PREVALENCE OF METABOLIC SYNDROME AMONG POSTMENOPAUSAL WOMEN IN MONTENEGRO - RELATION TO HYPERURICEMIA

PREVALENCA METABOLIČKOG SINDROMA KOD ŽENA U POSTMENOPAUZI U CRNOJ GORI - POVEZANOST SA HIPERURIKEMIJOM

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Summary: Aim: The data regarding the prevalence of metabolic syndrome (MetS) among postmenopausal women in Montenegro is limited. Therefore, the aim of this study was to evaluate this prevalence and to examine its association with serum uric acid level, an established cardiometabolic risk factor. Methods: A total of 242 postmenopausal women (aging 43-68) were included. Fasting glucose, lipid parameters, and uric acid were determined with the standard procedure. Blood pressure and anthropometric parameters were obtained. MetS was diagnosed according to the modified US National Cholesterol Education Program Adult Treatment Panel III guidelines. Results: The prevalence of MetS in postmenopausal women was 42.1%. The most prevalent component was abdominal obesity (65.3%), following by hypertension (systolic blood pressure and diastolic blood pressure accounting for 54.1% and 49.2% respectively), hyperglycemia (40.5%), and dyslipidemia (high triglycerides and low HDL-c level accounting for 30.2% and 25.2% respectively). Uric acid levels were significantly higher in postmenopausal women with MetS than in those without MetS (P<0.001). Moreover, a significantly higher number of patients with MetS as compared to subjects without diagnosed MetS across uric acid tertiles was found (χ^2=27.02, P<0.001). Conclusion: MetS is highly prevalent among postmenopausal women in Montenegro and correlated with higher uric acid level. Abdominal obesity is the most prevalent feature of the syndrome. This suggests the importance of reducing obesity and lowering uric acid level in prevention of cardiometabolic diseases.

Keywords: abdominal obesity, metabolic syndrome, postmenopausal, uric acid

Sažetak: Cilj: Nema podataka o prevalenci metaboličkog sindroma (MetS) kod žena u periodu postmenopauze u Crnoj Gori. Stoga je cilj studije bio da se utvrdi ova prevalenca i ispita povezanost MetS-a sa mokraćnom kiselinom u serumu, poznatim kardiometaboličkim faktorom rizika. Metode: U studiju su uključene 242 žene u postmenopauzi (starosti 43–68 godina). Glikemija našte, lipidni status i mokraćna kiselina su određivani standardnom procedurom. Mereni su i krvni pritisak i antropometrijski parametri. MetS je dijagnostikovan prema modifikovanim smernicama Američkog nacionalnog programa za edukaciju o holesterolu – Preporuke panela III za lečenje odraslih. Rezultati: Prevalenca MetS-a kod žena u postmenopauzi je iznosila 42,1%. Najučestalija komponenta je bila abdominalna gojaznost (65,3%), potom hipertenzija (sistolna – 54,1% i dijastolna – 49,2%), hiperglikemija (40,5%), dislipidemija (hipertrigliceridemija – 30,2%) i niske vrednosti lipoproteina velike gustine (HDL-holesterol – 25,2%). Srednje vrednosti serumske mokraćne kiseline bile su značajno više kod žena sa MetS-om u poređenju sa kontrolnom grupom (P<0,001). Takođe, značajno veći broj ispitanica sa MetS-om je zabeležen u tercilnoj grupi sa najvišom koncentracijom mokraćne kiseline u serumu (χ^2=27,02; P<0,001). Zaključak: Zabeležena je visoka prevalenca MetS-a kod žena u postmenopauzi u Crnoj Gori, kao i povezanost sa višom koncentracijom mokraćne kiseline u serumu. Centralna gojaznost je najučestalija karakteristika sindroma. Ovo ukazuje na značaj smanjenja gojaznosti i mokraćne kiseline u ovom periodu u cilju prevencije i smanjenja kardiometaboličkih poremećaja.

Ključne reči: abdominalna gojaznost, metabolički sindrom, postmenopauza, mokraćna kiselina

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INTRODUCTION

A key feature of the menopausal transition is the reduction in estradiol levels [1]. Consequently, many of the components of metabolic syndrome (MetS) (central obesity, dyslipidemia, impaired fasting glucose and hypertension) are often seen in that period [2], and numerous studies have shown that being affected by MetS increases the risk, as well as morbidity of cardiovascular disease (CVD) [3, 4]. The prevalence of the MetS is increasing rapidly throughout the world. Studies about MetS have shown that females were more affected than males [5]. Moreover, the prevalence of MetS increases in women after menopause [6].

Although the MetS is multifactorial in origin, impaired glucose tolerance, dyslipidemia, and hypertension are caused by the same underlying mechanism-endothelial dysfunction primarily mediated by oxidative stress. A growing body of evidence suggests that increased oxidative stress to adipocytes is central in the pathogenesis of CVD in MetS [7].

On the other hand, uric acid is regarded as independent risk factor for CVD [8]. In addition, elevated uric acid impairs endothelial function by inducing intracellular oxidative stress and inflammation through activation of the local renin-angiotensin system, and the pro-oxidant effect of uric acid per se, once absorbed into endothelial cells [9].

In line with this, it is speculated that uric acid is one of the determinants of the MetS [10]. The elevated serum uric acid level observed in the MetS has been attributed to hyperinsulinemia, since insulin reduces renal excretion of uric acid [11].

Data concerning the prevalence of MetS among postmenopausal women in Montenegro are limited. Therefore, the aim of this study was to evaluate the prevalence of this syndrome and to examine its association with serum uric acid, an established cardiometabolic risk factor.
Materials and methods

STUDY POPULATION

The study enrolled a total of 242 women (ages 43-68 years) who developed menopause and who volunteered to participate in the study. Participants were consecutively recruited in the study when seeking gynaecologic healthcare in the Primary Health Care Centre in Podgorica, in a period from October 2012 to May 2013. All the participants completed a questionnaire including demographic characteristics, somatic illnesses, medications use, and lifestyle habits. Menopause is defined as having last menstrual cycle for more than one year. Inclusion criteria were: women without signs and symptoms of acute inflammatory disease, with no history or the presence of malignancy, hypo- and hyperthyroidism, or CVD. Participants who had gout, renal dysfunction, hepatic dysfunction, cardiovascular disorders were excluded from the study, as well as those who used anti-inflammatory medications or hormonal replacement therapy. The participants were instructed not to perform any vigorous physical activity the day before the blood samples were taken. Medical history and clinical examinations were carried out on the same day. All the participants provided written informed consent. The study protocol was approved by Ethical Committee of Primary Health Care Centre in Podgorica and the research was carried out in compliance with the Declaration of Helsinki [12].

Anthropometric measurements

Basic anthropometric measurements: body height (cm), body weight (kg) and waist circumference (WC) (cm) were obtained twice in the morning on the same day and the mean values were used for the analysis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m2). All measurements were taken by the same trained evaluator. Blood pressure was measured with a sphygmomanometer after the subject had been seated for 15 minutes. The average of three measurements taken on the right arm was recorded.

The participants were divided into two groups: group of postmenopausal women without MetS (n=140), and group of postmenopausal women with MetS (n=102). MetS was diagnosed according to the modified US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [13]. The participants met with at least three or more of the following conditions were diagnosed with MetS:
1. Waist circumference (WC) ≥ 88 cm;
2. Hyperglicemia ≥5.6mmol/L or antidiabetic medication use (instead of previous cut-off values of fasting plasma glucose ≥6.1mmol/L);
3. High density lipoprotein cholesterol (HDL-c) ≤1.29mmol/L;

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4. Triglycerides ≥1.70mmol/L or lipid lowering medication use;
5. Hypertension: systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥130/85 mm Hg and/or diagnosed hypertension treated with antihypertensive therapy.

Biochemical analyses

Blood samples were taken between 7-9 hours a.m., after 12-14 hours of an overnight fast. Samples were left to clot for 30 minutes and then centrifuged at 3000 rpm for 10 minutes. Serum levels of glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides (TG) and uric acid level were measured using standardized enzymatic procedures using a spectrophotometer (Roche Cobas 400, Mannheim, Germany).

Statistical analysis

Statistical analyses were performed using SPSS statistical package (version 15.0 for Windows, SPSS, Chicago, IL, USA). Data are presented as mean ± standard deviation or median (interquartile range), or counts and percentages. Differences in uric acid level between groups were evaluated with a Student's t test, and χ^2-test was used for categorical variables. Receiver Operating Characteristic (ROC) curve analysis was used with the purpose of testing discriminatory capability of uric acid with MetS status as dependent variable. In all analyses, P value of < 0.05 was considered as statistically significant.

RESULTS

Table 1 shows the general clinical and biochemical characteristics of the study participants.

Data are presented as mean ± standard deviation or median (interquartile range), or counts and percentages; BMI-Body mass index; WC-Waist circumference; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; SBP-Systolic blood pressure; DBP-Diastolic blood pressure

The prevalence of MetS and its components is presented in Table 2. MetS is diagnosed in 42.1% of women. As shown, the most prevalent feature was abdominal obesity (65.3%), following by hypertension (systolic blood pressure (SBP) and diastolic blood

pressure (DBP) accounting for 54.1% and 49.2% respectively), hyperglycemia (40.5%), and dyslipidemia (high triglycerides and low HDL-c level accounting for 30.2%, and 25.2% respectively).

Table 1. General characteristics of studied postmenopausal women
Tabela 1. Opšte karakteristike ispitivanih žena u postmenopauzi.

Characteristics	Postmenopausal women (n=242)
Age (years)	56.7± 4.52
BMI (kg/m^2)	27.2±4.00
WC (cm)	92.7±12.43
Fasting glucose (mmol/L)	5.40 (5.10-6.00)
Total cholesterol (mmol/L)	6.24±1.12
HDL-c (mmol/L)	1.56 (1.29-1.83)
LDL-c (mmol/L)	3.89 (3.25-4.58)
TG (mmol/L)	1.37 (0.99-1.76)
Uric acid (μmol/L)	276±62.0
SBP (mm Hg)	133±21.3
DBP (mm Hg)	83.7±12.3
Current smokers % (n)	16.9 (41)
Antihypertensive drugs % (n)	36.0 (87)
Lipid lowering drugs % (n)	13.2 (32)
Hypoglycemic drugs % (n)	19.4 (47)

Table 2. The prevalence of metabolic syndrome and its components among postmenopausal women
Tabela 2. Prevalenca metaboličkog sindroma i njegovih komponenti kod žena u postmenopauzi.

The prevalence of MetS and its components among postmenopausal women	%
MetS	42.1
WC ≥ 88 cm	65.3
Fasting glucose ≥ 5.6 mmol/L	40.5
HDL-c ≤ 1.29 mmol/L	25.2
TG ≥ 1.70 mmol/L	30.2
SBP ≥ 130 mm Hg	54.1
DBP ≥ 85 mm Hg	49.2

MetS-Metabolic syndrome; WC-Waist circumference; HDL-c-High density lipoprotein cholesterol; TG-Triglycerides; SBP-Systolic blood pressure; DBP-Diastolic blood pressure

In the current study we also aimed to test the association of MetS status with uric acid level. We found significantly higher number of

patients with MetS compared to subjects without diagnosed MetS across uric acid tertiles (χ2=27.02, P<0.001)), (Table 3). This confirmed, at least partially, the association of uric acid with MetS status in postmenopausal women in our study.

In addition, we found significantly higher uric acid levels were in postmenopausal women with MetS than in those without MetS (304±61.1 vs. 256±54.7 μmol/L, P<0.001), (Graph 1).

Table 3. Metabolic syndrome distribution in uric acid tertiles values subgroups
Tabela 3. Distribucija metaboličkog sindroma prema tercilnim vrednostima mokraćne kiseline.

MetS status	Uric acid tertiles values			P*
	I tertile (n=99) ≤251 μmol/L	II tertile (n=106) 252-350 μmol/L	III tertile (n=37) ≥350 μmol/L	
MetS +, n (%)	24 (23.5%)	52 (51.0%)	26 (25.5%)	χ2=27.02
MetS -, n (%)	75 (53.6%)	54 (38.6%)	11 (7.9%)	P<0.001

MetS+ women with Metabolic syndrome; MetS- women without Metabolic syndrome

Graph 1. Serum uric acid levels in postmenopausal women according to metabolic syndrome status
Dijagram 1. Serumske vrednosti mokraćne kiseline u odnosu na prisustvo metaboličkog sindroma.
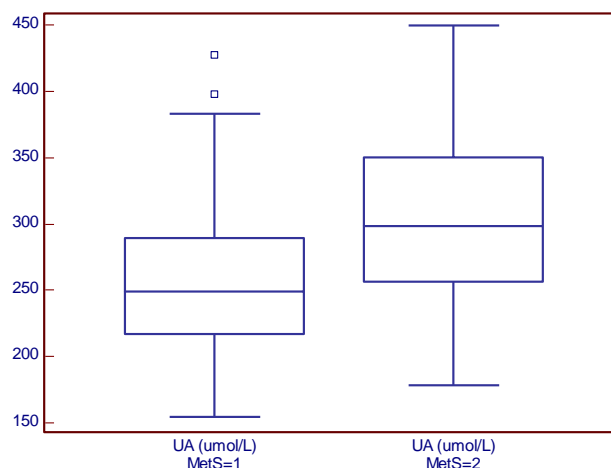
UA-uric acid; MetS=1-women without metabolic syndrome; MetS=2-women with metabolic syndrome

Thereafter, we conducted a receiver operating characteristic (ROC) analysis to test the discriminatory capability of uric acid regarding MetS status. Figure 1 shows ROC curve graph and Table 4 shows the most important ROC parameters: area under the curve (AUC) with 95% confidence interval (CI) of selected parameter.

ROC curve showed good discriminatory capability (AUC=0.722, according to Hosmer and Lemeshow's rules) toward the MetS status [14].

Table 4. Area under the curve, 95% Confidence Interval and Standard error for the uric acid discriminatory capability regarding the metabolic syndrome status
Tabela 4. Površina ispod krive, 95% Interval poverenja i standardna greška diskriminacione moći mokraćne kiseline u odnosu na metabolički sindrom.

Parameter	AUC	95% CI	SE	Sensitivity (%)	Specificity (%)	P
Uric acid	0.722	0.661-0.777	0.034	64.7	71.4	<0.001

AUC - area under ROC curve; CI- Confidence interval; SE-standard error

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Figure 1. ROC curve of the uric acid discriminatory capability regarding the metabolic syndrome status
Slika 1. ROC kriva diskriminacione moći mokraćne kiseline u odnosu na metabolički sindrom.
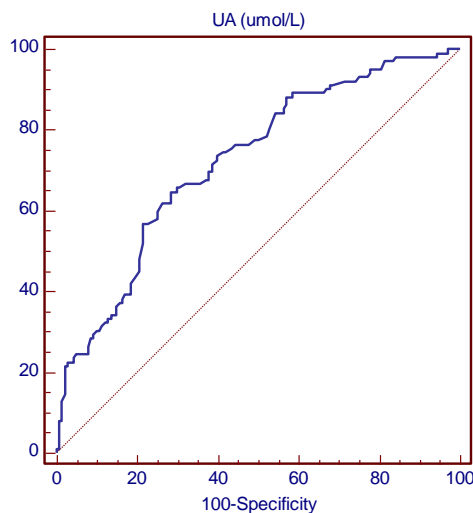
DISCUSSION

The incidence of MetS among postmenopausal women was found to be drastically increased in the world. In the current study the prevalence of MetS was 42.1%, with abdominal obesity as the most prevalent feature (65.3%) which is similar with the results of the other studies [15]. The high prevalence of MetS among postmenopausal women in the world varies from 32.6% in Austria, to 54.6% in South Korea [16]. In Chinese postmenopausal women the prevalence of MetS was 33.7% [17]. According to a study of Pandey et al. [18] the prevalence of MetS among Indian postmenopausal women was 55%. Moreover, MetS was highly prevalent among Brasilian postmenopausal women [19], and the most prevalent risk factor was abdominal obesity, affecting 62.5% of women. MetS also seems to be a major health problem among postmenopausal women in many developing countries, like Bangladesh, accounting for 39.3% of postmenopausal women having MetS. Even more, the prevalence of MetS was 1.78 times higher in postmenopausal women than in premenopausal ones [19]. Neto et al. [6] found that women between 40 and 45 years had a prevalence of MetS of 14.1%, while for women between 56 and 64 years the prevalence was even 66.7%.

The obtained results of the current study are unexpected. Taking into account that Montenegro is the part of Mediterranean basin, and that Mediterranean-type dietary pattern would be expected as the preferable one due to easy access of consumers to the Mediterranean products, these results are discouraging. The possible explanation for this may be the sedentary lifestyle and unhealthy dietary pattern, with the increasing prevalence of obesity.

It is important to note that this prevalence would be expected to be even higher if we take into consideration the International Diabetes Federation criteria (IDF), with lower WC cut-off values ≤80 cm [20] than reported in the current study.

In addition to the assessment of traditional risk factors, as components of MetS, we have been explored serum uric acid level and showed its good discriminatory capability toward MetS status. In line with previous studies [21-23] we reported higher serum uric acid level in women with MetS, comparing to those without MetS. Moreover, in a prospective study conducted by Zurlo et al. [24] high serum uric acid levels significantly and independently predicted MetS in older women, but not in men, over a 4.4-year follow-up.

The underlying mechanism of the association between serum uric acid levels and MetS risk remains poorly elucidated. The elevated serum uric acid level observed in the MetS has been attributed to hyperinsulinemia, since insulin reduces renal excretion of uric acid [11]. In animal studies, hyperuricemia might induce MetS by two mechanisms. Firstly, hyperuricemia may have a causal role in the pathogenesis of insulin resistance. High levels of serum uric acid inhibit endothelial nitric oxide

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(NO) bioavailability and insulin requires endothelial NO to stimulate skeletal muscle glucose uptake. Secondly, hyperuricemia induces oxidative and inflammatory changes in adipocytes, inducing MetS in obese mice [25].

In addition to this, we previously reported a significant relationship between serum uric acid level and anthropometric parameters, stronger with WC than with BMI, implicating that visceral adipose tissue is the main determinant of serum uric acid level [26]. Furthermore, in our previous study we showed that uric acid correlated with the majority of components of MetS, including insulin resistance. However, these correlations were not retained in multiple regression analysis, while only abdominal obesity (as measured by WC), which is the most prevalent feature of MetS in the current study, remained significant independent predictor of higher uric acid levels. Central obesity progressively increases hepatic and adipose tissue insulin resistance with consequent metabolic abnormalities like impaired glucose tolerance, decreased HDL-c, elevated triglycerides and hypertension [27]. These results suggest an important mechanism through which obesity and hyperuricemia can influence on higher risk of MetS and CVD.

Several limitations of our study must be emphasized. The subjected patients were not asked to discontinue their medications, such as antihypertensive, lipid-lowering and hypoglycemic drugs. Furthermore, since this was a cross-sectional study, the causal relationship between MetS and uric acid level in postmenopausal women could not be established. Above of this, as our study was not based on general population, selection bias might have affected the outcome of the study. Thus larger sample size in general population may be required to confirm the results of the present study.

CONCLUSION

To our knowledge the current study is the first one to examine the prevalence of metabolic syndrome among postmenopausal women in Montenegro. The obtained results are discouraging, but do not significantly differ from other countries, which is in accordance with the results of the increasing prevalence of MetS among postmenopausal women in the world. It is clear that weight gain and central obesity drives the increased prevalence of MetS in postmenopausal women. The most prevalent feature in our study was abdominal obesity which supported these findings. Furthermore, women with MetS displayed higher serum uric acid levels, as compared with those without MetS. This suggests the importance of reducing obesity and lowering uric acid level in prevention of cardiometabolic diseases.

Conflict of Interest Statement
The authors have declared no conflicts of interest.

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