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THE RELATIONSHIP BETWEEN BODY MASS INDEX AND ESTIMATED GLOMERULAR FILTRATION RATE

Marija Klačar, Marija Zarić, Jagoda Popović

DOM ZDRAVLJA „DR SIMO MILOŠEVIĆ", POŽEŠKA 82, BEOGRAD, SRBIJA

Abstract: INTRODUCTION: The increasing prevalence of chronic kidney disease (CKD) is a major health problem. The prevalence of obesity has also been rapidly increasing worldwide. Few studies have examined the relationship between excess body weight and CKD risk. Aim: To evaluate the possible contribution of increased body mass index (BMI) to impaired renal function in the general population sample. **METHODS:** The study involved 500 participants older than 30 years (228 men, 272 women, age 57.58±13.68) who visited their general practitioner in Health Center „Dr Simo Milosevic". Blood samples, blood pressure anthropometric measures were performed on each participant. Estimated glomerular filtration rate was calculated using the abbreviated equation from MDRD study ("The Modification of Diet in Renal Disease Study") and CKD was defined as eGFR less than 60 ml/min/1.73m^2. Statistical analysis was performed using SPSS 19.0 software (IBM, Somers, New York, USA). **RESULTS:** The mean BMI was 25.09±3.54 kg/m2with 0.6% in underweight (BMI<18.5 kg/m2), 17.6% in lower normal (BMI 18.5 to 21.9 kg/m^2), 33.2% in upper normal (BMI 22.0 to 24.9 kg/m^2) and 48.6% in overweight or obese (BMI>25.0 kg/m^2) body mass category. The mean eGFR was 100.33±30.78 ml/min/1.73m^2 with 112±8.62 in underweight, 116.94±3.8 in lower normal, 102.37±2.39 in upper normal and 92.78±1.72 in overweight or obese category. Estimated GFR values decreased significantly with increasing BMI specially in those in upper normal compared to lower normal ($p<0.001$) and overweight and obese compared to lower normal body mass category ($p<0.001$). Compared with participants with lower normal body mass, the non-adjusted odds ratio (OR) for mildly or moderately reduced renal function (eGFR<90 ml/min/1.73m^2) was 2.54 (95% CI 1.41-4.56) for upper normal and 3.26 (95% CI 1.88-5.70) for overweight and obese participants. After adjusting for potential confounding variables (age, sex, diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia and smoking status) OR for mildly or moderately reduced renal function was 2.23 (95% CI 1.21-4.10) for upper normal 2.65 (95% CI 1.44-4.87) for overweight or obese participants compared to those in lower normal body mass category. **CONCLUSION:** Estimated GFR values decreased significantly with increasing BMI specially in those in upper normal compared to lower normal ($p<0.001$) and overweight and obese compared to lower normal body mass category ($p<0.001$). This study showed that increasing BMI is strongly associated with decreasing eGFR in the general population. The underlying mechanism behind this association remains to be investigated through prospective population- based studies.

Key words: body mass index, estimated glomerular filtration rate, chronic kidney disease, renal function, general population

INTRODUCTION

Chronic kidney disease (CKD) is a global health problem and represents a big economic burden for health systems. Global prevalence of CKD lies between 11 and 13% with the third stadium having the largest share. All CKC stadiums are related to the increased risk for cardiovascular morbidity, early death and/or poorer quality of life [1].

The prevalence of obesity has also been rapidly increasing worldwide so much that obesity acquired the proportions of a global epidemic of chronic noncommunicable disease of the 21st century. The prevalence of obesity (body mass index ≥30 kg/m^2) almost doubled in the period between 1980 and 2008. In 1980 5% of men and 8% of women were obese while in 2008 it was 10% of men and 14% of women which makes more than half a billion people [2]. If this secular trend continues it is estimated that by 2030 38% of adult world population will be overweight while 20% will be obese [3].

Overweight and obesity have adverse metabolic effects on blood pressure, leading to

hypercholesterolaemia, hypertriglyceridaemia and insulin resistance. Coronary disease risk, ischemic stroke and diabetes mellitus type 2 increases proportionally with the increase of BMI. Increased BMI also increases the risk of developing breast, colon, prostate, endometrial, kidney and gallbladder cancers [4].

All over the world at least 2.8 million people die each year from overweight and obesity [2].

Obesity is a big risk factor for the development of a renal disease. It increases the risk for the development of ''major'' risk factors for CKD such as diabetes and hypertension and has a direct impact on the development of CKD and terminal renal insufficiency [5].

Purpose of the study is examination of possible contribution of increased body mass index (BMI) to the impaired renal function in the general population sample.The hypothesis that the increased BMI is associated with glomerular filtration rate decrease was tested. According to our knowledge, this is the first study which examined the correlation between body mass index and glomerular filtration rate in these regions in the population sample in primary health care.

MATERIAL AND METHOD

The study was conducted as an observational analytical cross sectional study. The study involved participants older than 30 years who visited their general practitioner in Health Center 'Dr Simo Milošević'. Data collection was completed a month after the sample of 500 participants was formed. Blood samples, blood pressure and anthropometric measures were performed on each participant. Laboratory measurements involved determining of glucose, urea, creatinine, total cholesterol and triglyceride concentrations and were performed on each of the participants. Blood pressure was measured on the left upper arm in a sitting position. Body mass and height were measured in the office and BMI was calculated as the quotient of body mass expressed in kilograms and square height expressed in meters. Based on the BMI values, the participants were classified into the categories shown in Table 1 [6].

Table 1. BMI categorization

Category	BMI (kg/m2)
malnutrition	<18,5
lower normal body mass index	18,5 - 21,9
upper normal body mass index	22,0- 24,9
overweight	25,0 do 29,9
obesity	> 30

Participants stated whether they were non-smokers, former or active smokers. Glomerular filtration rate was determined using the shortened formula from "The Modification of Diet in Renal Disease Study" [7].

$$\mathrm{eGFR} = 32788 \times \mathrm{Serum\ Creatinine}^{-1.154} \times \mathrm{Age}^{-0.203} \times [1.210\ if\ Black] \times [0.742\ if\ Female]$$

Stadiums of renal insufficiency were given in the table 2 [8].

Table 2. Classification of chronic kidney disease

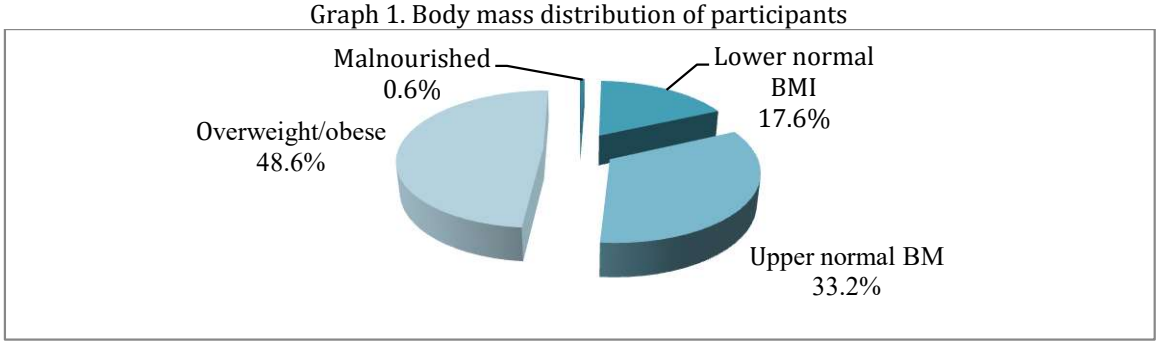
Stadium	GFR	Description
1	>90	Normal renal function but pathological urine findings or structural abnormalities or genetic traits indicate kidney disease
2	60-89	Slightly reduced renal function and other findings (as for stadium 1) indicate renal disease
3A **3B**	45-59 30-44	Moderately reduced renal function
4	15-29	Seriously reduced renal function
5	<15 ordialysis	Very severe renal impairment or end-stage renal insufficiency

CKD is defined as GFR less than 60 ml/min/1.73m^2. SPSS 19.0 software (IBM, Somers, New York, USA) was used to create the database and analyze it. For testing of correlation between body mass index and glomerular filtration ratewith adjusting in relation to the associated variable logistical regression was used. The level of significance was 0.05.

RESULTS

The study involved 500 participants, 228 (45.6%) men and 272 (54.4%) women. BMI mean value was 25.09±3,54 kg/m^2 with 0.6% participants in the category of malnourished (ITM<18.5 kg/m^2), 17.6% in the group of body mass in the range of lower normal (BMI 18.5 up to 21.9 kg/m^2), 33.2% in the group with upper normal body mass (BMI from 22.0 to 24.9 kg/m^2) and 48.6% in the group of overweight or obese (ITM>25.0 kg/m^2) .

Graph 1. Body mass distribution of participants



GFR mean value was 100.33 ± 30.78 ml/min/1.73m^2. GFR mean values in categories according to BMI are presented in table 3.

Table 3. eGFR in BMI categories

BMI categories	GFR (ml/min/1.73m^2)
Malnourished	112±8.62
Lower normal	116.94±3.8
Upper normal	102.37±2.39
Overweight and obese	92.78±1.72

GFR considerably decreased with the increase of the BMI values particularly in the category of overweight and obese participants compared to the participants with lower normal body, (p<0.001) as well as in the group with upper normal body mass compared to the group of lower normal body mass (p<0.001). In comparison to the participants in the group with lower normal body mass, the non-adjusted odds ratio (OR) for mild or moderately reduced renal function (GFR<90 ml/min/1.73m^2) was 2.54 (95% CI 1.41-4.56) for participants with upper normal body mass and 3.26 (95% CI 1.88-5.70) for participants in the group of overweight and obese.

After adjustment in relation to potential contributing factors (age, gender, diabetes mellitus, hypertension, hypercholesterolaemia, hypertriglyceridemia and smoking status) OR for mild or moderately reduced renal function was 2.23 (95% CI 1.21-4.10) in the group with upper normal body weight while it was 2.65 (95% CI 1.44-4.87) in the category of overweight and obese participants compared to those in the category with lower normal body mass.

DISCUSSION

Several previous studies pointed to the significance of the increased body mass index in the development of chronic renal disease. A cross-sectional study conducted in general population in Japan showed that the increased BMI is associated with the decrease of GFR only in men [9]. In the study conducted by Fox et al. ORfor the development of new CKD was 23% (OR, 1.23; 95% CI, 1.08–1.41) for the BMI increase by one SD [10]. Gelber et al. showed that the initial increased BMI as well as its increase during the follow-up period of 14 years is associated with increased risk from CKD [11].

Other studies that examined the relationship between obesity and CKD are presented in table 4.

Table 4. Studies that examined the association between obesity and chronic kidney disease

Study	Participants	Risk factors	Outcome	Results	Comment
PREVEND study [12]	7676 Danish people without diabetes	Increased BMI (overweight orobesity) and central distribution of fat (waist / hip circumference ratio)	Albuminuria 30-300 mg/24h increased or decreased GFR	Obesity + central distribution:higher risk for albuminuria Obesity +/-central distribution: higher risk for increased GFR Central distribution +/- obesity associated with decreased GFR	Cross-sectional study
CARDIA [13]	2 354 people from general population with normal renal function aged 28-40	Obesity (ITM>30 kg/m^2) Risk factors associated with nutrition and the way of life	Incidental microalbuminuria	Obesity (OR 1.9)and unhealthy diet (OR 2.0) are associated with albuminuria	Low-frequency
National population study in Sweden [14]	926 Swedish people with mild/advanced CKD compared to 988 control	BMI ≥ 25 against<25 kg/m^2	CKD against absence of CKD	Higher BMI associated with 3x higher risk from CKD	- The greatest risk lies with diabetic participants but it is also significantly increased in the nondiabetic participants - Cross-sectional study
National population study in Israel [15]	1 194 704 male and female adolescents,candidates for joining the Army	Increased BMI (overweight and obesity) compared to normal BMI	Incidence of terminal CKD	Overweight and obesity associated with higher risk for terminal CKD	Strongest correlation for diabetic CKDbut also significantly higher for nondiabetic CKD
Nord-Trøndelag Health Study (HUNT-1)[16]	74 986 of adult Norwegian people	BMI categories	Incidence of terminal renal insufficiency or renal death	BMI > 30 kg/m^2 associated with more unfavorable outcome	Correlation not present in participants with TA (?)<120/80 mmHg
National cohort of American veterans [17]	453 946 veterans with the initial GFR< 60 ml/min/1,73 m^2	BMI categories from < 20 to>50 kg/m^2	Incidence of tCKD Doubling of serum creatinine Decrease of GFR	Mild and severe overweight are associated with major kidney impairment	Correlation present but weaker in participants with advanced CKD
Kaiser Permanente Northern California study [18]	320 252 adults with/without CKD	Overweight, categories I, II and extreme obesity compared to normal BMI	Incidence of terminal renal disease	Linearly higher risk in higher BMI categories	Correlation still exists after adjustment for the presence of diabetes, hypertension, and initial CKD

Most studies showed existence of a higher risk for CKD in participants with the BMI which is equal to or greater than 25 kg/m^2 while results of our study show increased risk for mild and moderately impaired renal function in the group of participants with upper normal body mass (BMI 22.0 to 24.9 kg/m^2) as well as in the category of overweight and obese (BMI≥25 kg/m^2) compared to the participants from the category of lower normal body mass.

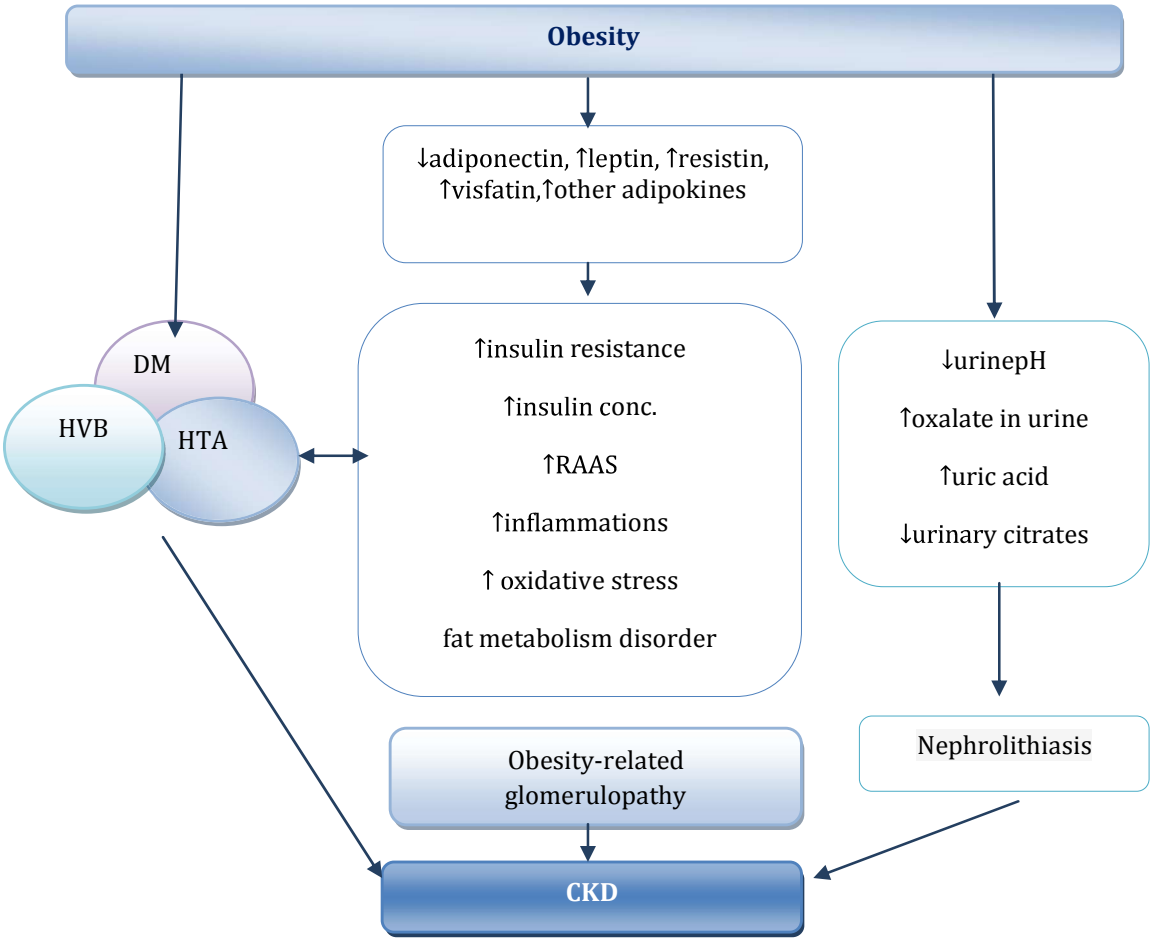
The exact mechanism of contribution of obesity to the development or worsening of CKD

is still insufficiently known. In support of the claim that obesity itself is not responsible for the development of CKD is the fact that most obese people never develop CKD and as many as 25% of obese people do not have metabolic disorders [19]. However, the frequency of so-called glomerulopathy associated with obesity (obesity-related glomerulopathy) which in the observational studies was proven to affect the development of CKD increased by 10 times in the period from 1986 to the year 2000 [20]. Adipose tissue has its endocrine function through the production of adiponectin [21], leptin [22], resistin [23] and numerous other mediators which leads to oxidative stress [24], inflammation [25], insulin resistance [26], RAAS activation [27] and impaired fat metabolism [28]. The effect of the above on the kidneys is reflected through ectopic fat accumulation and increased fat deposition in the renal sinuses [29], development of glomerular hypertension as well as hyperfiltration with consequent damage to the glomerular basement membrane and increased permeability resulting in glomerulomegaly and focal segmental glomerulosclerosis [20].

Obesity is also associated with increased risk for nephrolithiasis. Higher body weight is associated with lower urine pH [30] and increased oxalate excretion [31], uric acid, sodium and phosphate [32]. A diet with a lot of proteins and salt decreases urine pHand citrate concentration, which contributes to the formation of stone. Also, through effects on tubular Na-H transporter and ammoniogenesis, insulin residence may contribute to urinary acidity favouring nephrolithiasis [33].

Apart from obesity having a direct impact to kidneys in pathophysiology of CKD, traditional risk factors such as diabetes mellitus, arterial hypertension and chronic vascular diseases proven to be more frequent in obese persons play a major role here.

Figure 1. Assumed mechanisms of the role of obesity in the development of chronic kidney disease



CONCLUSION

Estimated GFR values decreased significantly with increasing BMI specially in those in upper normal compared to lower normal ($p<0.001$) and overweight and obese compared to lower normal weight category ($p<0.001$). This study showed that increasing BMI is strongly associated with decreasing eGFR in the general population. The underlying mechanism behind this association remains to be investigated through prospective population - based studies.

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Vol. 45 (2020) No. 4 TIMOK MEDICAL GAZETTE Original papers

INFLUENCE OF SOCIO-DEMOGRAPHIC FACTORS AND LENGTH OF DISEASE ON ADHERENCE OF PATIENTS WITH ARTERIAL HYPERTENSION

Marijana C. Jandrić-Kočič (1), Snežana B. Knežević (2)

(1) DOM ZDRAVLJA KRUPA NA UNI; (2) DOM ZDRAVLJA KRALJEVO

Summary: INTRODUCTION: The World Health Organization defines patient adherence as the willingness to adapt its behavior (in terms of therapy, diet, lifestyle, and diagnostic procedures) to the recommendations agreed with the healthcare provider. Objective. The study aimed to determine the impact of socio-demographic factors and length of elevated blood pressure on the adherence of patients with arterial hypertension. **METHOD:** The study was performed as a cross-sectional study. The sample consisted of 170 patients, 88 (51.8%) women and 82 (48.2%) men, with a mean age of 58 ± 7.9 years. In addition to the general questionnaire, the study used the Adherence in Chronic Diseases Scale. **RESULTS:** Statistically significantly higher adherence was found in subjects aged 60-69 years and participants in the study with arterial hypertension for more than 15 years ($p<0.05$). Subjects with completed primary school had statistically significantly lower adherence ($p<0.05$). Place of residence, employment status and gender of the respondents did not show a statistically significant influence on the adherence of the respondents (NS). **CONCLUSION**: It uses the age, educational status and duration of arterial hypertension in the adherence of examination statistics. Place of residence, employee status and gender of respondents do not show a statistically significant impact.

Keywords. Hypertension, patient s adherence, cooperation, medical doctor.

INTRODUCTION

Arterial hypertension is one of the leading causes of death in the world (5 - 13% of global mortality). Suboptimal blood pressure control due to poor adherence is cited as the main reason for high mortality [1,2,3]. The World Health Organization (WHO) defines patient adherence as the willingness to adjust their behavior (in terms of respect for therapy, diet, lifestyle and implementation of diagnostic procedures) to the agreed recommendations of the health worker [1,4,5]. On the other hand, poor adherence implies refusal or inadequate use of medications, unadapted lifestyle or diet, refusal or inadequate implementation of diagnostic procedures. Poor adherence can be primary (the patient is unable to meet the agreed recommendations) and secondary (there is an intention not to follow the agreed recommendations or they are inadvertently violated due to demographic, social, psychological or clinical variables) [1,4,5]. Patient adherence is negatively affected by: treatment complexity, drug side effects, imbalance between established medical guidelines and own beliefs, poor patient-physician communication, patient dissatisfaction with health system, socioeconomic factors, socio-demographic factors, high treatment costs, and lack of medical insurance [3]. The absence of manifest symptoms in the initial phase of the disease, younger age and low level of education were identified as the most constant etiological factors.

A large number of studies indicate the ubiquitous poor adherence of patients with arterial hypertension. It is estimated that one third of patients are fully compliant with the recommended treatment, another third sometimes in compliance, while a last third is never compliant with the recommended treatment. Suboptimal blood pressure control due to poor adherence leads to 54% of cerebrovascular incidents and 47% of ischemic heart disease. Adherence can be assessed in two ways, in direct contact with patients or by reviewing medical records. Interventions to improve adherence include supportive measures, reviewing drug needs, and improving communication with the patient [1,4,5,6,7,8].

OBJECTIVE

The study aimed to assess the influence of socio-demographic factors and the duration of

high blood pressure on the adherence of patients with arterial hypertension.

METHOD

The research was performed as a cross-sectional study in a period of seventeen months, from 02/01/2019. to 07/01/2020. The study sample consisted of 170 individuals, heterogeneous socio-demographic and health characteristics selected by random selection. Criteria for inclusion of respondents in the study were: arterial hypertension for at least twelve months, age between 40 and 69 years, completed primary school. Excluded from the study were: people over 69 and under 40, with arterial hypertension lasting less than twelve months. Data were collected through a general and specific questionnaire. The general questionnaire collected socio-demographic data (age, gender, place of residence, level of education, employment status).

The Adherence in Chronic Diseases Scale (ACDS) was developed by a group of authors from Poland with the aim of assessing the adherence of patients with chronic diseases. It consists of 7 questions, ie five questions about adherence and two questions about doctor-patient communication. To each question, respondents have five offered answers that are scored with a score of 0-4. The total score <21 corresponds to low adherence, while the score 21-26 speaks in favor of moderate adherence. A score> 26 confirms the high adherence of the respondents [9,10]. Descriptive statistical methods were used for data analysis: arithmetic mean, standard deviation and percentages. An x^2-independence test was used to determine statistical significance. The significance level is set to 95% confidence interval. The results are presented textually, tabularly and graphically.

RESULTS

The study included 170 respondents. Among them were 88 (51.8%) women and 82 (48.2%) men. The largest number of participants in the study was aged 60-69 years, 72 (42.4%) respondents. The mean age of the study population was 58 ± 7.9 years. 84 (49.4%) participants in the research lived in the village, and 86 (50.6%) in the city. 17 (10.0%) respondents completed primary school, 108 (63.5%) secondary school. There were 45 (26.5%) respondents with a university degree. 81 (47.6%) respondents were employed, 89 (52.4%) were unemployed (Table 1).

Table 1. Socio-demographic characteristics of research participants

Characteristics		N (%)
Gender	Men	82 (48.2%)
	Women	88 (51.8%)
Age (years)	40 - 49	40 (23.5%)
	50 - 59	58 (34.1%)
	60 - 69	72 (42.4%)
Living place	Village	84 (49.4%)
	City	86 (50.6%)
Level of education	Primary school	17 (10.0%)
	High school	108 (63.5%)
	College	45 (26.5%)
Employment status	Employed	81 (47.6%)
	Unemployed	89 (52.4%)

35 (20.6%) subjects had arterial hypertension for 1 - 5 years, and 30 (17.7%) for 6-10 years. Arterial hypertension lasting 11 - 14 years was found in 40 (23.5%) respondents. The largest number of participants in the study had arterial hypertension lasting over 15 years, 65 of them (38.2%). Low adherence was verified in 40 (23.5%) subjects, moderate in 72 (42.4%), while 58 subjects (34.1%) had high adherence.

High adherence was found in 22 (26.8%) men and 36 (40.9%) women. The sex of the participants in the study did not have a statistically significant effect on adherence (p=0.06). 2 (5.0%) subjects aged 40-49 years, 9 (15.5%) subjects aged 50-59 years and 47

(65.3%) subjects aged 60-69 years had high adherence. Statistically significantly higher adherence was found in participants in the study aged 60-69 years (p<0.05). Strong adherence was confirmed in 23 (27.4%) respondents living in rural areas and 35 (40.7%) respondents residing in the city. The place of residence of the study participants did not have a statistically significant effect on adherence (p=0.08). Only 1 (5.9%) respondents with completed primary school had high adherence. Strong adherence was found in 38 (35.2%) respondents with a high school diploma and 19 (42.2%) respondents with a university degree. Statistically significantly lower adherence was found in participants in the study with completed primary school (p<0.05). High adherence was verified in 32 (39.5%) employed respondents and 26 (29.2%) unemployed respondents. Respondents' employment did not have a statistically significant effect on adherence (p=0.09) (Table 2).

Table 2. Influence of sociodemographic factors on the Adherence in Chronic Diseases Scale index

Characteristics		ACDS score < 21**	ACDS score 21-26***	ACDS score >26***	p value*
Gender	Men	18 (22.0%)	42 (51.2%)	22 (26.8%)	NS, 0.06
	Women	22 (25.0%)	30 (34.1%)	36 (40.9%)	
Age (years)	40-49	19 (47.5%)	19 (47.5%)	2 (5.0%)	p < 0.05
	50-59	19 (32.8%)	30 (51.7%)	9 (15.5%)	
	60-69	2 (2.8%)	23 (31.9%)	47 (65.3%)	
Living place	Village	23 (27.4%)	38 (45.2%)	23 (27.4%)	NS, 0.08
	City	17 (19.8%)	34 (39.5%)	35 (40.7%)	
Level of education	Primary school	12 (70.6%)	4 (23.5%)	1 (5.9%)	p < 0.05
	High school	20 (18.5%)	50 (46.3%)	38 (35.2%)	
	College	8 (17.8%)	18 (40.0%)	19 (42.2%)	
Employment status	Employed	15 (18.5%)	34 (42.0%)	32 (39.5%)	NS, 0.09
	Unemployed	25 (28.1%)	38 (42.7%)	26 (29.2%)	

According to hi square test or Fisher test; Low adherence; ***Intermediate adherence; ****High adherence.

High adherence was found in 3 (8.6%) subjects with arterial hypertension for 1 - 5 years, 5 (16.7%) subjects with arterial hypertension for 6 - 10 years, 6 (15.0%) subjects with arterial hypertension for 11 - 15 years and 44 (67.7%) subjects with arterial hypertension for> 15 years. Statistically significantly higher adherence was found in participants in the study with arterial hypertension for more than 15 years (p<0.05) (Table 3).

Table 3. Influence of duration of arterial hypertension on subjects adherence to Adherence in Chronic Diseases Scale index

Duration of arterial hypertension (years)	ACDS score < 21**	ACDS score 21-26***	ACDS score >26****	p value*
1-5	20 (57.1%)	12 (34.3%)	3 (8.6%)	p < 0.05
6-10	10 (33.3%)	15 (50.0%)	5 (16.7%)	
11-15	8 (20.0%)	26 (65.0%)	6 (15.0%)	
> 15	2 (3.1%)	19 (29.2%)	44 (67.7%)	

According to hi square test or Fisher test; Low adherence; ***Intermediate adherence; ****High adherence.

DISCUSSION

High adherence was detected in 38.3% of study participants. A study by a group of authors from Ethiopia found full adherence in 31.4% of respondents. Similar results were obtained in studies conducted in China 21.3–35.2%, Ghana and Nigeria 33.3%, Kenya 31.8%, Palestine 36.2% and Nepal 35.4%. A slightly more significant percentage of high adherence was verified by studies in Italy 48.6%, Brazil 52.9%, the United Arab Emirates 54.4%, the United States 57.6% and Pakistan 77.0%. A study by a group of authors from Korea verified adequate adherence in 81.7% of respondents. Differences in the availability and quality of health care are cited as a possible reason for

differences in adherence in the mentioned research [3,11,12]. In our study, there was no statistically significant influence of gender on the adherence of the subjects.

A significant number of studies did not identify gender as a statistically significant factor in the adherence of the respondents, but it emphasizes a slightly higher adherence in females. The lack of gender differences in adherence in adolescents is explained by the fact that parents take responsibility for adhering to the therapeutic regimen in this age group. The better adherence observed among young women arises as a consequence of earlier cognitive maturation. The need for social desirability (the desire to meet social expectations) and a better perception of the disease in women may contribute to the observed differences. [13,14]. The study verified a statistically significantly higher adherence in people aged 60-69 years. Numerous studies have identified aging as a statistically significant factor in increasing patient adherence. A middle-aged person often inadvertently violates the therapeutic protocol due to lifestyle factors, social or psychological variables. Elderly patients devote more time to the treatment regimen and use a number of aids such as tablet boxes and a calendar. In addition, older people often have comorbidities and show greater concern for their health. Possible unintentional reduction of adherence in persons over the age of eighty occurs as a consequence of cognitive and physical deficiencies [1,5,15,16].

The research did not detect the existence of a statistically significant influence of place of residence on the adherence of the respondents. A study by a group of authors from Bangladesh found statistically significantly lower adherence in people residing in rural areas. Poor adherence of the rural population occurs as a result of lower socio-economic status, poorer access to health care, lack of specialist services and frequent changes in health care staff [15]. A judge from a group of authors from Australia determined a distance of more than 10 kilometers from the nearest health facility as an independent predilective factor of poor adherence [17].

The study noted the existence of statistically significantly lower adherence in study participants with completed primary school. Studies by a group of authors from Ethiopia, Pakistan, Poland, Ghana and Nigeria have found a negative impact of lower education on the adherence of subjects with arterial hypertension. Low income, unemployment, lack of awareness about the complications of hypertension and the importance of optimal blood pressure control are cited as possible reasons [3,9,10]. A study conducted in Ghana indicates that a low level of education may play an important role in a patient's decision to replace antihypertensive therapy with herbs and spiritual healing [18]. The study noted the existence of statistically significantly higher adherence in respondents who were employed. Studies by a group of authors in Iran found a statistically significant weakening of adherence in unemployed respondents with limited access to medicines. Participants in the low-income study were 18.5 times more likely to have poor adherence than respondents whose incomes were average [3,6]. The study detected a statistically significant increase in adherence with prolonged hypertension. A study conducted in China detected the duration of hypertension for an independent predictor of quality adherence [3]. Prolonged duration of hypertension is often accompanied by comorbidities but also an increase in awareness of the importance of optimal blood pressure control. Research by authors from Ethiopia has determined the negative impact of prolonged hypertension on the adherence of patients [19]. Participants in the study with a duration of hypertension of five or more years were more than five times more likely to have poor adherence compared to subjects in whom hypertension was diagnosed less than two years ago. With the stabilization of blood pressure, a significant number of patients are considered cured. In addition, long-term use of drugs burdens patients and leads to inadequate use or discontinuation of antihypertensive therapy [3,19]. A study by a group of authors from Malaysia did not establish a statistically significant association between the duration of hypertension and adherence [20]. According to the same, problems with adherence occur in the first six months after the introduction of antihypertensive therapy and persist for up to 4 years. At the end of this period, no statistically significant differences in therapeutic adherence were verified [20].

CONCLUSION

Adherence of the subjects was statistically significantly affected by age,

educational status and duration of arterial hypertension. Place of residence, employment status and gender of respondents do not show a statistically significant impact

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METABOLIC SYNDROME IN THE POPULATION OF PSYCHIATRIC PATIENTS IN NOVI SAD

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Summary: OBJECTIVES: The aim of this study is to determine the prevalence of metabolic syndrome (MetS) in a sample of hospitalized patients and to relate it to socio-demographic characteristics, psychiatric diagnosis and psycho-pharmacotherapy. **METHODS:** The study was conceived as a retrospective cohort study. Data of interest for this research were collected from the medical history of hospitalized patients at the Clinic for Psychiatry KCV in the period from January 2018 to January 2020. **RESULTS:** Out of a total of 2409 patients hospitalized at the Psychiatric Clinic, 1327 patients had criteria for metabolic syndrome, with a high prevalence of 55.1% among this population. Although there are more respondents in the sample (55.7%), males with a diagnosis of MetS (58.1%) dominate. The data show that the prevalence of metabolic syndrome increases statistically significantly with the age of psychiatric patients. However, the prevalence of metabolic syndrome in the study population younger than 30 years is about 33%. Among patients with incomplete primary school, 67% have a diagnosis of metabolic syndrome, which is statistically significantly higher than other compulsory profiles ($p < 0.001$). The study sample shows a statistically significantly higher prevalence of metabolic syndrome among patients treated for psychotic disorders, with as much as 67% prevalence. Therapy with atypical antipsychotics was most associated with metabolic syndrome in 67.5% of patients, followed by a combination of 2 or more antipsychotics with 60.7% ($\chi^2=26.99$, $p<0.0019$). Abdominal obesity is the strongest predictor of the response that the subjects will suffer from the metabolic syndrome, the quotient of which is 1.34 by logistic regression. Another important predictor refers to triglyceridemia, whose probability quotient is 1.12. **CONCLUSION:** The prevalence of metabolic syndrome in psychiatric patients in Novi Sad is alarmingly high, in more than half of patients, especially those treated for psychotic and mood disorders and using atypical antipsychotics and combinations of antipsychotics. In a patient with metabolic syndrome there is male dominance, low educational profile and the prevalence increases statistically significantly with increasing age of psychiatric patients

Keywords: Abdominal Obesity, Metabolic Syndrome, Mental disorders

INTRODUCTION

Mass non-communicable diseases are in the first place in terms of morality and morbidity within the general population. In this group of diseases, metabolic diseases such as obesity and diabetes predominate, which are accompanied by an increased risk of cardiovascular and cerebro-vascular incidents, and a consequent fatal outcome. In the population of psychiatric patients, however, it is known that the rate of premature mortality from all causes is far higher than in the general population. Studies have shown that the life expectancy of patients with significant psychiatric disorders is reduced by 7 to 24 years [1,2,3,4]. On the other hand, about 60% of premature deaths of psychiatric patients occur due to somatic illnesses, predominantly due to cardiovascular diseases. The risk of cardiovascular diseases, increased by comorbidities such as diabetes, obesity, stroke, is multiplied in patients with several different psychiatric diseases such as psychotic disorders, mood disorders and anxiety disorders. [1,2,3,4,5].

MetS is defined as a combination of multiple comorbid conditions such as abdominal obesity, high arterial blood pressure, low "good", HDL cholesterol, hypertriglyceridemia and hyperglycemia. MetS is therefore the first step on the so-called. A "metabolic pathway" that ultimately ends in premature death. This concept of MetS is in line with the recommendations of the International Diabetes Federation. The concept of MetS has proven to be the most appropriate universal predictive

factor that allows to select groups with increased risk and to prevent the progression of the "metabolic pathway" by timely medical and nutritional action [6,7].

The prevalence of MetS in the general population is between 10% and 15%, while in the population of psychiatric patients the value is many times higher and ranges from 30% to as much as 60% [8,9,10]. Most of the world's research points to psychotropic therapy as one of the main causes of the multiple incidence of MetS within a group of psychiatric patients [11,12]. Weight gain is often a side effect of a large number of psychotropic drugs. Today it is clear that some drugs used in psychiatry as a side effect disrupt fat and sugar metabolism [13,14].

We did not find studies of the prevalence of MetS in a group of psychiatric patients in Serbia. Therefore, this study was conducted to assess the prevalence of MetS in a sample of patients hospitalized at the Clinic for Psychiatry of the Clinical Center of Vojvodina (KCV) in Novi Sad and linked it to socio-demographic characteristics, psychiatric diagnosis and psycho-pharmacotherapy used in psychiatric patients and to single out possible predictor risk factors for MetS screening.

MATERIAL AND METHODS

The study was designed as a retrospective cohort study. Data of interest for this research were collected from the medical histories of hospitalized patients at the Clinic for Psychiatry KCV in the period from January 2018 to January 2020. Data on 2409 patients were collected. Patients under the age of 18 were not included in the study, as well as those who did not have a primary psychiatric discharge diagnosis according to ICD-10, and those patients for whom there were no complete data from medical histories. Those patients who were treated more than once in the study period were counted only once in the total sample. There were no patients treated for addiction in the sample. Sociodemographic and clinical data are taken from the history of the disease. The primary psychiatric diagnosis was taken from the discharge card according to the code system ICD-10. All diagnoses are grouped into four categories: psychosis (F20-29), mood disorders (F30-34), anxiety disorders (F40), and other mental disorders. The MetS is determined by the criteria envisaged by the agenda of the International Diabetes Federation.

1) Waist circumference values > 102 cm for men and> 88 cm for women,
2) triglyceridemia> > 1,7mmol /L (1.5 mg / ml)
3) HDL cholesterolemia HDL< 1.03 mmol/L (men) or < 1.29 mmol/L (women) (<0.4 mg/ml for men and <0.5 mg/ml for women),
4) arterial blood pressure> 135/85 mmHg,
5) fasting glycemia> 6.1 mmol / l.

If at least three of the above criteria are met, it is considered that there is a diagnosis of MetS. Patients with a history of associated arterial hypertension and diabetes mellitus were also included in the study.

Data on psycho-pharmaceuticals that patients, included in the study, drank were also recorded. Medications are divided into five groups - classic and atypical antipsychotics, antidepressants, mood stabilizers. A large number of patients were not on monopsychopharmacotherapy, so another group was formed where patients who took 2 or more drugs were classified. It is considered that a patient is on therapy with a certain psychopharmaceutical if he has been drinking it for the last 30 days in the prescribed therapeutic dose.

Statistical data processing initially consisted of descriptive variables. Frequencies and proportions were used for their processing, while standard deviations, means and medians were used to represent quantitative variables. The chi square test was used to assess the difference in the prevalence of MetS between the sexes. Comparison of the prevalence of MetS in different diagnoses was performed using the ANOVA (F) test, and in the case of a statistically significant difference, the t and χ^2 test was applied. A binary logical regression model was applied to identify the most important factors for the dichotomous outcome - the presence or absence of MetS in the study group. For all applied statistical tests, the error level was set to an acceptable level of $p < 0.05$. Statistical data processing was done in the computer program SPSS 12.0.

The conduct of such a study was approved by the Ethics Committee of the KCV. The study is conducted according to internationally recognized ethical standards set in the field of biomedical research.

RESULTS

A total of 2409 psychiatric patients participated in the study. The prevalence of MetS among this population is 1327 and 55.1%, respectively.

Table 1. Sociodemographic characteristics

		Metabolic syndrome		Statistical analysis	
	Overall	Yes	No	χ^2	P
Sex					
Male	1068 (44,3%)	621 (58,1%)	447 (41,9%)		
Female	1341 (55,7%)	706 (52,6%)	635 (47,4%)	7,045	0,008
Age					
AS+-SD	46,87±18,09	47,06+-17,97	46,64+-18,24		
< 30 years	953 (39,6%)	321 (33,7%)	632 (66,3%)		
od 31 do 50 years	817 (33,9%)	449 (55,0%)	368 (45,0%)		
> 51 yers	639 (26,5%)	357 (55,9%)	282 (44,1%)	0,230	0,891
Marital status					
Married	527 (21,9)	255 (48,4%)	272 (51,6%)		
Single	752 (31,2%)	467 (62,1,%)	285 (37,9%)		
Divorced	862 (35,8)	427 (49,5%)	435 (50,5%)		
Widowed	268 (11,1%)	178 (66,4%)	90 (33,6%)	49,157	0,000
Number of children					
AS+-SD	1,56±0,60	1,56+-0,61	1,55+-0,60		
None	1205 (50,0%)	660 (54,8%)	545 (45,2%)		
1-3 children	1062 (44,1%)	586 (55,2%)	476 (44,8%)		
> 3 children	142 (5,9%)	81 (57,0%)	61 (43,0%)	0,271	0,873
Educational level					
Illiterate	477 (19,8%)	322 (67,5%)	155 (32,5%)		
Primary/less	629 (26,1%)	344 (54,7%)	285 (45,3%)		
Secundary/less	799 (33,2%)	436 (54,6%)	363 (45,4%)		
University/other	504 (20,9)	225 (44,6%)	279 (55,4%)	57,079	0,000

Note: AS - arithmetic mean, SD - standard deviation, χ^2 - statistical, p - statistical significance

Although there are more female respondents in the sample (55.7%), there are more male respondents with a diagnosis of MetS (58.1%) than women. The average age of the patient is about 47 years. About 40% of the sample consists of respondents younger than 30 years, a third from 30 to 50 years, and a quarter over 50 years of age. In the population of patients younger than 30, one third record the criteria for the diagnosis of MetS. It can be observed that among widows and singles there are more subjects with MetS compared to patients who are married or divorced. On average, respondents have less than two children. In terms of education, one third of respondents have completed secondary school, one fifth do not even have completed primary school, and one in four respondents has only primary school, and about 20% of them have a high school diploma. Among patients with incomplete primary school, almost two thirds of them are diagnosed with MetS. It can be seen that there is a statistically significant correlation between the sex of the subjects and the prevalence of MetS χ^2 (7.045, p=0.008). Men have a relatively higher prevalence of MetS χ^2 (49,157, p=0,000). There is a statistically significant correlation between the level of education of the subjects and the prevalence of MetS χ^2 (52,079, p=0,000.)

Approximately half of the patients included in the study are being treated for psychotic disorders, a third are suffering from mood disorders, and a fifth are suffering from anxiety disorders. The study sample shows a statistically significantly higher prevalence of metabolic syndrome among patients treated for psychotic disorders, with as much as 67% prevalence. Therapy with atypical antipsychotics was most associated with metabolic syndrome in 67.5% of patients, followed by a combination of 2 or more antipsychotics with 60.7% (χ^2=26.99, p <0.0019). The diagnosis of metabolic syndrome is most common in patients

up to 5 years of age and is over 65%. The body mass index averages about 28, but is 10 units higher among the population of subjects who have MetS. The situation is similar when it comes to waist circumference. The average waist circumference among the psychiatric population in the sample was 95 cm, while among subjects with MetS the waist circumference was higher by almost 20 cm compared to those without MetS.

Table 2. Clinical characteristics

		Metabolic Syndrome		**Statistical analisys**	
	Overall	Yes	No	χ^2	p
Psychiatric diagnosis					
Psychotic disorder	1098 (45,6%)	742 (67,5%)	356 (32,5%)		
Mood disorder	806 (33,5%)	429 (53,2%)	377 (46,7%)		
Anxious disorder	454 (23,2%)	142 (31,3%)	312 (68,7%)		
Other mental disorders	51 (2,1%)	19 (37,2%)	32 (62,8%)	181,05	0,000
Psychofarmacs					
Atypical antipsychotic	898 (37,3%)	594 (66,1%)	304 (33,9%)		
Antidepresive	287 (11,9%)	160 (55,7%)	127 (44,3%)		
Clasical antipsychotic	448 (18,6%)	246 (54,9%)	202 (45,1%)		
Mood stabilizator	267 (11,1%)	141 (52,8%)	126 (47,2%)		
Mix of 2 or more psychofarmacs	509 (21,1%)	309 (60,7%)	200 (43,8%)	26,99	0,0019
Bigining og illness (year)					
AS+-SD	26,18±5,46	26,14+-5,37	26,22+-5,57		
< 25	1023 (42,5%)	568 (56,5%)	455 (44,5%)		
25 – 50	1386 (57,5%)	759 (54,8%)	627 (45,2%)	0,138	0,711
Duration of psychiatric disease (years)					
AS+-SD	20,73±16,87	20,97+-16,86	20,45+-16,89		
<=1	504 (20,9%)	206 (41,0%)	298 (59,0%)		
1-5	501 (20,8%)	325 (64,9%)	176 (35,1%)		
6-10	396 (16,4%)	247 (62,5%)	149 (37,5%)		
> 10	1008 (41,8%)	509 (50,5%)	499 (49,5%)	3,653	0,312
Obesity indicators					
BMI	27,82±5,92	32,50+-3,50	22,08+-1,76		
Waist circumference (cm)	94,97±13,82	103,67+-11,90	84,28+-6,65		
Blood pressure					
Systolic (mmHg)	126,37±21,68	126,22+-21,63	126,54+-21,75		
Diastolic (mmHg)	80,72±16,41	80,88+-16,35	80,53+-16,49		
Laboratory tests					
Fasting blood glucose (mmol/L)	5,80±2,61	7,78+-2,62	5,91+-2,60		
Triglycerides (mmol/L)	2,77±1,59	2,75+-1,58	1,79+-1,62		
HDL- Cholesterol (mmol/L)	1,12±0,60	1,00+-0,59	1,23+-0,62		

Note: AS - arithmetic mean, SD - standard deviation, χ^2 - statistical, p - statistical significance

It has been shown that there is a statistically significant difference in BMI values between subjects with MetS and those who do not have this syndrome. In subjects with MetS, a significantly higher value of the mentioned index is recorded in relation to subjects without MetS, where the magnitude of the impact is large and amounts to 0.86. Also, there is a statistically significant difference in the value of the waist circumference indicator between subjects with MetS and those who do not have this syndrome. Subjects with MetS have a significantly larger waist circumference compared to subjects without MetS, with a large impact size of 0.76.Table 3 also shows that there is a statistically significant difference in blood sugar, triglyceridemia and HDL cholesterol level between subjects with MetS and those who do not have this syndrome.

Table 3. Mann-Whitney U test to examine differences between patients with and without metabolic syndrome in terms of body mass index (BMI) and waist circumference, arterial blood pressure values and laboratory measurements

Obesity indicator	Metabolic syndrome	Md	N	Mann-Whitney U	Wilcoxon W	Z	p
BMI	Yes	31,70	1327	0,000	585903,000	-42,278	0,000
	No	22,20	1082				
Waist circumference (cm)	Yes	102,00	1327	84069,500	669972,500	-37,327	0,000
	No	84,30	1082				
Blood pressure							
Systolic (mmHG)	Yes	125,90	1327	711884,500	1593012,500	-0,355	0,723
	No	126,90	1082				
Diastolic (mmHG)	Yes	80,90	1327	708787,500	1294690,500	-0,537	0,591
	No	80,20	1082				
Laboratory tests	**Metabolic syndrome**	**Md**	**N**	**Mann-Whitney U**	**Wilcoxon W**	**Z**	**p**
Fasting blood glucosae (mmol/L)	Yes	7,78	1327	713267,500	1594395,500	-18,273	0,005
	No	5,40	1082				
Triglycerides (mmol/L)	Yes	2,75	1327	711881,500	1593009,500	-12,355	0,200
	No	1,79	1082				
HDL-Cholesterol (mmol/L)	Yes	1,00	1327	713133,500	1594261,500	-10,281	0,000
	No	1,23	1082				

Note: Md - median, N - number of subjects, Mann-Whitney U - test value, Wilcoxon W - statistician, Z - standardized statistician, p - statistical significance

As shown in Table 4, two independent variables made a unique statistically significant contribution to the model (abdominal obesity and triglyceridemia). The strongest predictor of the answer that the respondents will suffer from the MetS is the waist circumference, whose quotient is 1.34. Thus, the probability that the subject will be diagnosed with metabolic syndrome is 1.34 times higher with an increase in abdominal obesity (waist circumference), when all other factors are equal. Another important predictor refers to triglyceridemia, whose probability quotient is 1.12. Thus, the probability that the subject will be diagnosed with MetS is 1.12 times higher with an increase in triglyceride values, when all other factors are equal.

Table 4. Estimation of the influence of predictor variables on the probability of obtaining metabolic syndrome - binary logistic regression

							95% C.I. EXP (B)	
Varijable	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp (B)**	**Down limes**	**Uper limes**
Bibining of illness	-0,02	0,01	2,82	1,00	0,09	0,98	0,96	1,00
Waist circumference	0,29	0,01	516,82	1,00	0,00	1,34	1,31	1,38
Triglycerides	0,12	0,05	6,47	1,00	0,01	1,12	1,03	1,23
Constant	-26,39	1,18	497,05	1,00	0,00	0,00		

Note: B - regression coefficient, S.E. - standard error, Wald - indicator value, df - number of degrees of freedom, Sig. - statistical significance, Exp (B) - odds ratio, 95% C.I. for EXP (B) - 95% confidence interval for the probability quotient

DISCUSSION

As far as the author knows, this is the first work in the Autonomous Province of Vojvodina, but also in the entire territory of the Republic of Serbia, which deals with the examination of the prevalence of MetS in the population of psychiatric patients. It is known that patients with serious psychiatric illnesses have a far higher risk of developing MetS than the general population. In this study, the prevalence of MetS in the study population was 55.1%. This percentage is significantly higher than values from similar studies conducted worldwide where the prevalence ranges between 25 and 35% [8,14,15,16]. Although the study from the United Arab Emirates records an approximately high value of 48.1% prevalence of MetS in the group psychiatric patients [17]. Regarding the prevalence of MetS in the general population of Serbia, which is quite high and ranges from 38.4 to 42.7%, we see that psychiatric patients in Serbia are also classified as a vulnerable group in terms of metabolic status [18]. It is clear that a person with a mental

illness is about 30% more likely to develop MetS. High rates of MetS in both the general population and the population of psychiatric patients in Serbia are certainly significantly associated with a predominantly sedentary lifestyle characterized by minimal physical activity and predominantly calorie-dense foods represented in the diet.

The prevalence of MetS increases with the age of psychiatric patients, but that in the population aged 30 to 50 and over 50 is approximately the same and amounts to about 55%. Such conclusions are in agreement with the findings of several different studies on similar topics worldwide [19]. However, what is worrying is that the incidence of MetS in the study population under the age of 30 is about 33%. The prevalence of MetS among older adolescents (16-18 years) in Serbia is 13% [20]. How much psychiatric illness is an additional aggravating factor in the life of a young person for the development of comorbid physical diseases is clear from the fact that in practically 10 years from the end of adolescence to 30 years of age the incidence rate of MetS almost urtostructs. The high prevalence of MetS in the general population in general can be explained by the high prevalence of MetS components in the elderly, such as hyperglycemia and dyslipidemia [21]. Although some studies suggest that the high incidence of MetS in the elderly is due to functional and metabolic changes which are a consequence of aging. And that would mean that the MetS is a common companion of the aging process, which practically does not stand.

In relation to the differences in the prevalence of MetS in the population of psychiatric patients in terms of gender, unlike most similar world studies, it was found that men with psychiatric diseases significantly more often meet the criteria for diagnosis of MetS [22,23]. Male, older age, single life, lower level of education and higher number of children in this study were selected risk factors for higher risk for the development of MetSin the psychiatric population. All these characteristics of the model of a psychiatric patient at risk for the diagnosis of MetS have been confirmed by studies from South Korea [24]. This deviation can be explained precisely by the characteristics of the risk population itself. Single, middle-aged men, middle and lower level of education and level of economic power, who have a psychiatric illness and therefore insufficient and inadequate social support have all the prerequisites to practice a bad lifestyle, often accompanied by harmful habits such as smoking and alcohol use leading to metabolic development. syndrome.

Psychiatric patients have been shown to have a significantly higher risk of having some of the components of MetS. [8] And for the general population, the overall contribution of MetS diagnosis to overall mortality is estimated at 6-7%, 12-17% as the prevalence of arterial hypertension and 30-52% regarding diabetes mellitus [25,26,27]. This study showed that the duration of psychiatric illness plays a very important role as a risk factor for the development of MetS in patients. Over 60% of psychiatric patients treated for up to 5 years, as well as over 5 to 10 years, have a MetS. Two meta-analyzes by American authors find that the duration of psychiatric illness is the greatest risk factor for the development of MetS [27,28]. The duration of psychiatric illness is certainly related to the age of such patients, but also to the time of exposure to psychotropic medication, which both have a positive impact on the development of MetS.

According to recently published studies, there are no statistically significant differences between the prevalence of MetS among patients with different psychiatric diagnoses — studies that directly compared schizophrenic patients with patients with bipolar disorder. However, there are review studies that find a much higher incidence of MetS among the population of schizophrenic and bipolar disorders [29]. The current study sample shows a significantly higher prevalence of MetS among patients treated for psychotic disorders, with as much as 67% prevalence. While in the second place are patients with a diagnosis of mood disorders. Both samples showed a statistically significant difference in relation to the occurrence of MetS. Certainly, patients with these two psychiatric diseases are most often treated with atypical antipsychotics, mood stabilizers and antidepressants, as well as a combination of several different psychopharmaceuticals, which seems to be the strongest contributing factor to metabolic disorders, in addition to practicing unhealthy lifestyles and harmful habits. But the use of psychotropic drugs is the main difference between the population of psychiatric patients and the general population. It is certainly a mixed constellation of different risk factors such

as the clinical characteristics of the diagnosis itself with a predominance of negative symptoms, lack of adequate social support that together condition such a somatic risky lifestyle of psychiatric patients.

Atypical antipsychotics, but also a combination of several different psychopharmaceuticals, were the only ones that stood out as statistically significantly associated with the development of MetS. Such findings agree with most of the world's findings linking the use of atypical antipsychotics and the development of metabolic anchor. The CATIE study showed that after 3 months of olanzapine exposure, there was a significant increase in the number of patients who met the criteria for MetS [28]. Metabolic deterioration was also observed during long-term research of patients treated with clozapine [29]. As the indication field for atypical antipsychotics has significantly expanded today - from affective disorders to mood disorders, the population of patients using these drugs has increased significantly. Therefore, the risk of metabolic abnormalities should be considered when choosing an appropriate psychotropic drug, especially atypical antipsychotics.

Waist circumference and triglyceridemia stand out as the two most common contributing factors for the development of MetS in psychiatric patients. The risk that a psychiatric patient is diagnosed with MetS is 1.34 times higher with an increase in waist circumference, when all other factors are equal. Another important predictor refers to triglyceridemia, whose probability quotient is 1.12. These findings agree with the findings of several world studies, which certainly find a statistically significant association between visceral obesity, waist circumference and poor mental health in patients [30]. Although some studies do not find an increased value of triglycerides in the blood as a statistically significant predictor for the development of MetS. these are the levels of cholesterol in the blood [31]. The reasons for this finding in the current study may lie in the fat metabolism itself. If it is known that triglycerides are only the initial component in the formation of cholesterol, it can be concluded that a high value of triglycerides also significantly contributes to metabolic risk, albeit indirectly through the consequent increase in cholesterol. The main reason for the increased blood cholesterol values in the patients included in this study is the diet rich in fats and refined simple sugars that dominates in the Autonomous Province of Vojvodina.

CONCLUSION

The prevalence of MetS in psychiatric patients at the Clinical Center of Vojvodina in Novi Sad is alarmingly high. in more than half of patients, especially those treated for psychotic and mood disorders and using atypical antipsychotics and combinations of antipsychotics. In a patient with metabolic syndrome there is male dominance, low educational profile and the prevalence increases statistically significantly with increasing age of psychiatric patients. These findings once again emphasize the importance of continuous, long-term and multisystem monitoring of psychiatric patients, and the need to provide better organized social and health support, especially vulnerable from the group of psychiatric patients - the elderly, singles, singles. especially atypical antipsychotics, as drugs that have stood out as those most strongly associated with the development of MetS in a group of psychiatric patients. Waist circumference and blood triglyceride values are suggested as the best predictor factors for the development of MetS.

Conflict of interest: None.

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IMPORTANCE OFHAEMODYNAMIC STABILITY AND ADJUVANT THERAPY IN THE TREATMENT OF PATIENTS WITH SEPSIS AND SEPTIC SHOCK

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Summary: Sepsis represents a life-threatening condition that requires prompt recognition, detailed initial assessment and energetic administration of therapy. Guidelines published in 2016 emphasized the importance of early fluids replacement and infection control together with assessment based on laboratory parameters and precise monitoring of hemodynamic status of septic patients within the first 3-6 hours after diagnosis. Revision that followed in 2018 stressed that all therapeutic actions should be initiated within the first hour after diagnosis. Urgent administration of isotonic saline and balanced crystalloids in a dose of 30ml/kg should provide adequate hemodynamic stability of septic patients. If the fluid replacement fails to achieve hemodynamic stability and mean arterial pressure >65 mmHg, addition of vasopressors is mandatory. The vasopressor of choice for septic patients is norepinephrine. It may be used alone or in combination with other vasopressors such as epinephrine, vasopressin, terlipresine or phenylephrine. Septic patients with inadequate cardiac output after fluid replacement, and cardiomyopathy induced by sepsis or those with combined shock may need treatment with inotropic medication such as epinephrine or dobutamine. Adjuvant therapy with steroids, immunoglobulins, anticoagulants, statins, vitamin C and B1, may be useful, but no benefit regarding the overall outcome was observed. In conclusion, early detection of sepsis and septic shock within the first hour and immediate adequate fluid administration with vasoactive medications to maintain hemodynamic stability, are crucial for achievement of better outcome of these patients.

Key words: sepsis, fluid replacement, vasoactive drugs, adjuvant therapy, corticosteroids, immunoglobulins

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INTRODUCTION

Sepsis is urgent medical condition caused by inadequate immune response to infection. Septic shock encompasses circulatory, cellular and metabolic disorders presented as hypotension resistant to fluid replacement with urgent need for vasopressor therapy [1]. Early recognition of these conditions, detailed initial estimation and prompt therapy are of primary importance for reduction of death rate in sepsis. Guidelines published in 2016, underlined the importance of early fluid supplementation and control of the source of infection. Furthermore, appropriate laboratory estimation and hemodynamic monitoring are crucial for improvement of treatment outcome. This literally implies lactate level measurement, hemoculture sampling before administration of antibiotics, preferred use of broad-spectrum antibiotics and rapid crystalloid supplementation in the dose of 30ml/kg. In hypotensive cases resistant to fluid replacement, vasopressors should be given within 3 - 6 hours since diagnosis was made [2]. The latest recommendations for treatment of sepsis from 2018 have confirmed all treatment modalities published in 2016 with the update concerning the timing of treatment initiation. The new recommendation stressed that treatment should be initiated and rapidly administrated within the first hour after diagnosis of sepsis [3]. The shift in timing needs reconsideration of fluid replacement intensity and dynamics, appropriate and timely vasopressor administration as well as the use of adjuvant

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therapy, which is going to be discussed in the following review.

FLUID REPLACEMNET, HEAMODYNAMIC STABILITY ESTIMATION, AND THE USE OF VASOACTIVE DRUGS IN SEPTIC PATIENTS

Sepsis is a life-threatening condition associated with generalized endothelial damage, increased capillary permeability, decreased circulatory blood volume and decreased preload into the right atrium. These hemodynamic effects result into decreased tissue perfusion and organ disfunction. One of the main goals in reanimation of septic patient is to renew circulatory blood volume and normalize oxygen delivery to tissues that is the prerequisite for improvement and elimination of organ damage. It is recommended to initiate fluid supplementation with crystalloid boluses within first hour in dose of 30 ml/kg. Dose should be completely administered within third hour after the sepsis or septic shock diagnosis [2].

Fluid supplementation in septic patients is usually performed in four phases:

- Rescue phase: initiated within few minutes, lasting for a few hours after diagnosis in cases with life-threatening decompensated shock (low blood pressure, signs of decreased tissue perfusion). The volume of given crystalloids should be 30 ml/kg.
- Optimization phase: is applicable for a patient with sepsis in a state of compensated shock, whose life is not immediately endangered. Administration of additional volume of fluids is more cautious and should be titrated until achievement of optimal cardiac output and tissue perfusion. Undesirable hypervolemia should be avoided in this phase.
- Stabilization phase usually occurs within 24-48 hours after diagnosis, with patient being in good general condition. Volume of administered fluid should be enough to compensate standard renal, gastro-intestinal or other unclear fluid losses. Patients are neither in the state of shock, nor in immediate danger to develop this condition.
- De-escalation phase is characterized by absence of shock in patient and by recovery of all organ functions. Fluids should be given in order to provide net-neutral or slightly negative fluid balance. In this way, iatrogenic unnecessary fluid overload is be avoided [4,5].

For initial fluid replacement, in rescue phase, recommendations are in favor for isotonic salt or balanced crystalloids solutions. In the last 10 years, Ringer or Ringer-lactate solutions are considered advanatagous. If non-balanced isotonic solutions are administered, hyperchloremic and metabolic acidosis is more likely to occur, with consecutive renal vasoconstriction and blood flow reduction through the renal cortex. If balanced solutions are used, renal insufficiency may develop less frequently with less need for dialysis and with decreased mortality in critically ill patients [6,7,8]. The clinical use of colloids was sometimes justified by the need to improve low oncotic pressure or to reduce capillary leakage or in some cases with the idea to reduce excessive fluid volume replacement. Unfortunately, the use of colloids showed no advantage over balanced crystalloids in sepsis and septic shock. Furthermore, no benefit was seen when albumins were administered during initial reanimation comparing to balanced crystalloids and the treatment cost was higher in this group of patients [9]. Other colloids such as hydroxyethil starch are also not recommended in sepsis, since their use was associated with renal insufficiency and increased mortality [10].

The goal of every fluid replacement strategy is to maintain median arterial pressure (MAP) above 65 mm Hg thus providing adequate tissue perfusion. While attempting to achieve desirable MAP, it is often possible to cause volume overload if large volumes of fluids are given. State of overload is manifested by pulmonary oedema, hypoxemic respiratory insufficiency, swelling of peripheral tissue, development of intrabdominal hypertension with prolonged duration of stay in intensive care (ICU) and higher death rate [4,11]. For this reason, continuous estimation of fluid volume status is mandatory through the measurement of both static (median arterial pressure, central-venous pressure, hourly urine output) and dynamic parameters. Static parameters have shown considerable inferiority comparing to dynamic measures for prediction of volume overload [12,13,14]. Also, dynamic parameters enabled more appropriate fluid replacement, affecting positively the cardiac output,

shortening duration of mechanical ventilation and ICU stay with the decrease in mortality [15,16,17]. Dynamic measures are performed after administration of bolus fluids or after passive leg elevation. The latter maneuver may return 200 - 300 ml of blood from lower extremities to systemic circulation. Consecutive changes in the cardiac output may be directly measured using thermodilution or echocardiography or by registering changes in pulse pressure. Changes of cardiac output during inspiratory and expiratory phase of mechanical ventilation could be estimated through the variations of the pulse pressure, stroke volume and diameters of v. cava inferior [16,17].

Apart from dynamic measurements, fluid replacement during rescue phase can beassessed through an analysis of lactate levels and central venous oxygen saturation (ScvO2). Increase in lactate levels during sepsis may result from tissue hypoxia, increased aerobic glycolysis induced by β-adrenergic stimulation, but the increase may also be the result of effects of certain drugs (epinephrine, β2 agonists) or hepatic insufficiency. Lactate follow up, may objectively estimate response to resuscitation attempts and predict its inferior outcome. This was particularly evidenced in septic patients with lactate levels above 4 mmol/l [18,19]. If serum lactate levels as markers of tissue hypoperfusion are above 2 mmol/l during initial assessment, measurements should be repeted every 2-4 hours until normalization [19]. Therapy driven by the levels of this biomarker, may significantly reduce mortality in septic patients [20,21]. Therapeutic effects of fluid supplementation may also be followed byScvO2and capillary refill assessment, although their follow up was not found to be advantageous,comparing to lactate level analysis [20,22].

Response to supplemented fluid in septic patients is considered adequate if systolic pressure rises above 90 mmHg, in case of hypotension reversion or when MAP reaches levels above 65 mmHg without vasopressor influence. Yet, certain number of patients (36.2%) remains refractory to fluid administration, as seen in a retrospective study done on 3686 patients [23]. These patients often need prolonged mechanical ventilation and longer stay at ICU with higher death rate. The most common causes of refractoriness to fluid supplementation are: delay in fluid administration after making diagnosis of sepsis (longer than 2 hours), the presence of heart failure as a comorbidity, hypothermia, coagulopathy, immunocompromised patients and serum lactate above 4 mmol/l at initial assessment of patients [23].

Rapid fluid renewal with satisfactory perfusion of vital organs aiming to correct MAP above the 65 mmHg, is essential for reanimation of critically ill patients and should not be delayed. If restoration of adequate tissue perfusion fails after initial fluid administration, vasopressor therapy, isolated orcombined with inotropic drugs should be initiated. Physiological effects of both vasopressor and inotropic drugs are the rise of blood pressure and cardiac output and improvement of oxygen delivery to tissues. Vasopressor dose should be carefully titrated until desirable MAP level, having in mind potential risks for development of arrythmiaor cardiac, mesenteric, cerebrovascular and peripheral ischemia caused by these drugs [24]. Failure of vasopressors to correct blood pressure above desirable threshold (MAP>65 mmHg), induces linear decline of tissue perfusion with significant reduction of hourly output of urine, with detrimental effect to mental status and lactate clearance [25]. Norepinephrine is the vasopressor of choice due to potent agonistic α-adrenergic effects and less potent β-adrenergic effects. Early administration of norepinephrine showed greater benefit in the treatment of septic shock due to better organ perfusion and reduced incidence of arrhythmias and mortality in these patients, compared to other vasopressors [26,27,28]. Immediate administration of norepinephrine (93 vs 192 minutes) after diagnosis of septic shock, was associated with better control of shock in the first 6 hours with reduced incidence of cardiogenic pulmonary oedema and newly arrhythmias compared to late administration of norepinephrine [29]. In order to implement this experience in everyday clinical practice, new studies with a higher degree of evidence are needed. Vasopressors other than norepinephrine such as: epinephrine, vasopressin, terlipresine or phenylephrine, may also be used [29,30]. Combined use of norepinephrine with any additional vasopressor may be applied if the isolated norepinephrine therapy was not able to achieve satisfactory MAP levels or if there is a risk for norepinephrine overdose (40 to 50 μg/min) in

septic patients. In spite of these recommendations, combined treatment showed no efficacy in a study of Zhou et al. [31]. Combination of norepinephrine and vasopressin in septic patients with preexisting cardiac insufficiency was associated with inferior survival of these patients due to occurrence of malignant arrhythmia compared to monotherapy with either norepinephrine or dopamine [31]. Considering these data, the choice of proper vasopressor for the treatment of septic shock, requires obtaining additional information about preexisting heart problems, before reaching the final decision. Apart from vasopressors, inotropic drugs are recommended especially in patients with inadequate cardiac output after fluid supplementation due to sepsis -induced cardiomyopathy or existence of a combined shock. Most commonlyused inotropic drugs are dobutamine and epinephrine [32,33]. Inotropic drugs may be given individually or in combination with vasopressors. It is worth saying that combined use of dobutamine with norepinephrine showed neither decrease in mortality nor influenced shock duration compared to sole administration of epinephrine [33]. Effects of inotropic drugs treatment must be checked through cardiac output, ScvO2 or through mesurments of other tissue perfusion parameters.

ADJUVANT THERAPY IN SEPTIC PATIENTS

Corticosteroids regulate inadequate inflammatory response that may be seen in sepsis and also may cause suprarenal gland insufficiency or may increase tissue resistance to glucocorticoids [34]. It is believed that in patients with septic shock, steroids may decrease the need for vasopressors and reduce the duration of a shock, the length of stay at ICU and duration of mechanical ventilatory support. So far, obtained results failed to prove any clinical benefit of corticosteroids on survival outcome for patients with sepsis or septic shock. For this reason, corticosteroids should not be given to septic patients, particularly if they achieve hemodynamic stability to fluid supplementation and vasopressors [35,36,37]. Corticosteroids are more frequently added as adjuvant therapy when there is a necessity for higher doses of vasopressors [34]. If the decision to use corticosteroids is made, recommended dose of hydrocortisone should be 200mg within 24 hours continusly or divided to 50mg every 6 hours through first three days [38]. With the administration of corticosteroids, the ICU and hospitalization stay was significantly reduced, while the 28-day and overall mortality of septic patients were reduced with moderate level of evidence. The risk of major complications occurrence, after corticosteroid use, was very low. Following its administration, one may also expect undesirable effects such as: muscle weakness, hypernatremia, and probably risk for hyperglycemia [39]. New studies are necessary in order to define proper timing and duration of corticosteroid treatment related to the beginning of septic shock, with close analysis of the patient's outcome.

With the administration of intravenous immunoglobulins in septic patients, the effects of antigen neutralization, blockade of Fc receptors on phagocytes and immunomodulation of the cytokine and cellular response can be achieved [40]. Although reduction of hospital mortality in septic patients after high doses (1.5-2 g/kg) of intravenous immunoglobulins, was observed in some studies, there are considerable limitations concerning these data, urging for stronger evidence before their use [41,42]. In order to get more adequate estimation of intravenous immunoglobulins efficacy in sepsis and septic shock, some authors suggest the need for analysis of additional parameters such as: the estimation of the amount of immunoglobulins present in administered drugs, timing of their administration related to sepsis onset (effects are better if immunoglobulins were given within 24 hours after sepsis onset), correlation between administeredimmunoglobulin dose and the degree of inflammation during infection [43]. Numerous contradictions and insufficient evidence about immunoglobulin efficacy in septic patients require further studies for the purpose of shedding light on immunoglobulin effects.

Even though numerous trials have shown efficacy of anticoagulant drugs in adjuvant treatment of septic patients, there is not much evidence about their benefit to mortality reduction in of septic patients. The greatest benefit in anticoagulant use was noticed in patients with sepsis-induced disseminated intravascular coagulopathy [44].

Statin drugs administration has been associated with significant reduction in mortality of septic patients in certain

observational studies compared to randomized studies. For this reason, further studies should answer the questions concerning efficacy, safety and finding the adequate dose of statins in septic patients [45]. Many other aspects of adjuvant therapy in septic patients need clarifications. This is the case of the usefulness of early administration of intravenous vitamin C and B1 considering the registered deficiency of these vitamins in these patients. Although the early administration of these vitamins had no impact on overall survival of septic patients, it is considered that along with standard therapy vitamin supplementation may be beneficial in septic patients [46,47].

CONCLUSION

Treatment of patients with sepsis and septic shock is extremely complex, considering that sepsis is multifactorial. Good understanding of pathophysiological processes, early diagnosis of sepsis and septic shock, urgent and adequate fluid supplementationis initiated within the first hour after the diagnosis with administration of vasoactive drugs aiming to achieve hemodynamic stability, may be crucial for better outcome of these patients. Adjuvant therapy like corticosteroids, immunoglobulins, anticoagulants or administration of vitamins C and B1, has some benefit in septic patients' treatment, but final decision about their use might be reached after collecting firm evidence from further clinical studies.

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Vol. 45 (2020) No. 4 TIMOK MEDICAL GAZETTE Case report

SELF-MUTILATION IN UROLOGIC PATIENTS - CASE REPORT

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Summary: Self-mutilation is intentionally injuring oneself. Generally, the most common self-inflicted wounds are burns and cuts which can be closed and open. In extreme cases it could be a suicidal attempt. In urology, genitals are usually the object of mutilation. Because of their anatomical features and topographic location, they are most commonly exposed to these procedures. There may be cuts on the penis, perineum, scrotum; scrotum avulsion, orhiectomia, castration to penile amputation. These are mental patients suffering from paranioid schizophrenia. As part of their delusions, they have bodily-cinesthetic hallucinations that manifest discomfort in the genital area. There is a delusional idea that the only solution to eliminate the hallucinations present is to self-mutilate. Because these organs are very blood-borne, they are always shocked after the ritual because of bleeding and pain. We present a 46-year-old patient with severe genital injury, scrotum avulsion, and subtotal penile amputation. Since more than 2 hours had passed since self-mutilation, the suture of the penis could not be done, so after resuscitation, a suture of the scrotum, tunica albuginae and an external urethral opening were done. After leaving the recovery room, he was transferred to a psychiatric ward and later to a higher health care facility.
Key Words: paranoid schizophrenia, self-mutilation, penil amputation.

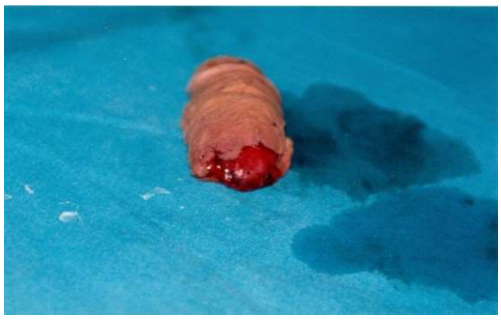
INTRODUCTION

Self-mutilation represents intentionally injuring oneself. Most frequently these are cuts or burns.It is often a way for a person to deal with emotional problems.

Very rally it is a suicidal attempt.Due to their anatomic features and topographic position, male genitals are exposed to injuries even if they are covered by clothes and protected. Injuries can be injuries at work, while doing sports, in traffic accidents, sexual injuries caused by masturbation and in sexual ecstasy unintentionally or in acute affectivity intentionally. The wounds can be closed and open.

Amputation is one of the most severe injury of male genitalia,an extremely rare injury and it includes a complete or partialinterruption of the continuity of the body of the penis[1]. Complete amputation is characterized by cutting the corpora cavernosa and urethra and partial by cutting only one part of it. (Figure 1).

Figure 1. Complete amputation

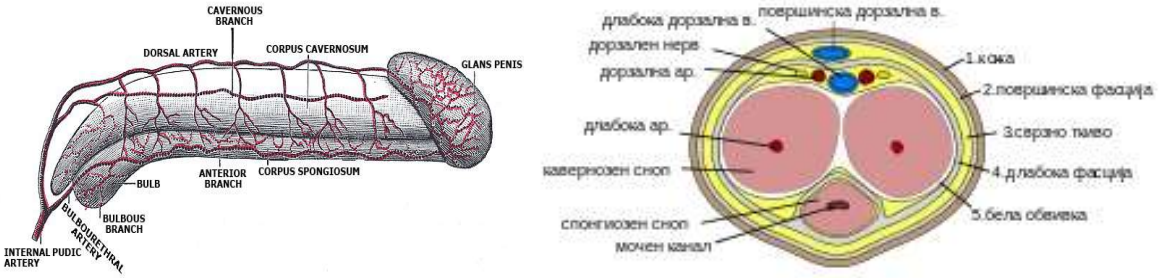


The penis is an organ which is anatomically divided into three parts:the base of the penis, the shaft of the penis and the glans penis. The base is located below the pubic bone and it provides the firmness of the penis in erection. The shaft consists of two cavernous parts and one spongy part. The urethra runs through the spongy part to the external urethral orifice –

meatus, located at the tip of the glans penis. They are also called erectile bodies because they enable erection of the penis. The glans is a distal expansion of the spongy part covered with mobile skin – Prepuce.

The penis is innervated from the right and left dorsal nerves and from the branches of the pudendal nerve. It is vascularized by the internal pudendal artery of the femoral artery branch (SHEMA 1).

SHEMA 1. ANATHOMICAL DETAILS: VASCULARISATION OF PENIS AND TRANSVERSAL SECTION OF PENIS.



Open injuries of the penis are most often inflicted with firearms or sidearms. Complete or total amputation is characterized by cutting the cavernous parts and the urethra.

History records a special way of amputation of the penis (as a part of castration) in eunuchs, which dates from the 21st century BC. Over the centuries eunuchs performed various duties in various cultures as temple guardians, opera singers, soldiers, clerks [2,3]. Cases of sexual aggression were described as the causesforpenis amputation. For 70 years in Thailand women amputated the penises of their husbands caught in adultery [4]. The diagnosis is obvious on the basis of physical examination. Through a detailed anamnesis one can reach the reason for the injury and the mental state of the patient [5]. Considering that these organs have very high blood flow, the open wounds are accompanied by heavy bleeding, and the person is shocked by the pain and hemorrhage. In such cases, after resuscitation, surgery takes place.Treating the wounds with large tissue defect requires application of the methods of plastic and reconstructive surgery, which uses skin flaps taken from the skin of the scrotum, pubic region, abdomen [6]. Sex-related injuries of external genitalia should be treated multidisciplinary and not only surgically with antitetanus protection always applied.

CASE STUDY

46 years old man, from around Zaječar, came to the urology department in the morning, accompanied by his father. Pale, in poor general condition. At the reception the father takes a nylon bag from his pocket which contained a cut off penis. Examination under cotton-wool soaked with blood reveals an open wound with the left testicle outside the scrotum and subtotal amputation of the penis. Urgent laboratory showed haemoglobin to be 72 g/l. In heteroanamnesis, Patient is divorced, has a 17-year-old son who lives with his mother while he himself lives with his parents. He had been treated from schizophrenia for a long time and kept calling himself Zorana. The day before he came to the department he put a mirror in front of himself at the height of his genitalia andwith a slashing knife began to rearrange his gender identity (Figures 2 and 3). Accidentally his mother came into his room finding him in the pool of blood.

After urgent resuscitation there followed a surgical care of the injury. Scrotal injuries were sutured first, followed by restitution of the cavernous part andsuturing of tunicae albuginae. Then drainage. The external opening of the urethra was formed. A catheter was inserted.

Upon leaving the recovery room, the patient was transferred to a psychiatric ward, from where he was further transferred to a higher health institution – Specialized hospital for psychiatric diseases ''Gornja Toponica''.

Figure 2. Amputation of the penis and open wound of the scrotum.

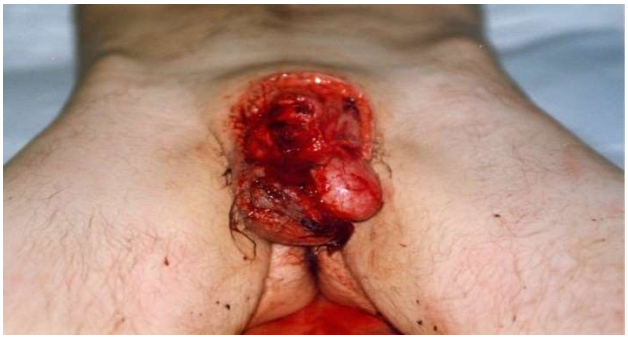
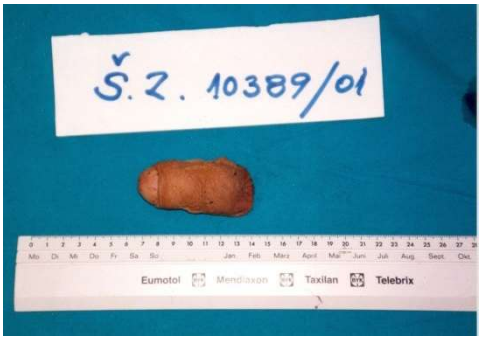


Figure 3. Amputated part of the penis.



DISCUSSION

All sexual actions including those sexually deviant which can result in mutilation of genitalia take shape in the brain [1]. The wounds can be closed and open. Closed wounds on the penis take place accidentally during sex when the penis is in erection (Penile fracture), because of the rupture of tunicae albuginae blood from the cavernous part forms a hematoma subcutaneously. Open wounds can come from the other person or very rarely in self-mutilation from cuts on the scrotum (with cutting off of the sheaths with testicles outside the scrotal sac), cuts on the penis, amputation of the penis. Through careful anamnesis one can get to know the causes of the injury. Depending on the objective findings therapy is introduced. Injuries on the scrotum are repaired – after refreshing the edges and hemostasis, if the testicles are outside the scrotum, they return to the scrotal sac, the sheathsare sutured, there follows subcutaneous drainage and suture of the skin. If it's been less than 2 hours since the amputation, it is possible to perform a suture with microsurgery in higher professional institutions [6,7]. In other cases, after resuscitation, proper hemostasis and urethral restitution for normal urinationshould be performed.

Traumatic penile amputation is a rare urological and surgical emergency. A systematic review of 80 cases from 1996 to 2007 reported only 37.5% of cases that underwent successful re-implantation [8]. The main etiology of penis amputation is self-mutilation, accidents, circumcision, seizures and animal attacks. As early as the 1970s, an epidemic of penis amputations was recorded from Thailand, where women amputated their husbands' genitals due to infidelity. This series of cases of 18 patients is still the largest to date [4].

schizophrenia (Schizophrenia paranoides). As part of his insanity, he has body-synesthetic hallucinations (synesthesia, the ability of one uns stimulated sense to feel the stimulus of another sense), which is manifested by discomfort in the area of the sexual organ. There is a crazy idea that the only solution to remove the present hallucinations is to cut the genitals, which he does, giving a crazy explanation "to become a woman". Because of that, after the surgical care, he was sent to a mental hospital.

CONCLUSION

We have presented an extremely rare case of self-harm. Restitution of the severed penis was not attempted, as more than 2 hours had passed from the moment of penis cut-off to the arrival at the urology department. The bleeding was not more copious because the penis was not in erection.

After resuscitation, the scrotum, tunica albuginae and the shape of the external opening of the urethra were performed. After leaving the shock room, he was transferred to the psychiatric departement.

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FROM LOUIS BRAILLE TO THE FIRST SERBIAN SPELLING BOOK FOR THE BLIND

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SUMMARY: INTRODUCTION. Blindness is a multiple problem of a psychological-economic-social nature, viewed from different points through the centuries. Louis Braille is the creator of the letter that enabled blind people around the world to become literate and educated. THE LIFE AND WORK OF LOUIS BRAILLE. Blind from the age of three after an eye injury with an awl, Louis Braille (1809-1852) had the opportunity to learn about the possibilities of educating blind people early on. However, his talent, recognized in time and a desire to acquire new knowledge, will enable him to attend the "Royal Institute for Blind Youth" in Paris, where young Braille continues his education, creation, living, and later became a lecturer. A PRECURSOR TO BRAILLE. Until the creation of the Braille script, a relief linear script was used to educate the blind. THE ORIGIN OF BRAILLE. The meeting with the French captain Charles Barbie (1821), the introduction to the communication system for the needs of soldiers "night writing", was the starting point for the future Braille (1825), a dotted alphabet method for the blind, which the author adapted later for writing music and mathematical symbols (1837). The Braille alphabet was chosen as the official method of reading and writing intended for blind people only in 1878 at the World Congress in Paris, and later on adapted to more than two hundred languages and dialects. IN 1917, BRAILLE "SPOKE"IN CYRILLIC. The beginnings of the education of the blind in Serbia are related to 1917 and Bizerte, where, as part of the rehabilitation of the blind Serb soldiers with disabilities ,for the first time in the "Printing House of Serbian Disabled People", the Braille "spoke" in Cyrillic. "My first joy" is the name of the first Serbian spelling book by Veljko Ramadanović (1874-1943), who at that time was the only one who knew pedagogical work with the blind, and was also their first teacher and future school principal. CONCLUSION. Louis Braille is one of the most inventive personalities in history, the creator of the letter that enabled blind people around the world to become literate and educated, as well as our brave Serbian army during the First World War.

Key words: blindness, Louis Braille, letter for the blind, Veljko Ramadanović, World War I.

INTRODUCTION

" Vision is not everything, but what is everything without sight? "
Schopenhauer A., German philosopher

According to the International Classification of Diseases, there are the following levels of visual functionality: normal vision, mild and severe visual deficit defined as low vision (LV) and blindness [1]. Blindness is a multiple problem, of a psychological-economic-social nature, viewed from different angles through the centuries. Luisa Hofmann describes how a blind person experiences their condition in 1981 in the author's publication of the same name: "Blindness cannot be understood by just closing your eyes for a few minutes or trying to orient yourself in the dark... blindness is much more complicated and problematic." [1]. Different definitions of blindness are mentioned in the literature. If there is congenital and early acquired blindness, it is also called "double blindness", it has a special weight, because such people do not have a proper idea of the outside world around them, and often lag behind in mental development, unlike later blind people who have retained "spiritual sight", ie the idea of previously seen things based on memory [2].

Louis Braille is one of the most inventive figures in history in general, the creator of the letter that enabled blind people around the world to become literate and educated.

THE LIFE AND WORK OF LOUIS BRAILLE

Louis Braille (1809-1852) was born on 4th January, 1809, at Couvray, near Paris. The date of his birth was marked as the International Day of Braille. Braille is the emissary of light in the lives of the light denied. He was the youngest of four children in the family. His father Simon-Rene was a master, a cooper. Little Louis loved to watch him as he worked leather, skillfully cut and made harnesses, bridles and saddles for country horses. In his father's absence, Louis injured his eye. At three years of age, an accident deprived him of his sight. At that time, there was no hope for the possibility of education and employment for the blind person without a rich background.

Louis' education was started by his father, who taught him to read the alphabet by pressing his index finger over wooden boards carved in the shape of letters and writing, guiding his hand and holding it in him hand. Father Poli was priest of the church of St. Peter in his birth place. He continued to teach a little Louis. Thanks to his engagement, and with a previous real assessment of the boy's quality, Bray received a scholarship for Royal Institute for Blind Youth at Paris (the first institution for the blind in the world), where he left in 1819 to study; to live and where be later on became a lecturer. The institute was founded in 1785 by the French professor of calligraphy Valentin Haüy (1745-1822), who came up with the idea that blind people could "read with their fingers" [3].

A PRECURSOR TO BRAILLE

A relief linear script was used to educate the blind until the creation of the Braille script. The convex, embossed text obtained by a special procedure should have been suitable for reading with the sense of touch, ie with the fingertips. The earliest information about the existence of a relief letter for the blind dates from 1312 and it is related to the name of a blind professor at the Baghdad High School, Zain-Din al Amid. "Quipos" is a system of knots of various shapes and sizes on a rope, which blind Indians, marked certain words, letters and dates from their calendar in the 16th century [3]. Other techniques likes engraving letters and signs in wooden tiles in the form of bas-reliefs, imprinting movable convex letters from letters on paper, writing linear letters on a wax board, etc. were used in Europe during the 16th and 17th centuries [3]. Common to these attempts was that blind people were trained to write the letters for "seeing", on plain paper, with accessories, which was not an adequate solution, because it is not just about enabling the blind to write on the way of "seeing" with a pen, pencil or pen, it is already necessary to find a letter that the blind could write quickly and safely and then easily read it themselves " [3].

THE ORIGIN OF BRAILLE

Young Bray realized that the embossed Latin alphabet was difficult to use after reading all the books the institute owned. He thought that there must be a way to read faster, "to make the letters on paper feel faster", so he started experimenting with drilling leather in the shape of circles, squares and triangles, in an attempt to develop an alphabet for the needs of the blind. At the same time, Charles Barbie, a captain in the French army, developed a communication system for soldiers during the night shift. "Night Writing" was represented by a lattice structure composed of twelve convex dots and dashes on cardboard. By grouping and combining points in different ways, Barbie marked letters and sounds, hoping that his method would be applicable to the needs of blind people as well. Louis Bray became acquainted with this system in 1821, when Captain Barbie visited the Royal Institute for Blind Youth and showed his method to the school principal. Although it had many shortcomings, the system served as inspiration and encouragement to the clever thirteen-year-old Bray, to adapt it for the needs of blind people and thus develop the method of the dotted alphabet. From the original twelve, Bray reduced the "cell" to eight, and then to six points. The "six-point" of the established schedule and nomenclature became the basis of his letter. He formed convex dots into an upright rectangle, with three dots grouped vertically and two horizontally, and he also designed a simple pen and writing frame. He was sixteen years old (1825) when he finished and presented to the director his system of "points" originally intended for the students of the Institute in which he was educated. Dr. Pinier, director of the Institute, realizing all the ingenuity of this new method, encouraged Louis to supplement his letter with mathematical and musical notation, which was done in 1837. Bray published his first book for blind people, entitled "A Method for Writing Words, Music, and

Polyphony with the Help of Dots," in 1829, at the age of only twenty. It explains for the first time a new, simple method of reading and writing, according to which blind people read by dragging the index finger of the right hand from left to right, and write in the opposite direction. Louis Bray continued to perfect and develop his system of dotted alphabet. He removed the dashes that were present in the first, original version, because, although easy to read, they made writing difficult, and at the request of English students from the Institute, he added the letter "w", which did not exist in the original version. The genius of Braille was demonstrated to the public only in 1843. During the celebration on the occasion of the opening of the new school building, the assistant director of the Institute gave a speech dedicated to the Braille method, praising it wholeheartedly and presenting to the audience all the advantages that this letter can provide to blind people. It was the first official presentation of Braille. Simple and acceptable to blind people, but too much of a novelty at the time, the introduction of Braille was very slow, with strong resistance that existed in official circles. Eight years before Louis Braille's death (1844), the letter was accepted in France, which only in 1854 officially recognized the Braille alphabet as translated into English, Italian, French, German, Spanish and Latin. Countries around the world, one after another, recognized the advantages and benefits that the Braille alphabet provided. At the World Congress held in Paris in 1878, the Braille alphabet was chosen as the official method of reading and writing intended for the blind. In 1890, it was adapted for the needs of schools in Europe (Austria, Belgium, Denmark, England, Germany, Spain and Scotland), and only in 1917 was it recommended in the USA. Under the auspices of the United Nations, work began on adapting the alphabet in 1949 in more than two hundred languages and dialects. Thus, Braille became a universal language for blind people around the world. Louis Braille rests in the Paris Pantheon, where his remains were transferred during a ceremony organized in 1952, and one hundred years after his death.

IN 1917, BRAILLE "SPOKE"IN CYRILLIC

The treatment and recovery of the Serbian army in the period from 1916 to 1919 was realized in North Africa, which served as a solid base in which Serbian soldiers could be treated, recovered, trained and retrained in peace, in the deep background. According to the third allied plan for rescuing the Serbian army, it was specified that the destination would be Bizerte, and the deployment of troops in the Tunisian desert [1]. The first naval transport of the Serbian army from the shores of the Albanian coast from Durres to Bizerte was realized on 6 th January, 1916. That date is one of the most important in the history of the Serbian army and state, it marked its turning point, Easter, salvation and deliverance, and unfortunately it was suppressed from our history. From that day on, not only from the homeland, but also from the Balkans and Europe, the entire army, state and part of the people found themselves in exile [1]. The wounds of the "Albanian Golgotha" have not yet healed, and in mid-August of the same year, ships with the wounded from the Thessaloniki front arrived in the North African ports, and then the evacuation of wounded and sick soldiers from the Thessaloniki port continued for another 32 months to North Africa and from other destinations, all with the song "The French ship is moving". After complete medical care and successful treatment, the soldiers were sent to the Convalescent Department in Lazouz, and from there, according to the degree of recovery, to the front [4].

Except for the Serbian army, no other had such a large disability formation, and great importance was attached to their treatment and recovery. Serbia and the descendants of old warriors owe immense gratitude primarily to French doctors and hospital staff engaged in the treatment of the wounded and sick. However, two names rise above all, and that is Émile Paul Aimable Guépratte (1856-1939), "Serbian mother", who, contrary to the order of the superior command, made a saving decision for the Serbs to settle in the best possible conditions upon arrival in Africa. and Dr. Salijez, the "good daddy" of all Serbs who stayed in Tunisian hospitals. Along with the French team, 14 of our doctors certainly played a big role in rescuing and treating the Serbian army [4,5]. In order to reduce the consequences and prepare the war invalids to accept the reality and the future in the best way, schools, courses and workshops are being formed in the Lambert barracks in order to train the disabled and learn crafts such as carpentry, footwear, typographic, printing, etc. All the contents of the work of our soldiers

and their daily activities were in the function of rehabilitation.

The beginnings of the education of blind Serbs are also connected to the same renunciation. Namely, in the Lambert barracks, on December 13, 1917, the first Serbian school for the blind in distant Africa was opened, in Bizerte (Institute for the Blind and Deaf Disabled), the forerunner of today's school for visually impaired students in Zemun. Its first participants were blind Serbian warriors from the First World War. In order for the school to work smoothly, books and primers adapted to the blind were necessary. Such books were printed in Braille. Of the five printing houses operating in Bizerte, two were Serbian. For the first time in the "Printing House of Serbian Disabled People", Braille for the blind disabled "spoke" in Cyrillic (N. Gizdavić, 1922) [4].

The headmaster of the school and their first teacher was Veljko Ramadanović (1874-1943), at that time the only one who knew pedagogical work with the blind. He faced many difficulties in such circumstances, and managed to overcome them with his dedicated work and with the material help of the allied humanitarian missions of France, America and England. Ramadanović saw the task of educating the blind and providing the knowledge necessary for future life with the help of handy teaching aids as a life mission [3].

In 1896, after returning from school in Prague, Veljko Ramadanović adapted the Braille alphabet and adapted it to the Serbian language. As there was no school for the blind at that time, this letter did not immediately find its use. It is only in Bizerte that it experiences its adequate application. In order to be able to engage in teaching work, Ramadanović started making the first Serbian primer for the blind called "My first joy". He took over the material for the primer from the primer by Steva Čuturilo printed in 1916 in Corfu. He considered it the most suitable, methodically best conceived for teaching in primary schools, and used it to print his primer. To print the primer, he used a sheet of used cans and kerosene cans, straightened it and folded it like a sheet of paper. He trimmed the pages according to the desired format of the book, then placed them in a handwritten board for the blind and with the help of a steel awl, the top of which was rounded, using a hammer, typed point by point in Braille letters for the blind. He made double tin clichés, put paper in between, closed the clichés and put everything together in an ordinary office press, screwed and thus transferred the text of the cliché to paper. This process was repeated for each sheet of primer. He folded the printed sheets and bound them in a book. The primer was completed in the spring of 1918. The format of the primer is 17 x 24 cm, printed on one side and had 20 pages (Miodrag Janković, MA: Presentation of the oldest Serbian publication in Braille, primer "My first joy" by Veljko Ramadanović) [3].

By an act of the Ministry of Education and Religion of the Kingdom of Yugoslavia in 1918, the government approved the printing of the primer and its use for teaching. One copy of the oldest primer printed in 1918 is the private property of the family of the late blind warrior Luja Lovrić from Crikvenica. The second edition of the primer was printed in Paris in 1919. In the Museum of the School for Visually Impaired Students "Veljko Ramadanović" in Zemun and the Pedagogical Museum in Belgrade, there is one copy of the oldest edition of this primer [3]. After the liberation in 1919, by moving the disabled from the barracks in Bizerte to the premises of the barracks of the Austro-Hungarian army to the current location in Zemun, new perspectives of further development of education for the blind in Serbia opened up. In 1923, the Institute for the Disabled was transformed into a school for blind children, which was initially called the "Braille School". After the visit of King Alexander I, the school changed its name to "Home of the Blind King Alexander I" in Zemun. From that time, the school gradually began to acquire today's physiognomy [3]. Since Veljko Ramadanović, who made Braille's adaptation for the Serbian language in 1896, typhlopedagogical practice and theory have gone through an evolutionary path conditioned by the economic, political and cultural circumstances in Serbia.

CONCLUSION

Louis Braille is the creator of a letter that enabled blind people around the world to become literate and educated (1825). The adaptation of Braille for the Serbian language was done by Veljko Ramadanović (1896). In 1917, in Bizerte, in the "Printing House of Serbian Invalids", for the first time, the Braille alphabet for the blind "spoke" in Cyrillic. Beginning of work with blind Serbian soldiers in Bizerte was the beginning of today's

comprehensive educational work with visually handicapped people and their social care.

Conflict of interest: Gordana Stanković-Babić, Rade Babić None.

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ACKNOWLEDGEMENTS. List all contributors who contributed to the creation of the work but did not meet the criteria for authorship, such as those providing technical assistance, writing assistance, or managing a department that provides general support. Financial and material assistance, in the form of sponsorships, scholarships, gifts, equipment, medicines and more, should also be listed

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