanika iznosio je 51,1 ± 8,2 s prikupljenim urinom volumena 1487 ± 667 ml (1). Istraživači su koristili tri prediktivne jednadžbe za određivanje unosa soli kod ispitanika (Kawasaki, INTERSALT i Tanaka) (1).

Utvrđena je značajna razlika za svaku metodu procjene u usporedbi s izmjerenim 24–satnim izlučenim natrijem u urinu (sve p vrijednosti <0,001). Srednja vrijednost za izmjereno 24–satno izlučivanje natrija iznosila je 220,8 ± 78,5 mmol/d što odgovara unosu soli od 12,9 ± 4,6 g/d, dok su srednje vrijednosti dobivene prediktivnim jednadžbama redom bile sljedeće; Kawasaki 246,1 ± 66,8 mmol/d, INTERSALT 143,6 ± 24,7 mmol/d te Tanaka 183,7 ± 39,0 mmol/d. Sve vrijednosti izlučenog 24–satnog natrija dobivene prediktivnim jednadžbama pretvorene su u ekvivalente unosa soli dnevno (NaCl, g/d) a odstupanja prediktivnih jednadžbi prilikom klasifikacije pojedinaca u 4 kategorije dnevnog unosa soli (< 9, 9 – 11,9, 12 – 14,9 i ≥ 15 g/d) prikazana su u tablici 2 (1).

Tablica 2.
Prikaz klasifikacije ispitanika s obzirom na procijenjene dnevne unose soli na temelju jednadžbe Kawasaki, INTERSALT i Tanaka u kineskoj populaciji (1)

Pretvorba 24-satne ekskrecije natrija u dnevni unos soli					
Metoda	**< 9 g (*n* = 29)**	**9 - 11,9 g (*n* = 39)**	**12 - 14,9 g (*n* = 32)**	**≥ 15 g (*n* = 41)**	**Ukupno (n = 141)**
Kawasaki					
<9 g	6 (20,7)	2 (5,1)	2 (6,2)	1 (2,4	-
9-11,9 g	6 (20,7)	7 (17,9)	8 (25,0)	5 (12,2)	-
12-14,9 g	9 (31,0)	18 (46,2)	12 (37,5)	8 (19,5)	-
≥15 g	8 (27,6)	12 (30,8)	10 (31,2)	27 (65,9	-
Pogrešno klasificirano	23 (79,3)	32 (82,1)	20 (62,5)	14 (34,1)	89 (63,1)
INTERSALT					
<9 g	22 (75,9)	30 (76,9)	22 (68,8)	20 (48,8)	-
9-11,9 g	7 (24,1)	8 (20,5)	10 (31,2)	20 (48,8)	-
12-14,9 g	0 (0,0)	1 (2,6)	0 (0,0)	1 (2,4)	-
≥15 g	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	-
Pogrešno klasificirano	7 (24,1)	31 (79,5)	32 (100)	41 (100)	111 (78,7)
Tanaka					
<9 g	11 (37,9)	7 (17,9)	8 (25,0)	4 (9,8)	-
9-11,9 g	13 (44,8)	25 (64,1)	18 (56,2)	13 (31,7)	-
12-14,9 g	3 (10,3)	7 (17,9)	6 (18,8)	18 (43,9)	-
≥15 g	2 (6,9)	0 (0,0)	0 (0,0)	6 (14,6)	-
Pogrešno klasificirano	18 (62,1)	14 (35,9)	26 (81,2)	35 (85,4)	93 (66,0)

U navedenoj studiji autori zaključuju da prediktivne jednadžbe nisu dovoljno dobro procijenile dnevni unos soli. Procijenjena ekskrecija natrija iz svake od 3 jednadžbe pokazala je nisku do umjerenu korelaciju s izmjerenim vrijednostima pri čemu je Kawasaki formula najmanje odstupala, dok je formula INTERSALT najviše odstupala od izmjerenih dnevnih vrijednosti soli u kineskoj populaciji (1). Navedena otkrića su u skladu s rezultatima studije provedene u Kini - PURE[1] (28) ali nisu u skladu s istraživanjem provedenim u populaciji Sjedinjenih Američkih Država u dobi od 18 do 39 godina, gdje je utvrđeno da je jednadžba INTERSALT najmanje odstupala prilikom izračuna dnevnog unosa soli među odraslim osobama u SAD-u (1,29). Kawasaki formula predložena je na temelju japanske populacije, dok se INTERSALT formula temelji na zapadnoj populaciji. Stoga oprečni rezultati mogu biti posljedica razlika u prehrambenim obrascima i ponašanju povezanim s rasom, etničkom pripadnošću i kulturom. Autori zaključuju da je unos kuhinjske soli unutar azijske populacije veći u odnosu na unos kuhinjske soli u zapadnim zemljama te je zbog toga teško postići ciljeve koje preporuča SZO o dnevnom unosu kuhinjske soli (≤ 5g/d). Stoga su znanstvenici predložili prosječni unos soli od 9 g kao prvi korak u smanjenju dnevnog unosa soli u Kini (1). Istraživači u nacionalno reprezentativnom uzorku Južnoafrikanaca procjenjuju valjanost četiriju postojećih jednadžbi (Kawasaki, Tanaka, INTERSALT i Mage) za predviđanje 24–satnog izlučivanja natrija iz slučajnih uzoraka urina (30).

Slučajni uzorci i 24–satni uzorci urina prikupljeni su u podskupini (n = 438) sudionika iz Studije Svjetske zdravstvene organizacije o globalnom starenju i zdravlju odraslih (SAGE)[2] u Južnoj Africi. Podudarnost između izmjerenih vrijednosti natrija iz 24–satnog urina i predviđenih vrijednosti izlučenog natrija iz 24–satnog urina dobivenih iz jednadžbi Kawasaki, Tanaka, INTERSALT i Mage izmjerila se Bland – Altman analizom. Isključni kriteriji prilikom prikupljanja 24–satnog urina bili su ukupni volumen urina ≤ 300 ml, ekskrecija kreatinina ≤ 4 mmol/d kod žena odnosno ≤ 6 mmol/d kod muškaraca. Kao i u prethodnom članku, sve vrijednosti pretvorene su u ekvivalente unosa soli dnevno (NaCl, g/d) radi lakše interpretacije rezultata i dosljednosti izvještavanja u odnosu na preporučene dnevne količine unosa soli za optimalno zdravlje (30).

1 Prospective Urban and Rural epidemiological study (PURE), http://www.phri.ca/pure/

2 Study on global AGEing and adult health (SAGE), https://www.who.int/healthinfo/sage/en/

Tablica 3.
Izmjereni i procijenjeni natrij izlučen iz 24–satnog urina južnoafričke populacije, izražen kao ekvivalent soli dnevno (29)

	Izmjereno	INTERSALT	Tanaka	Kawasaki	Mage
Ukupno, *n* = 438	7,0 (4,4 – 10,5)	3,0 (2,5 – 3,5)	8,0 (6,8 – 9,5)	13,1 (10,2 –16,7)	25,5 (15,7 – 41,7)
Muškarci, *n* = 106	7,7 (4,6 – 11,2)	3,7 (3,1 – 4,2)	8,1 (6,9 – 9,1)	18,5 (14,8 –22,3)	25,9 (16,6 – 42,5)
Žene, *n* = 332	6,5 (4,4 – 10,3)	2,8 (2,4 – 3,2)	7,9 (6,7 – 9,6)	11,9 (9,7 –14, 9)	25,4 (15,2 – 41,4)
Negroidi, *n* = 319	6,4 (4,4 – 10,6)	3,0 (2,6 – 3,5)	8,0 (6,8 – 9,5)	13,2 (10,2 –16,7)	27,0 (16,7 – 43,1)
Ostale rase, *n* = 119	7,5 (4,3 – 10,3)	2,8 (2,4 – 3,4)	8,0 (6,5 – 9,7)	12,9 (9,8-16,5)	22,2 (12,0 – 35,0)
Iznad 50 godina, *n* = 284	6,1 (4,2 – 8,9)	2,9 (2,3 – 3,4)	8,0 (6,5 – 9,6)	12,8 (9,9 –16,5)	23,1 (13,1 – 40,0)
Ispod 50 godina, *n* = 154	8,5 (5,1 – 13,9)	3,1 (2,8 – 3,5)	8,0 (6,9 – 9,2)	13,7 (10,5 – 16,8)	30,7 (20,6 – 44,2)
Razlika[b]		3,77 (1,64; 7,09)	-1,28 (-3,52; 1,97)	-6,24 (-9,45; -2,22)	-17,18 (-31,96; -8,42)
***p* vrijednost[b]**		<0,001	0,0118	<0,001	<0,001

Svi podaci su prikazani kao medijan (IQR, interkvartilni raspon)
[a] 24 - satna sol (NaCl) ekvivalent (g/dan) = (24–satni Na (mg/dan) / 1000 x 2,5
[b] Razlika je zbirna varijabla razlike između izmjerene i predviđene 24 -satne ekskrecije soli iz urina za svakog ispitanika, procijenjena uporabom Wilcoxonovog testa sume rangova

Na temelju analize prikupljenih 24–satnih uzoraka urina izlučivanje natrija variralo je s opaženim vrijednostima između 1 – 40 g soli dnevno, a medijan unutar grupe od 6,7 g soli dnevno (4,4 – 10,5) (30). Srednja vrijednost dnevno izlučene soli bila je veća u mlađoj skupini ispitanika (< 50 godina) i iznosila je 8,5 (5,1–13,9) g soli/dan u usporedbi sa starijom skupinom (> 50 godina) gdje je iznosila 6,1 (4,2–8,9) g soli/dan; p < 0,001. Nisu opažene statistički značajne razlike između muškaraca i žena niti između ispitanika koji žive u urbanim nasuprot onih koji žive u ruralnim krajevima (30). U tablici 3. prikazane su vrijednosti izmjerenog i predviđenog izlučenog natrija iz 24–satnog urina, izražene kao ekvivalent soli dnevno. Rezultati ovog istraživanja navode da se vrijednosti natrija iz prediktivnih jednadžbi značajno razlikuju od izmjerenih 24–satnih vrijednosti te navedene prediktivne jednadžbe nisu prikladne za upotrebu u odrasloj populaciji Južne Afrike. Tanaka, Kawasaki i Mage jednadžba precijenjuju dnevni unos soli. Suprotno tome, jednadžba INTERSALT sustavno podcjenjuje dnevni unos soli. Kao što je istaknuto u radu autora Cappucio i D'Elia, postoji potreba za procjenom dnevnog unosa soli u populaciji kako bi se podržalo praćenje ali i inicijativa za smanjenje soli, izbjegavajući teret 24-satnog sakupljanja urina (31). Globalni akcijski plan Svjetske zdravstvene organizacije postavio je granične vrijednosti za maksimalni dnevni unos soli no autori smatraju da se praćenje napretka u ostvarenju tog cilja do 2025. godine koristeći procjene natrija iz slučajnih uzoraka urina ne može postići, barem ne u Južnoj Africi. Nadalje, politika smanjenja unosa soli u Južnoj Africi (objavljena u lipnju 2016. godine) očekuje smanjenje unosa soli u populaciji za 0,85 g/d. Neprihvatljivo velike oscilacije u izračunima navedenih prediktivnih jednadžbi ukazuju na nemogućnost identifikacije ciljanih vrijednosti redukcije dnevnog unosa soli. Autori su mišljenja da bi nemogućnost većine prediktivnih jednadžbi da precizno odrede dnevni unos soli mogla dovesti do netočnih pretpostavki u vezi uspjeha strategije smanjenja dnevnog unosa soli (30).

Na području grada Vitória (Brazil) istraživači su analizirali podatke prikupljene od 272 ispitanika iz nasumičnog uzorka domaćinstva, starosne dobi 20 – 69 godina, od čega 129 muškaraca (47,43 %). Ispitanici su prikupljali 24–satni urin te dva slučajna uzorka urina unutar istoga dana (1 urin natašte, 1 urin poslijepodne). U uzorku je bilo 23,5 % pretilih (ITM ≥30 kg/m^2), 31,2 % s povišenim krvnim tlakom i 7,0 % ispitanika s dijabetesom. Isključni kriteriji za sudjelovanje u istraživanju bili su ispitanici s akutnim bolestima, slabe pokretljivosti i nepokretni, s poteškoćama u komunikaciji te trudnice i dojilje.

U tablici 4. prikazane su vrijednosti izmjerenog izlučenog natrija iz 24–satnog urina i onog predviđenog formulama Tanaka i Kawasaki. Vidljivo je da Kawasaki formula precjenjuje izlučivanje natrija i soli i kod muškaraca i kod žena, dok Tanaka formula navedene varijable podcjenjuje kod muškaraca te precjenjuje kod žena. Autori navode ograničenje unutar istraživanja, činjenicu da nije moguće procijeniti gubitak natrija znojenjem, što je važan čimbenik posebice u zemljama tropskog pojasa (32).

Tablica 4.
Usporedba vrijednosti izmjerenog izlučenog natrija iz 24–satnog urina i procijenjenih vrijednosti jednadžbama Tanaka i Kawasaki u južnoameričkoj populaciji (31)

Varijable	24-satni urin (Izmjereni)			
	Muškarci		Žene	
NaUr (mmol/dan)	204,00 ± 73,0 (187,00)		152,00 ± 59,00 (143,00)	
Sol (g/dan)	11,90 ± 4,20 (10,90)		8,80 ± 3,40 (8,40)	
	Slučajni uzorak urina 1 (Procijenjeni)			
	Tanaka		Kawasaki	
	Muškarci	Žene	Muškarci	Žene
NaUr (mmol/dan)	168,00 ± 34,0 (168,00)	156,00 ± 37,0 (155,00)	223,00 ± 59,0 (235,00)	190,00 ± 54,0 (189,00)
Sol (g/dan)	9,80 ± 1,90 (9,80)	9,10 ± 2,10 (9,00)	13,10 ± 3,50 (13,80)	11,10 ± 3,10 (11,00)
sol (g/dan)	2,10	0,30	1,20	2,30
	Slučajni uzorak urina 2 (Procijenjeni)			
	Tanaka		Kawasaki	
	Muškarci	Žene	Muškarci	Žene
NaUr (mmol/dan)	180,00 ± 34,0 (177,00)	167,00 ± 32,0 (169,00)	255,00 ± 60,0 (250,00)	206,00 ± 47,0 (206,00)
Sol (g /dan)	10,50 ± 1,92 (10,40)	9,80 ± 1,80 (9,90)	14,90 ± 3,50 (14,60)	12,00 ± 2,70 (12,10)
sol (g/dan)	1,40	1,00	3,00	3,20

Rezultati su prikazani kao srednje vrijednosti ± standardne devijacije i medijan.
NaUr: natrij iz urina; sol: razlika između izmjerene količine soli i količine soli predviđene formulama

* Vrijednosti su preuzete iz izvornih podataka (31) i preračunate na SI sustav (mol).

ZAKLJUČAK

Navedena istraživanja procjenjuju mogu li se najčešće korištene prediktivne jednadžbe upotrijebiti za procjenu dnevnog unosa soli. Utvrđeno je da pouzdanost prediktivnih jednadžbi varira unutar svakog tako i međusobno između odabranih članaka. U analiziranim člancima prediktivne jednadžbe nisu prikladne za procjenu dnevnog unosa soli iz koncentracije natrija u slučajnim uzorcima urina te autori ističu potrebu razvijanja vjerodostojnijih metoda kojima će se precizno procijeniti dnevni unos soli u populaciji.

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SUMMARY

PREDICTIVE EQUATIONS IN THE ESTIMATION OF DAILY SALT INTAKE

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It is generally accepted that excessive salt intake is a major determinant contributing to the increased rate of hypertension in the population, but assessment of daily salt intake is a highly challenging issue. The gold standard in determining salt in the body is estimating salt intake in 24-hour urine. The 24-hour urine collection method usually burdens respondents, leading to incomplete data and, consequently, exclusion of respondents from research. Analysis of random urine sample is used as an alternative. The authors of the studies analyzed in this paper used several predictive equations and the results suggest that sodium values of the predictive equations differed significantly from the measured 24-hour values and that the reliability of the equations was unsatisfactory. In conclusion, considering a continuous increase in the prevalence of cardiovascular diseases, it becomes necessary to develop an appropriate method of measuring 24-hour urine for estimating daily salt intake in the population.

Key words: **hypertension, salt intake, 24-hour urine, predictive equation, sodium**

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SPOLNE RAZLIKE U UČESTALOSTI I KLINIČKOJ PREZENTACIJI AKUTNOG INFARKTA MIOKARDA U IZVANBOLNIČKOJ HITNOJ MEDICINSKOJ SLUŽBI

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Cilj: Glavni cilj ovog istraživanja bio je ispitati postoje li spolne razlike u učestalosti, dobnoj distribuciji i kliničkoj prezentaciji kod bolesnika s akutnim infarktom miokarda koji su zatražili intervenciju Hitne medicinske službe. ***Metode:*** Učinjena je retrospektivna analiza baze podataka našeg Zavoda za hitnu medicinu u razdoblju od travnja 2014. do listopada 2019. godine. Koristili smo program e-Hitna te uključili sve bolesnike s dijagnozom akutnog infarkta miokarda (I21 prema MKB-10 klasifikaciji). Za sve bolesnike analizirali smo nekoliko karakteristika: dob, spol, prisutnost šećerne bolesti te tri kliničke karakteristike (bol u prsima, poremećaj svijesti, hemodinamska nestabilnost). ***Rezultati:*** Ukupno je uključeno 377 pacijenata s dijagnozom akutnog infarkta miokarda. Muškaraca je bilo 219 (58,1 %), a žena 158 (41,9 %) ($p < 0,001$). Prosječna dob obolijevanja muškaraca iznosila je 64 godine, a žena 73 godine ($p<0,001$). Nije zabilježena razlika u pojavnosti šećerne bolesti između spolova ($p=0,88$). Što se tiče kliničkih karakteristika bolesnika, nije zabilježena razlika u pojavnosti i jačini boli u prsima ($p=0,07$) te hemodinamske nestabilnosti ($p=0,49$) između muškaraca i žena. Međutim, žene češće imaju poremećaj svijesti (62,2 %) u odnosu na muškarce (37,8 %) ($p<0,01$). ***Rasprava:*** Akutni infarkt miokarda češći je u muškaraca što potvrđuju i brojne studije. Naše istraživanje pokazalo je da se infarkt miokarda javlja u starijoj dobi kod žena s razlikom prosječne dobi obolijevanja od čak 9 godina. Takva razlika tumači se drugačijim utjecajem rizičnih čimbenika na razvoj kardiovaskularnih bolesti između spolova te protektivnim djelovanjem estrogena u žena prije menopauze. Od navedenih kliničkih karakteristika poremećaj svijesti javlja se češće u žena što je u skladu s mnogim istraživanjima koja navode da žene češće imaju atipične simptome. ***Zaključak:*** Kardiovaskularne bolesti se javljaju češće u muškaraca, ali su glavni uzrok smrti u oba spola. Muškarci obolijevaju i do 10 godina ranije, ali spolne se razlike starenjem smanjuju. Potrebna su daljnja istraživanja o uzroku razlika u kliničkoj prezentaciji akutnog infarkta miokarda između spolova.

Ključne riječi: akutni infarkt miokarda, spolne razlike, hitna medicina

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UVOD

Kardiovaskularne bolesti glavni su uzrok smrti u svijetu, uzimajući oko 17,9 milijuna života svake godine (1). Na razini Europe odgovorne su za 4,3 milijuna smrti/godina, odnosno 48 % svih smrti. Nešto manje od polovice smrti od kardiovaskularnih bolesti uzrokovano je ishemijskim bolestima srca te su one na prvom mjestu smrtnosti i u muškaraca i u žena (2). Prema desetoj reviziji Međunarodne klasifikacije bolesti i srodnih zdravstvenih problema (MKB-10) ishemijske bolesti srca (I20-I25) pripadaju u bolesti cirkulacijskog sustava, gdje dijagnoza I21 označava akutni infarkt miokarda (3).

Akutni infarkt miokarda nastaje zbog naglog smanjenja koronarnog protoka krvi, što je posljedica trombotične okluzije koronarne arterije koja je ranije bila sužena aterosklerozom. Najčešći simptom akutnog infarkta miokarda je bol u prsima ili epigastriju koja se može širiti u ruke, abdomen, leđa, donju vilicu i vrat. Najmanje 15-20 % infarkta miokarda prezentira se bez bolova što je češće u žena, bolesnika s dijabetesom te u poodmakloj dobi. Rjeđe se opisuju pojave kao što

su iznenadno otežano disanje, nagli gubitak svijesti, stanje mentalne smetenosti, osjećaj teške slabosti, pad arterijskog tlaka ili mučnina (4).

Framinghamska studija pokazala je kako su pušenje, arterijska hipertenzija, povišena razina ukupnog kolesterola i LDL kolesterola, smanjena razina HDL kolesterola i dijabetes glavni rizični čimbenici za razvoj kardiovaskularnih bolesti. Pretilost i fizička neaktivnost utječu na razinu glukoze u krvi, krvni tlak i lipidni profil te tako direktno povećavaju kardiovaskularni rizik (5). Istraživanja su pokazala da su muškarci češće pušači dok su žene češće pretile i fizički neaktivne (6). Bitno je istaknuti i hormonske razlike između spolova što se vidi po učestalosti kardiovaskularnih bolesti koja je niska u žena prije menopauze, raste u žena u postmenopauzi te se smanjuje ako takve žene primaju terapiju estrogenima. Glavni protektivni učinci estrogena na kardiovaskularni sustav su snižavanje koncentracije serumskih lipida, vazodilatacija i inhibicija odgovora krvne žile na ozljedu (7).

Iako muškarci i žene dijele većinu rizičnih čimbenika za razvoj kardiovaskularnih bolesti, akutni infarkt miokarda u žena razvija se u prosjeku 8 do 10 godina kasnije nego u muškaraca te još uvijek nije jasno razlikuje li se prema kliničkoj prezentaciji (8).

CILJ RADA

Cilj ovog istraživanja bio je ispitati postoje li spolne razlike u učestalosti, dobnoj distribuciji i kliničkoj prezentaciji akutnog infarkta miokarda kod bolesnika koji su zatražili intervenciju hitne medicinske službe.

ISPITANICI I METODE

Retrospektivno je analizirana baza podataka Zavoda za hitnu medicinu Brodsko-posavske županije u razdoblju od 29. travnja 2014. do kraja listopada 2019. godine. Podatci su analizirani iz programa e-Hitna koji je od 2014. godine postao obavezan način bilježenja intervencija izvanbolničke hitne medicinske službe.

U ispitivanje su uključeni bolesnici s dijagnozom akutnog infarkta miokarda (I21 prema MKB-10 klasifikaciji). Za sve uključene bolesnike analizirano je nekoliko karakteristika: dob, spol, prisutnost šećerne bolesti u tri kliničke karakteristike pacijenata (bol u prsima, poremećaj svijesti, hemodinamska nestabilnost).

Bol u prsima definirali smo u tri kategorije prema izborniku u e-Hitna programu: bez boli, blaga bol i jaka bol. Poremećaj svijesti iščitavali smo iz izbornika stanja svijesti i *Glasgow Coma Score*-a te svrstali pacijente u dvije skupine: bez poremećaja svijesti, s poremećajem svijesti. Hemodinamsku nestabilnost definirali smo kao pad sistoličkog tlaka ispod 90 mm Hg uz prisutne karakteristike kao što su blijeda, oznojena i hladna koža te svrstavali pacijente u dvije skupine: hemodinamski stabilni i hemodinamski nestabilni.

Podatke smo analizirali u *Microsoft Office Excel*-u. Studentov T test koristili smo kako bismo analizirali statističko značenje spolnih razlika prema dobi. Hi-kvadrat test koristili smo za analizu drugih binarnih varijabli u odnosu na spol. P vrijednost od 0,05 smatrana je statistički značajnom. Podatci su prikazani u tablicama i grafički.

REZULTATI

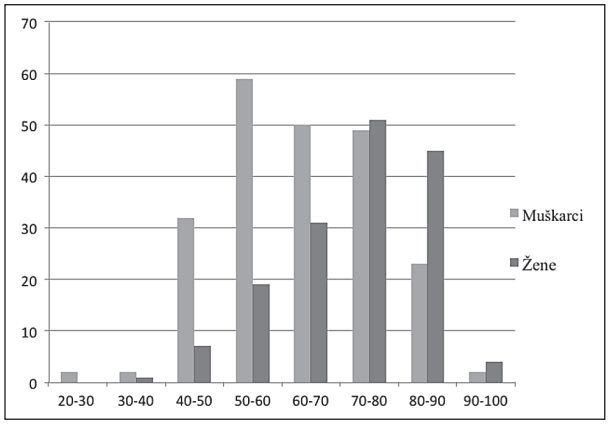
U ispitivanom razdoblju prikupljeno je ukupno 377 pacijenata s dijagnozom akutnog infarkta miokarda (I21) . Od toga je žena bilo 158 (41,9 %), a muškaraca 219 (58,1 %) ($p<0,001$). Najmlađi pacijent imao je 30, a najstariji 96 godina. Prosječna dob u kojoj su obolijevali od akutnog infarkta miokarda iznosila je 67 godina. Za muškarce je prosjek godina iznosio 64, a za žene 73 godine ($p < 0,001$). Distribucija bolesnika s akutnim infarktom miokarda prema dobnim skupinama i spolu prikazana je u tablici 1.

Od ukupno 56 bolesnika sa šećernom bolesti bilo je 42,9 % žena i 57,1 % muškaraca ($p = 0,88$) (sl. 1). Iz sl. 2 vidljiva je jednolika raspodjela žena i muškaraca sa šećernom bolesti i bez šećerne bolesti.

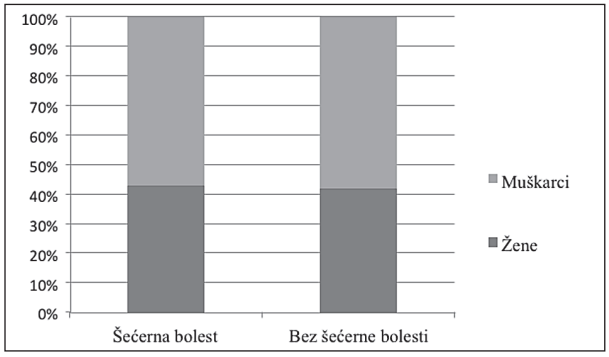
Tablica 1.
Raspodjela pacijenata s akutnim infarktom miokarda prema dobnim skupinama i spolu

Dobne skupine (godine)	Ukupan broj bolesnika (N)	Muškarci (N) (%)	Žene (N) (%)
20-30	2	2 (100)	0 (0)
30-40	3	2 (66,7)	1 (33,3)
40-50	39	32 (82,1)	7 (17,9)
50-60	78	59 (75,6)	19 (24,4)
60-70	83	50 (60,2)	31 (39,8)
70-80	100	49 (49)	51 (51)
80-90	68	23 (33,8)	45 (66,2)
90-100	6	2 (33,3)	4 (66,7)
Ukupno	377	219 (58,1)	158 (41,9)

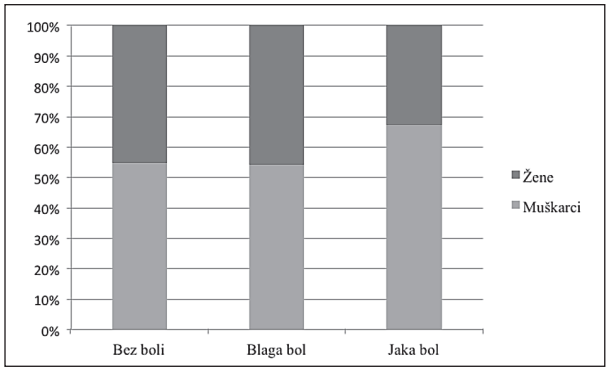
Što se tiče boli u prsima, naši podatci su pokazali da nema statistički značajne razlike u pojavi i jačini boli u prsima u odnosu na spol ($p = 0,07$). Doduše, u sl. 3 se ističe manji udio žena koje su se žalile na jaku bol (32,7 %) u odnosu na muškarce (67,3 %).



Sl. 1. *Spolne razlike pacijenata s akutnim infarktom miokarda po dobnim skupinama*



Sl. 2. *Spolna raspodjela pacijenata sa šećernom bolesti i bez šećerne bolesti*



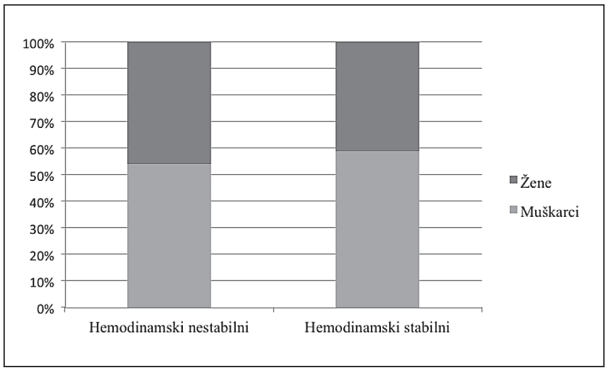
Sl. 3. *Bol u prsima kao simptom akutnog infarkta miokarda*

Od 61 pacijenta koji su bili hemodinamski nestabilni 54,1 % bilo je muškaraca, a 45,9 % žena, što je vidljivo u sl. 4 (p = 0,01).

Tablica 2.
Poremećaj svijesti kao simptom akutnog infarkta miokarda

	Poremećaj svijesti, N (%)	Bez poremećaja svijesti, N (%)
Muškarci	14 (37,8)	205 (60,3)
Žene	23 (62,2)	135 (39,7)
Ukupno	37 (9,8)	340 (90,2)

Ukupno je 37 pacijenata imalo poremećaj svijesti (9,8 %). Žene češće imaju poremećaj svijesti (62,2 %) u odnosu na muškarce (37,8 %) što je vidljivo u tablici 2 (p = 0,49).



Sl. 4. *Hemodinamska nestabilnost kao simptom akutnog infarkta miokarda*

RASPRAVA

Ispitivali smo spolne razlike u učestalosti, dobnoj raspodjeli i kliničkim karakteristikama kod bolesnika s akutnim infarktom miokarda koji su zatražili intervenciju izvanbolničke hitne medicinske službe.

Od ukupno 377 pacijenata bilo je 16,2 % više muškaraca (p < 0,001). Ovi se e-podatci slažu s brojnim istraživanjima koja su pokazala da je infarkt miokarda češći u muškaraca (9-13).

Iz tablice 1 vidljivo je kako se udio muškaraca s akutnim infarktom miokarda mijenja ovisno o dobi i to smanjivanjem udjela muškaraca u odnosu na dob. U najmlađim dobnim skupinama postotak muškaraca je zamjetno veći u odnosu na žene (npr. 82,1 % muškaraca u dobi od 40 do 50 godina u odnosu na samo 18,0 % žena u toj dobnoj skupini). Starenjem pacijenata, omjeri muškaraca i žena se mijenjaju, a u dobnoj skupini od 70 do 80 godina oni su gotovo identični (51 % žena i 49 % muškaraca). Znatno veći postotak žena zapaža se u dobnoj skupini od 80 do 90 godina gdje žene prevladavaju sa 66,2 %. Prikažemo li iste podatke grafički, dobivamo histogram koji još jače ilustrira navedene razlike (sl. 1).

Naše je istraživanje dokazalo da se infarkt miokarda javlja u starijoj dobi kod žena, s razlikom prosječne dobi obolijevanja od čak 9 godina. Prosječna dob obolijevanja muškaraca iznosila je 64 godine, a žena 73 godine (p < 0,001). Ovi su rezultati u skladu s brojnim istraživanjima istog problema gdje se spominje raspon od 7 do 10 godina razlike (14). Starija dob javljanja infarkta miokarda u žena tumači se protektivnim učin-

kom estrogena na endotel krvnih žila. Ova hipoteza temelji se na činjenici da incidencija akutnog infarkta miokarda značajno raste u postmenopauzalnih žena (7,15).Drugi razlog svakako bi mogao biti djelovanje rizičnih čimbenika na razvoj kardiovaskularnih bolesti. Iako žene i muškarci dijele većinu klasičnih rizičnih čimbenika, značenje i težina ovih čimbenika se razlikuju. Tako pušenje u ranoj dobi više povećava rizik prvog infarkta miokarda u žena nego u muškaraca smanjujući vazodilataciju endotela krvnih žila pod djelovanjem estrogena (16). Međutim, muškarci su češće pušači (12,13). Arterijska hipertenzija izraženija je u žena nakon menopauze zbog pojačane aktivnosti sustava renin-angiotenzin (14). Što se tiče razine lipida u krvi, u mlađoj dobi žene imaju manji rizik od hiperkolesterolemije. Nakon 65. godine prosječni LDL kolesterol je viši u žena nego u muškaraca (14).

Prisutnost šećerne bolesti poznati je rizični čimbenik za obolijevanje od akutnog infarkta miokarda(15).U našem istraživanju zabilježeno je 56 bolesnika sa šećernom bolesti (17,5 %). Prevalencija šećerne bolesti u Republici Hrvatskoj u 2014. godini iznosi 6,9 % za dobnu skupinu od 20 do 79 godina (17). S obzirom da su u naše istraživanje uključene i starije osobe ne možemo direktno zaključiti o povećanom udjelu dijabetesa u osoba s akutnim koronarnim sindromom te to ostavljamo za daljnja istraživanja. Što se tiče omjera muškaraca i žena koji su imali akutni infarkt miokarda, a boluju od šećerne bolesti, omjer je nešto viši u korist muškaraca (57,1 %) u odnosu na žene (42,9 %), ali ta razlika nije statistički značajna (p = 0,88). U drugim istraživanjima opisuje se čak i veći udio žena sa šećernom bolesti u odnosu na muškarce (12).

Suočeni s problemom nedostatnog opisivanja kliničke slike od nekih liječnika u opisnom dijelu programa e-Hitna, odlučili smo se kao kliničku prezentaciju izabrati tri karakteristike koje su nužno prisutne u svakom nalazu. To su bol, hemodinamska nestabilnost i poremećaj svijesti. Iz sl. 3 vidljiva je podjednaka raspodjela muškaraca i žena u kategorijama bez boli i blaga bol, dok se ističe kategorija jake boli gdje muškarci imaju znatno veći udio (67,3 %) u odnosu na žene (32,7 %), (p = 0,07). Što se tiče hemodinamske nestabilnosti naše istraživanje nije pokazalo statistički značajnu razliku između muškaraca koji su bili hemodinamski nestabilni (54,1 %) u odnosu na žene (45,9 %), (p = 0,49). Jedina klinička prezentacija akutnog infarkta miokarda koja se pokazala statistički značajnom je poremećaj svijesti što vidimo iz tablice 2. Žene imaju češće poremećaj svijesti (62,2 %) u odnosu na muškarce (37,8 %) (p < 0,01).

Razna istraživanja bavila su se različitom kliničkom prezentacijom akutnog infarkta miokarda u muškaraca i žena. Tako je opisano da muškarci imaju češće klasičnu kliničku sliku s primarnim simptomom boli u prsima, dok žene imaju češće atipičnu kliničku sliku akutnog infarkta miokarda, bez bolova u prsima, s bolovima drugih lokalizacija, nedostatkom zraka i mučninom (8,13,18). Vegetativni simptomi u žena ponekad maskiraju bol u prsima (14).Razlike u gubitku svijesti u nekim istraživanjima nije bilo (18).

ZAKLJUČAK

Kardiovaskularne bolesti javljaju se češće u muškaraca, ali su glavni uzrok smrti u oba spola. Muškarci ranije obolijevaju od akutnog infarkta miokarda zbog rizičnih čimbenika koji pogoduju razvoju kardiovaskularnih bolesti, a zaštitnog djelovanja estrogena na žene prije menopauze. Međutim, spolne razlike se starenjem smanjuju te je potrebno obrazovati i žene i muškarce o simptomima akutnog infarkta miokarda kako bi se pospješila pravovremena intervencija izvanbolničke hitne medicinske službe. Potrebna su daljnja istraživanja o uzroku razlika u kliničkoj prezentaciji akutnog infarkta miokarda između muškaraca i žena.

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SUMMARY

GENDER DIFFERENCES IN THE INCIDENCE AND CLINICAL PRESENTATION OF ACUTE MYOCARDIAL INFARCTION IN EMERGENCY MEDICINE

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The main objective of this study was to investigate whether there are gender differences in the incidence, age, distribution and clinical presentation of patients with acute myocardial infarction requiring emergency medical intervention. Retrospective analysis of the data base of our Department of Emergency Medicine from April 2014 to October 2019 was performed. We used the e-Hitna program and included all patients with acute myocardial infarction (I21 according to the ICD-10 classification). For all patients involved, we analyzed the following characteristics: age, gender, presence of diabetes, and three clinical characteristics (chest pain, disorders of consciousness, and hemodynamic instability). A total of 377 patients with acute myocardial infarction were included. There were 219 (58.1%) men and 158 (41.9%) women (p<0.001). The average age of men and women was 64 and 73 years, respectively (p<0.001). There was no gender difference in the incidence of diabetes (p=0.88). Regarding clinical characteristics of patients, there was no difference in the incidence and severity of chest pain (p=0.07) and hemodynamic instability (p=0.49). However, women were found to be more likely to have a disorder of consciousness (62.2%) than men (37.8%) (p<0.01). In conclusion, acute myocardial infarction is more common in men, as confirmed by numerous studies. Our study shows that myocardial infarction occurs in older women, with a 9-year difference in the average age. Such a difference is interpreted by different influence of risk factors for the development of cardiovascular diseases between the genders and the protective effect of estrogen in women before menopause. Of these clinical characteristics, consciousness disorders occur more frequently in women, which is consistent with numerous studies reporting that women have atypical symptoms more often. In conclusion, cardiovascular diseases occur more frequently in men, but are the leading cause of death in both genders. Men have myocardial infarction 10 years earlier on average, but gender differences are decreasing with age. Further studies on the cause of differences in the clinical presentation of acute myocardial infarction between genders are required.

Key words: acute myocardial infarction, gender differences, emergency medicine

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RISK MANAGEMENT IN THE CLINICAL HEALTH CARE PROCESS

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Risk management in the process of nursing clinical practice is a systematic process that requires expertise and skills in risk prevention. Patient safety at the hospital is the primary goal of every individual providing health care service, and at the same time of the organizations. Accordingly, it is necessary to develop strategies that minimize the risks in the hospital and successfully address adverse events in practice. The main hypothesis was that risk management in the healthcare process has a positive impact on the quality and safety of healthcare service. The following goals were set: 1) to identify the most common risks reported in the healthcare process; 2) to examine the ways and models of risk prevention in the healthcare process in hospitals; and 3) to examine the practice and attitude of nurses in the process of managing risks and adverse events. The survey was conducted among 115 nurses/medical technicians employed at the public health institutions-hospitals in the Federation of Bosnia and Herzegovina. The survey used the original questionnaire prepared by the authors in the electronic Google forms, which was available to the respondents via personal e-mail address, and they responded completely independently without the influence of another person. Comparison of risk events in practice showed a statistically significant decrease with advancing age of the respondents (rho=-0.274; p=0.003), longer work experience of the respondents (rho=-0.334; p=0.0001), higher education of the respondents (rho=-0.198; p=0.034), conducting patient categorization (rho=-0.289; p=0.002), and policies and procedures adopted (rho=-0.408; p=0.0001). A statistically significant effect on reducing the number of adverse events per patient was shown for the frequency of examination of patient skin and mucous membranes during hospital stay (rho=-0.200; p=0.032), use of scales to assess the risk of falls (rho=-0.422; p=0.0001), use of risk assessment scales for pressure ulcers (rho=-0.375; p=0.0001), frequency of intravenous cannula replacement (rho=-0.204; p=0.029), frequency of patient bathing (rho=-0.355; p= 0. 0001) and the method of performing nutritional evaluation of artificially fed patients (rho=-0.327; p=0.0001). In conclusion, patient safety in the hospital should be considered a paramount issue, and nurses who spend most time with patients are expected to provide conditions for secure hospital stay, conditions for safe and quality service in the health care process, and implementation of standardized procedures based on scientific and practical evidence. Continuous reporting of quality indicators in the health care process contributes to strengthening of the organizational culture, prevention of risks and adverse events, and planning of personnel and equipment necessary for the quality of the health care process.

Key words: risks, management, nursing practice, nursing care, hospitals, adverse event

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Risk is the probability or possibility that something dangerous will happen, that there will be a loss, injury, or some other adverse consequences.
(Oxford Dictionary)

INTRODUCTION

Healthcare risk management began in the 1960s (USA, UK, Australia, New Zealand). It has traditionally been driven by insurance and lawsuits. Today, health risk management is widely accepted through development of appropriate standards and educational programs (1).

Risk management within the organization should be recognized as an integral part of good management, or part of organizational culture. Risk management should be included in the organization's philosophy, practices and business plans, and not treated as a separate program (2).

The main components of risk are exposure to loss or damage (action taken or not taken) – material risks, probability (uncertainty) that loss or damage will occur – non-material risks, size of loss or damage – consequences, chance to increase benefits – consequences, level of risk exposure is a combination of the probability of a risky event occurring and the consequences of that event (3).

Risks can be viewed from three angles, i.e. organizational (epidemiological approach), individual (clinical approach in the treatment of a single patient), without approach; an alternative to risk management is risky management.

Risk management in the context of health care includes clinical and non-clinical services.

Risk is an integral part of everything we do in healthcare and medicine and cannot be 100% eliminated. Healthcare professionals manage risk consciously or unconsciously, but almost never systematically (4).

A solid risk management framework is needed at the level of each health facility. This includes development of strategies and other quality documents that prevent risks and minimize them. Risk can be managed by assessing all possible risks in all organizational units based on the probability, type and severity of consequences, which enables the management of both threats and opportunities. Some risks can be completely eliminated, and some can only be reduced. Financial mechanisms can be established to absorb the financial consequences of the remaining risks (residual risk) (5).

The risks in the clinical health care process are numerous. However, their management depends on the quality and skilled team of nurses who, within the scope of their practice, perform preventive actions towards risk factors that can lead to an adverse event or incident. Nurses are actively involved in the entire healthcare team, patients and family in the treatment and care process, which contributes to joint investment in the prevention of harm and the possible consequences of care.

In the health care process, there are five key elements of the risk management process, i.e. identification, assessment, control, financing and monitoring (6).

The most common risks that are monitored in the process of clinical care are as follows: fall of the patient, pressure ulcers, inadequate communication, inadequate medication administration, and risks of nosocomial infections (7,8).

In order to reduce the possible risks in the health care process, it is necessary to implement a system of quality and safety of health services. Introduction of a quality system into the health care process enables nurses to be continuously educated, to improve performance of their work tasks, to bring new guidelines based on evidence and good clinical practice as a team member, and to standardize all work tasks (9,10).

Standardization is a path to reduce risk in clinical health care. It enables nurses/medical technicians to harmonize the work activities they provide to patients, and serves as legal and professional protection.

Standardized documents on quality that define work tasks in the health care process are guides that appropriately manage work tasks and reduce the potential risk (11).

Within the construction of the risk management system in health care, it is necessary to establish a strategy that defines the following goals:

- Providing safer health services, based on policies and practices that take into account the potential risk.
- Protecting health care users by preventing the occurrence of adverse events (incidental situations), and ensuring that, when an adverse event occurs, steps are taken to address it with minimal adverse consequences.
- Establish and develop a clear and effective structure for managing clinical and non-clinical risks.
- Providing knowledge by each employee of his/her responsibilities in risk management and acceptance of these responsibilities within work activities.
- Using risk management processes to learn from one's own mistakes, as well as planning quality improvements to ensure the best possible health care.
- Further development of organizational security culture (12).

GOALS

1. Identify the most common risks reported in the healthcare process.
2. Examine the ways and models of risk prevention in the healthcare process in hospitals.
3. Examine the practice and attitude of nurses in the process of managing risks and adverse events

METHODS

The research was conducted among nurses/medical technicians by the method of random selection in se-

veral geographical areas of Bosnia and Herzegovina, i.e. Sarajevo, Mostar, Travnik, Tuzla and Zenica.

A total of 115 respondents participated in the study. Nurses listed the Sarajevo University Clinical Center as their place of employment in 29 (25.2%) cases, followed by respondents from the Travnik General Hospital in 25 (21.8%) and Tuzla University Clinical Center in 21 (18.3%) cases. An equal number of respondents (n=20, 17.4% each) answered the questionnaire from Dr. Safet Mujić Regional Medical Center in Mostar and Zenica General Hospital. The research was conducted in the period from September 1, 2019 to November 30, 2019.

The original questionnaire prepared by the authors in the Google forms was used in the research; it was available to the respondents *via* personal e-mail invitation, and they answered it completely independently without the influence of another person. The research was descriptive.

RESULTS

The sample included 36 (31.3%) male and 79 (68.7%) female nurses. The majority of nurses were in the 40-45 age group (n=45, 39.1%), followed by 30-35 (n=20, 17.4%), 35-40 (n=18, 15.7%), 50-55 (n=14, 12.2%), 25-30 (n=10, 8.7%) and 55-60 age groups (n=8, 7.0%). According to work experience, the majority of respondents had worked for 21-30 years (n=50, 43.5%), followed by the respondents having worked for 11-20 years (n=38, 33.0%), those having worked for more than 30 years (n=15, 13.0%) and those having worked for up to 10 years (n=12, 10.4%). According to the level of education, the majority of the respondents had graduated high school (n=73, 63.5%), followed by the respondents who had finished faculty (n=27, 23.5%) and college (n=15, 13.0%). Analysis of the position and function performing at the workplace revealed that the majority of respondents were ward nurses (n=79, 68.7%), followed by head nurses at the department (n=32, 27.8%) and head nurses of the institutions (n=4, 3.5%).

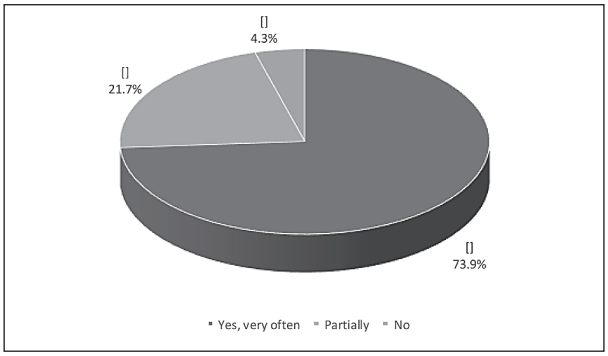

Fig. 1. *Risk management in everyday practice.*

It is evident that the largest number of respondents were very often able to timely prevent risk situations in 85 (73.9%) cases. They were partially successful in prevention in 25 (21.7%) cases, while it was not able to prevent the occurrence of a risk situation on time in only 5 (4.3%) cases. Accordingly, it can be concluded that risk management in the examined sample of health care institutions was good, if not excellent (73.9% of successful prevention).

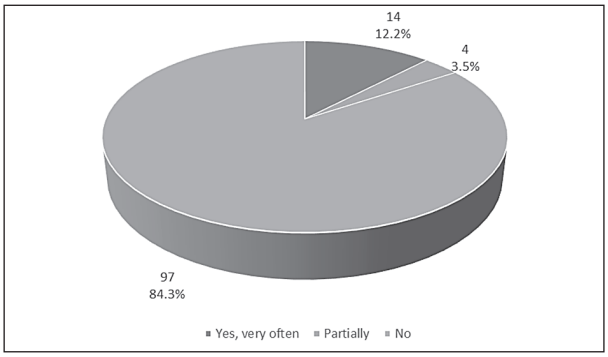

Fig. 2. *Adverse events in practice.*

Analysis of the occurrence of adverse events *per* patient in the past showed that it occurred as an absolute event in 14 (12.2%) cases, while partial adverse events were recorded in 4 (3.5%) cases. Harm for the patient from an adverse event was not reported in 97 (84.3%) cases. Thus, it can be concluded that risk management worked well in the institutions investigated because adverse events occurred in 15.7% of cases.

Adoption of the policies and procedures emphasizing risks in the health care process did not show to have a significant impact on the prevention of risk situations (χ^2=2.306; p=0.680; rho=-0.134; p=0.155), although those who had adopted the procedures were more likely to report successful prevention of risky situations.

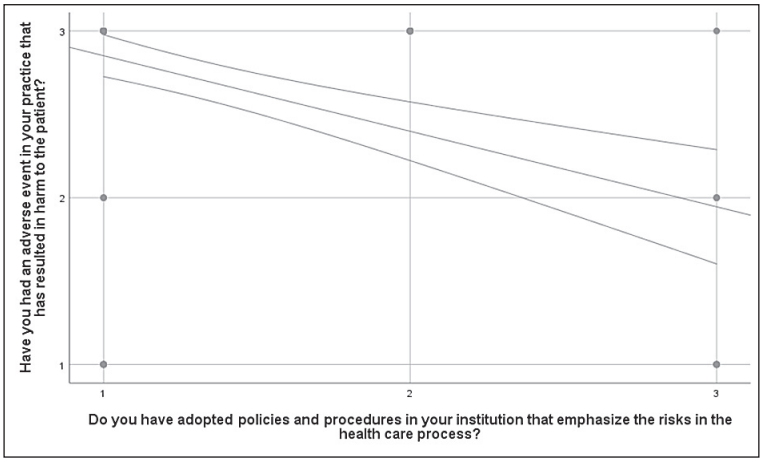

Fig. 3. *Correlation of adoption of policies and procedures with reduction of adverse consequences for patient.*
Legend: Adverse events for patient: 1 - yes; 2 - partially, 3 - no; Policies and procedures: 1 - yes; 2 - partially, 3 - no.

Policies and procedures showed a statistically significant effect (χ^2=41.069; p=0.0001; rho=-0.408; p=0.0001) on the reduction of adverse events that had harmful consequences for the patient. Analysis according to age showed that older respondents had more risk situations that they prevented on time (χ^2=24.469; p=0.006; rho=-0.274; p=0.003), as confirmed by the statistically significant correlation analysis, which indicated the number of risk situations prevented to have increased with advancing age of the respondents (p<0.05). This result was expected given that older respondents also had more work experience during which they had encountered risky situations.

On the other hand, analysis of the impact of the length of service on the number of adverse events did not show a statistically significant correlation (χ^2=4.178; p=0.653; rho=-0.140; p=0.134).

Education did not show an impact on the frequency of prevented risk situations (χ^2=4.309; p=0.366; rho=-0.038; p=0.689). However, education did influence the reduction of adverse events that resulted in harm to the patient, i.e. respondents with college and higher education more often cited these types of events in their practice (χ^2=9.540; p=0.049; rho=-0.198; p=0.034) p<0.05.

Categorization of patients showed a statistically significant impact on the occurrence of adverse events in patients, i.e. these events were less common in case of its implementation (χ^2=15.448; p=0.004; rho=-0.289; p=0.002).

The frequency of patient skin and mucous membrane examination during hospital stay had a significant impact on lower number of adverse events that resulted in harm to patient (χ^2=14.309; p=0.074; rho=-0.200; p=0.032).

Respondents who used scales to assess the risk of fall in the highest percentage stated that they used Morse scale (n=101, 87.8%), whereas one (0.9%) respondent reported using Stratify scale. The analysis indicated that the type of scale used did not influence prevention of risk situations (χ^2=3.029; p=0.220; rho=0.159; p=0.083) and frequency of adverse events with adverse consequences (χ^2=0.187; p=0.911; rho=0.039; p=0.678).

The use of risk assessment scales for pressure ulcers did not show a statistically significant impact on the prevention of risk situations (χ^2=4.071; p=0.396; rho=-0.149; p=0.112).

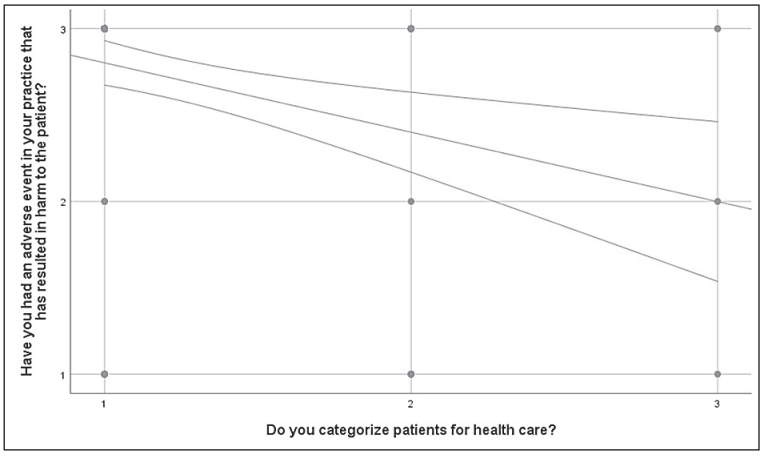

Figure 4. *Correlation of patient categorization and adverse events for patient.*

Legend: Adverse events for patient: 1 - yes; 2 - partially, 3 - no; Categorization: 1 - yes; 2 - partially, 3 - no.

The frequency of intravenous cannula exchanges in patients receiving intravenous medications did not show a statistically significant effect on the prevention of risk situations (χ^2=7.024; p=0.135; rho=-0.164; p=0.080). Yet, the frequency of intravenous cannula exchange had an effect of reducing adverse events (χ^2=9.828; p=0.043; rho=-0.204; p=0.029).

Monitoring of daily food intake in patients fed artificially showed a significant impact on the prevention of risk situations (χ^2=9.832; p=0.043; rho=0.208; p=0.026). This result should be taken with caution given the small number of respondents (only one) who answered that they did not monitor daily food intake.

DISCUSSION

Adverse events can occur even in the ideal working conditions. They also often occur in patients who are not assessed as being at risk and where we do not expect adverse events. They prolong hospital stay and increase the cost of treatment, often cause physical pain, and worsen mental health and quality of life of patients. It is necessary to perform all preventive procedures in order to reduce the risk of an adverse event to minimum and to record everything that has been done (8, 13).

The nurse has always been an advocate for the rights of the patient and it is she/he who takes care to provide the patient with appropriate care. Patient safety is the basis of quality health care and quality of care. Ensuring quality health care requires daily effort to provide a service according to professional standards and to approach each patient individually. Our study has shown that risk management in clinical health care is very important and that most respondents use all mechanisms to prevent this risk (14).

Most of the respondents stated that in their practice they carried out categorization of patients for health care and use scales to assess falls and pressure ulcers. The respondents stated that they used Morse scale to assess patient fall, and Norton and Braden scales for pressure ulcers. The largest number of respondents performed assessment using risk assessment scales (n=65, 56.5%), followed by examination of the patient including general inspection and direct inspection (n=48, 41.7%), whereas only two (1.7%) respondents did not perform risk assessment.

The way the nurses perform risk assessment in health care did not show a statistically significant impact on the prevention of risk situations or the occurrence of adverse events that have detrimental consequences for the patient.

A study on patient safety in the hospital conducted at the Šibenik General Hospital in 2015 included 90 nurses/medical technicians. A survey questionnaire was used for the research, and the results obtained indicated that the largest number of nurses rated patient safety at their work place with a very high grade (very good and excellent). The responses received from the surveyed nurses largely contained very satisfactory results in terms of adherence to protocols, availability of information, reporting of possible errors, as well as discussions on their prevention. When it comes to the quality of health care, and thus patient safety, pressure ulcers and patient decline are monitored.

Retrospective analysis of data obtained in the study conducted at Dubrovnik General Hospital from January 1, 2016 to December 31, 2016 confirmed the use of Braden scale, which estimates the risk of pressure ulcers, and which is recorded in the patient categorization program and in the pressure ulcer program. The results obtained by the research indicate that an adverse event in the health care process was pressure ulcer with a higher incidence in men as compared with women (61% *vs*. 39%). Analysis of data related to decline as an adverse event in the health care process and related to the method of admission, the frequency was slightly higher in patients admitted as an emergency than in those admitted through elective admissions (57.69% *vs*. 42.3%) (15).

The research conducted by Ovčina *et al*. at the Sarajevo University Clinical Center (SUCC) in the period from January 1, 2016 until December 31, 2018 showed the prevalence of nosocomial infections in hospitalized patients to have decreased following the study period. The regularity of registration in SUCC is 90%. The highest prevalence of isolates was, as expected, in the intensive care unit of the Department of Anesthesia and Resuscitation, where *Acinetobacter baumannii* significantly predominated in 2016. With the introduction of standardized quality documents, guidelines and algorithms for the prevention of nosocomial infections, this number decreased during 2017 by 60%, which is a special indicator of the quality of health services. Guidelines are based on scientific evidence and good medical practice have been introduced in the hospital. Good results were achieved by performing oral hygiene at least 2 times a day, placing the patient in a semi-sitting position, regular daily bathing with an iodine brush for surgical hand washing (10% iodine solution), and surveillance of clinical nutrition.

In 2016, 38 falls of patients were reported in SUCC, which did not result in permanent harm to the patient. Analysis of the incidents identified the risks of fall in the hospital and active steps were taken to prevent falls. Working groups in cooperation with the Department of Quality and Safety of Health Services created standardized quality documents that assess the risk of falls, improved the environment in patient rooms and strengthened supervision. In this way, the number of falls was reduced by 10 in 2017, in 2018 the total number of falls was 19, whereas in 2019 falls were recorded in 34 patients. Analysis of the reported falls showed that they occurred in less mobile patients, due to poor assessment by the patient him/herself, after getting out of bed, when going to the toilet, etc.

During the 2016-2019 period, the number of reported pressure ulcers in hospitalized patients was not worrying, if we look at the low rate of patients with confirmed pressure ulcers of 0.3% in 2016, with a si-

gnificant downward trend in 2017 and 2018 (0.03% and 0.08%, respectively), whereas in 2019 the rate was 0.25%-0.3%. Since a significant number of admitted patients requiring progressive health care was recorded and there was an insufficient number of workers in the health care process, the number of reported pressure ulcers in the hospital was rather small, i.e. 3 in 2016, 2 in 2017, 6 in 2018 and 14 in 2019. Generally, there was a significant number of pressure ulcers in patients hospitalized from home care or nursing homes. Pressure ulcers were most often recorded at Department of Neurology, Department of Cardiovascular Diseases and Rheumatism, and Department of Anesthesia and Resuscitation, Intensive Care and Therapy (16).

A study conducted by Hodak in 2016 at Osijek University Hospital Centre, which included opinions of 100 nurses/medical technicians on adverse events including pressure ulcers, declining patients, nosocomial infections, poor hand hygiene, and adverse drug side effects showed that nurses/medical technicians were active in improving safety culture (82%) and rated it as acceptable (57.1%). The results showed that highly educated nurses/medical technicians and bachelors were more likely to report adverse events (45.9%) and worked longer to provide the patient with the best care (61.7%). Nurses/medical technicians were active in improving the culture of patient safety (82%) and assessed it as acceptable (57.1%). Nurses/medical technicians agreed that they did not have enough staff to work, and only 50% of respondents agreed that the system was good in preventing adverse events. Most respondents (74.2%) felt reporting of an adverse event as a personal report rather than an event report as a difficulty in work. The majority of respondents agreed that they helped each other (86%) and treated each other with respect (47%). Only 40% of respondents agreed with the statement that hospital administration promoted the culture of patient safety (17).

A similar study was conducted in California in 232 acute hospitals. The study included adverse events including patient fall/injury, pressure ulcers, adverse drug side effects, and nosocomial infections. A multi-level analysis investigated the impact of nurses and patients and hospital characteristics on patient care outcomes. The results showed that patients experienced adverse events during hospital stay, necessitating reduction in adverse events in the health care system. Having appropriate nursing care was crucial in the context of some cases (18).

CONCLUSIONS

1. Results of our study indicate that risk management in everyday nursing clinical practice contributes to strengthening the organizational culture, which shows a significant impact of adopted policies and procedures on reducing the number of risk events.
2. The use of clinical scales and tests reduces the risk of adverse events in practice as shown by the reduction in the number of risk events in cases of using patient categorization, use of fall risk assessment scales and pressure ulcer risk assessment scales.
3. Reporting of adverse events in practice is related to the establishment of standardized quality documents that prevent events and possible errors as shown in this study with the use of scales for risk assessment and categorization of patients in relation to the need for health care.

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SAŽETAK

MENADŽMENT RIZIKA U PROCESU KLINIČKE ZDRAVSTVENE NJEGE

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Upravljanje rizicima u procesu sestrinske kliničke prakse je sistematičan proces koji zahtijeva stručnost i vještine u prevenciji nastanka rizika. Sigurnost bolesnika u bolnici je primarni cilj svakog pojedinca koji pruža zdravstvenu uslugu, a istodobno i same organizacije. U skladu s time neophodno je razviti strategije kojima će rizici u bolnici biti svedeni na minimum i kojima će se uspješno riješiti neželjeni događaji u praksi. Glavna hipoteza rada bila je da upravljanje rizicima u procesu zdravstvene njege ima pozitivan utjecaj na kvalitetu i sigurnost zdravstvenih usluga. Ciljevi rada bili su: 1. Utvrditi najčešće rizike koji se prijavljuju u procesu zdravstvene njege; 2. Ispitati načine i modele prevencije rizika u procesu zdravstvene njege u bolnicama; 3. Ispitati praksu i stav medicinskih sestara u procesu upravljanja rizicima i neželjenim događajima. Istraživanje je provedeno među 115 medicinskih sestara-tehničara zaposlenih u javnim zdravstvenim ustanovama, bolnicama u FBiH. U istraživanju je primijenjen originalni autorski anketni upitnik pripremljen u elektroničkom programu Google forms koji je ispitanicima bio dostupan putem osobne adrese e-pošte, a na njega su odgovarali potpuno samostalno bez utjecaja druge osobe. Usporedba rizičnih događaja u praksi pokazuje statistički značajno smanjenje u odnosu na stariju dob ispitanika (rho=-0,274; p=0,003), duži radni staž ispitanika (rho=-0,334; p=0,0001), višu stručnu spremu ispitanika (rho=-0,198; p=0,034), provođenje kategorizacije bolesnika (ro=-0,289; p=0,002), usvojene politike i postupke (rho=-0,408; p=0,0001). Na smanjenje broja neželjenih događaja za bolesnika statistički značajan utjecaj pokazali su: učestalost pregleda kože i sluznica bolesnika za vrijeme hospitalizacije (rho=-0,200; p=0,032), uporaba ljestvica za procjenu rizika od pada (rho=-0,422; p=0,0001), uporaba ljestvica za procjenu rizika za nastanak dekubitusa (rho=-0,375; p=0,0001), učestalost promjene intravenske kanile (ro=-0,204; p=0,029), učestalost kupanja bolesnika (rho=-0,355; p=0,0001) i način nutritivne procjene bolesnika koji se hrane umjetnim putem (rho=-0,327; p=0,0001). U zaključku, sigurnost bolesnika u bolnici treba biti na prvom mjestu, a od medicinskih sestara koje najviše vremena provode uz bolesnike očekuje se osiguranje uvjeta za siguran smještaj u bolničkom prostoru, uvjeta za sigurnu i kvalitetnu uslugu u procesu zdravstvene njege te primjenu standardiziranih postupaka osnovanih na znanstvenim dokazima i dokazima iz prakse. Kontinuirano izvještavanje o indikatorima kvalitete u procesu zdravstvene njege doprinosi jačanju organizacijske kulture, prevenciji rizika i neželjenih događaja te planiranju kadrova i opreme neophodne za kvalitetu procesa zdravstvene njege.

Ključne riječi: rizici, upravljanje, sestrinska praksa, zdravstvena njega, bolnice, neželjeni događaji

USING POLYETHYLENE GLYCOL PRECIPITATION TO CONFIRM MACROAMYLASEMIA

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To the Editor,

In the 2017 winter issue of Acta Medica Croatica, we published a case report with review of literature entitled Diagnosing Macroamylasemia in Unexplained Hyperamylasemia. The paper discussed a case of a young female patient with elevated levels of amylase only in serum without related symptoms (1). After excluding other causes, taking into consideration medical history, physical examination, and routine laboratory testing, we suspected and subsequently confirmed macroamylasemia with a formula, the only method available to us at the time working in general practice (1). As mentioned in our article, macroamylasemia is a benign condition where macroamylase complexes form with immunoglobulins, which cannot be normally secreted by the kidneys, leading to falsely elevated serum levels, possibly creating confusion among unaware clinicians (1). Although the formula we used is an acceptable method to confirm macroamylasemia, electrophoresis is considered a definite confirmation, resulting in a smeared band instead of defined bands of amylase subtypes (salivary and pancreatic) (1). This test is not routinely used in Croatia, and unfortunately, we could not confirm macroamylasemia in our patient with this test at the time (1).

Upon moving from general practice to hospital, we have become more aware of a routine test done for a similar but much more common condition, hyperprolactinemia. As prolactin commonly forms macrohormone complexes, macroprolactin presence in hyperprolactinemia is routinely tested using polyethylene glycol (PEG) precipitation. This test can also be used to confirm macroamylasemia, stipulated in our original paper as well, alongside the formula and electrophoresis (1). With this test in mind having the opportunity to invite our original patient presenting herself, the patient voluntarily came in for the PEG precipitation test to further confirm, or we could say, more definitely confirm her condition of macroamylasemia. The test was performed using the method by Levitt and Ellis (2). PEG precipitable activity (PPA) was subsequently calculated with the formula %PPA = ((activity blank x activity PEG)/activity blank) x 100, and a cut-off value of 60% was used, according to Davidson and Watson (2,3). The test result was positive for macroamylasemia, confirming our previous suspicion and calculation.

Considering our previous experience with macroenzymes, in particular our patient with macroamylasemia, and our further work with macroenzymes, a small study determining macroenzyme, that is, macro-aspartate (AST) and alanine transferase (ALT) prevalence in rheumatoid arthritis patients, and its effect on further diagnostics and treatment, of which preliminary results were presented at the 23rd IFCC/EFLM European Congress of Clinical Chemistry and Laboratory Medicine in May 2019 (4), the concept of macroenzymes and their detection using the PEG precipitation test was presented to internists, that is, gastroenterologists, in our centre, which was positively received as some of the doctors noted following up patients with elevated serum amylase without an underlying cause. Since then, the test has been in-

troduced into the repertoire of the laboratory, as it is simple and inexpensive, and already routinely done for the detection of macroprolactin, and gastroenterologists have been requesting the test for patients with unclear elevated serum amylase as a differential diagnosis. Although it is unclear how the availability of the test will influence the management of patients with hyperamylasemia, if it will save resources and time by avoiding other diagnostics, it is hoped that, if nothing else, it will diagnose some patients with previously unexplained hyperamylasemia.

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Table of Contents

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