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ORIGINAL RESEARCH

Uric acid level and the presence of metabolic syndrome: experiences from Vojvodina Region in Serbia

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ABSTRACT

Introduction: Uric acid level (UAL) might represent an indirect marker of metabolic syndrome (MS). Study investigates differences in UAL in the overall study group and in separate groups of normal weight, overweight and obese subjects, regarding the presence of MS. ***Patients and Methods:*** Cross sectional study included 1333 participants. Anthropometrical measurements and relevant blood analysis were performed. For diagnosis of MS we used NCEP ATP III criteria. ***Results:*** 50.64% of the participants have fulfilled criteria for MS diagnosis. In the overall study group, participants with MS were older ($p<0.0001$), more often male ($p=0.0025$), had higher BMI ($p<0.0001$) and UAL ($p=0.0003$). In the group of obese subjects, participants with MS were also older ($p<0.0001$), more often male ($p<0.0001$), had higher BMI ($p=0.0084$) and UAL ($p=0.0014$). In both cases, stepwise logistic regression showed independent association of all four parameters, which significantly differed in univariate analysis, with MS. In the group of normal weight subjects, participants with MS were more often male ($p=0.0001$), while in overweight subjects, participants with MS were older ($p=0.0005$). ***Conclusion:*** UAL is higher in subjects with MS in the overall study group and in the group of obese subjects, but not in groups of normal weight and overweight persons.

Keywords: *Uric acid, cardiovascular diseases, metabolic syndrome, obesity, overweight, normal weight*

Introduction

Uric acid (UA) is the end product of nucleic acid metabolism. High levels of blood UA are associated with gout.[1] Recent cohort studies suggest a causal relationship between hyperuricemia and risk of adverse cardiovascular events.[2, 3] However, some of the studies fail to demonstrate this association after controlling for various atherosclerotic risk factors.[4] Nevertheless, UA level (UAL) might represent an indirect marker of metabolic syndrome (MS)[5] and an indicator of "metabolically unhealthy" obesity[6], a term which usually refers to the obese persons with developed MS. Determination of UAL could be of great importance, especially in populations, such is population of Vojvodina, where 58.5 % of citizens are overweight and obese.[7]

Possible explanation for the association between higher waist circumference and hyperuricemia is generated from the evidence of independent correlation between UA and leptin levels, which could be a pathogenic factor responsible for UAL increase in obese patients.[8]

Association of triglycerides and UA lays in the fact that synthesis of fatty acids in the liver is associated with the de novo synthesis of purine and accelerated UA production.[9]

On the other hand, HDL cholesterol is associated with UA through action of insulin resistance.[10] Association of insulin resistance and impaired glucose metabolism with UAL rises from the insulin-induced urinary sodium retention and consequent decreased UA clearance.[11] Increased UAL are also associated with increased blood pressure through effects on the renin-angiotensin system and increased insulin resistance.[6]

UA contributes in development of MS also through inducing proinflammatory response.[1] This response is produced by the action of monosodium urate crystals, which directly trigger neutrophil activation, and indirectly activate NALP 3 inflammasome, throughout Toll-like receptor mediation.[1] It also increases the synthesis of monocyte chemoattractant protein 1.[12] UA acts proatherogenic via upregulation of expression of platelet-derived growth factor[13] and increase in proliferation of vascular smooth muscle cells.[14]

Study investigates the differences in UAL between persons without and with diagnosed MS in the overall study group and in separate groups of normal weight, overweight and obese subjects. We presumed that UAL is independently associated with the presence of MS in all study groups and thus can be

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used as an indirect marker of MS in the general population.

Patients and Methods

Cross sectional study included 1333 randomly selected patients, who came on regular health check examination at our outpatient clinic. Participants in study did not have previous history of diabetes, dyslipidemia or hypertension treatment and they were not taking any drugs which could affect the values of the analyzed parameters. Also, according to their knowledge, they were not suffering from any other acute or chronic illness which could have an effect on the analyzed parameters.

Study has been approved by the local ethics committee and it is performed according to Helsinki Declaration. All participants gave their written consent for partaking in the study. Patient's general information and medical history were noted and physical examination was conducted. After that, anthropometrical measurements were performed. Body height was measured with Martin anthropometer with accuracy of 0.1 cm, while body weight was measured with professional medical body weight scale. Body mass index (BMI) was calculated as a ratio of body weight and square value of body height expressed in meters. Waist circumference was measured at the middle of the line connecting the anterior superior iliac crest bone and arch ribs with a centimeter tape with a precision of 0.1 cm. Blood pressure was measured using sphygmomanometer according to Riva-Rocci. The measurement was performed in sitting position, after 10-15 minutes of the rest period. Blood was sampled for analysis of fasting glucose, lipid and lipoprotein parameters (triglycerides and high density lipoprotein (HDL) cholesterol) and UA. Fasting glucose was analyzed with Dialab glucosa GOD-PAP method. For the determination of triglycerides we used standard enzymatic method. HDL cholesterol was analyzed with method of precipitation with sodium-phospho-tungstate. UAL was determined with modified PAP method.

For diagnosis of MS we used NCEP ATP III criteria (National Cholesterol Education Program, Adult Treatment Panel III, 2001).[15] According to these guidelines, MS is defined with presence of three or more of the following risk determinants: increased waist circumference (>102 cm for men and >88 cm for women), elevated triglycerides (≥1.70 mmol/l), low HDL cholesterol (<1.03 mmol/l for men and <1.30 mmol/l for women), impaired fasting glucose (≥6.1 mmol/l) and hypertension (≥130/≥85 mmHg).

In statistical processing of the data we used mean values, proportions, Student`s t-test, test of proportions, Pearson's and Spearman's correlation coefficients and stepwise logistic regression.

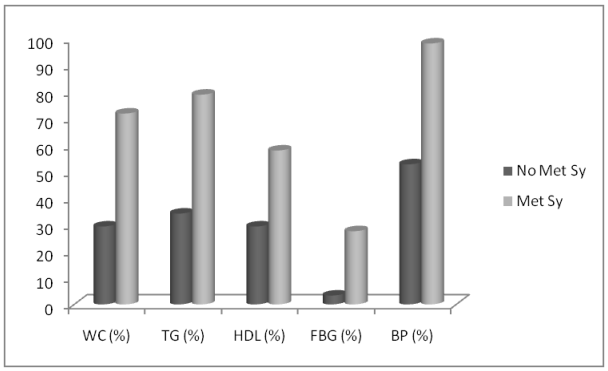
Table 1. Characteristics of study group

Parameter	Mean value/proportion (n=1333)
Age (years)	43.50 ± 10.43
Male gender (%)	52.59
Body mass index (kg/m²)	30.68 ± 7.55
Waist circumference (cm)	98.11 ± 15.80
Triglycerides (mmol/l)	2.08 ± 1.70
HDL (mmol/l)	1.13 ± 0.26
Fasting glucose (mmol/l)	5.18 ± 1.31
Systolic blood pressure (mmHg)	134.08 ± 17.93
Diastolic blood pressure (mmHg)	86.49 ± 12.25
Uric acid (μmol/l)	310.15 ± 90.96

Results

Seven hundred and one participants were men (Table 1). More than half of the examined participants have fulfilled criteria for MS diagnosis (50.64%). Hypertension had highest incidence of all MS risk determinants in the group with diagnosed MS and in the group without MS, as well (Figure 1).

Figure 1. Incidence of detected risk determinants of MS in groups without and with diagnosed MS



WC-waist circumference; TG-triglycerides; HDL-HDL cholesterol; FBG-fasting blood glucose; BP-blood pressure

As it was expected, incidence of obesity (BMI ≥ 30 kg/m2) was pronouncedly higher in the group of participants with MS with regard to the group without MS (Figure 2). Understandably, participants with MS had higher BMI. They were older and more often male. Also, they had higher UAL (Table 2).

Table 2. Age, gender, BMI and UAL differences between groups without and with diagnosed MS in the overall study group

Parameter	No MS (n=658)	MS (n=675)	p value
Age (years)	41.97 ± 10.41	45.00 ± 10.24	<0.0001*
Male gender (%)	48.33	56.74	0.0025*
BMI (kg/m²)	28.15 ± 6.27	33.15 ± 7.86	<0.0001*
Uric acid (μmol/L)	300.99 ± 94.68	319.08 ± 86.32	0.0003*

UAL did not show significant correlation with any of other analyzed parameters which significantly differed between two groups (age: r=0.02832, P=0.3016; male gender: rho=0.00630, P=0.8182; BMI: r=0.03479, P=0.2043). Stepwise logistic regression showed independent association of all included parameters (age, male gender, BMI and UAL) with MS (Table 3).

Table 3. Stepwise logistic regression with MS as dependent variable and age, male gender, BMI and UAL as independent variables in the overall study group

Parameter	p value	Odds ratio	95% confidence interval
Age	<0.0001*	1.0316	1.0192-1.0441
Male gender	<0.0001*	2.4926	1.9029-3.2650
BMI	<0.0001*	1.1477	1.1240-1.1718
Uric acid	0.0007*	1.0023	1.0010-1.0036

Based on the BMI calculation, participants were classified into: normal weight (24.68%), overweight (30.38%) and obese (44.94%) groups. In the separate group of normal weight subjects, participants with MS were more often male, while other parameters did not show significant difference between two groups (Table 4).

Table 4. Age, gender, BMI and UAL differences between groups of normal weight subjects without and with diagnosed MS

Parameter	No MS (n=225)	MS (n=74)	p value
Age (years)	39.83 ± 10.31	41.15 ± 12.54	0.3574
Male gender (%)	52.55	78.38	0.0001*
BMI (kg/m²)	22.72 ± 1.37	22.97 ± 1.34	0.1659
Uric acid (μmol/l)	295.60 ± 85.63	313.38 ± 91.40	0.1224

As far as for the separate group of overweight persons, subjects with MS were older, while other parameters also did not show significant difference between two groups (Table 5).

Table 5. Age, gender, BMI and UAL differences between groups of overweight subjects without and with diagnosed MS

Parameter	No MS (n=210)	MS (n=195)	p value
Age (years)	46.85 ± 8.17	49.49 ± 6.94	0.0005*
Male gender (%)	68.57	73.33	0.3452
BMI (kg/m²)	27.33 ± 1.40	27.58 ± 1.38	0.0714
Uric acid (μmol/L)	312.79 ± 94.89	317.02 ± 87.30	0.6416

With regard to the separate group of obese subjects, participants with diagnosed MS had higher BMI. They were older and more often male. Also, they had higher UAL (Table 6).

Table 6. Age, gender, BMI and UAL differences between groups of obese subjects without and with diagnosed MS

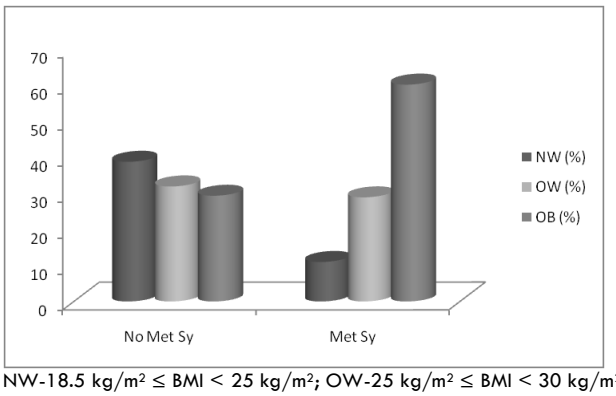
Parameter	No MS (n=193)	MS (n=406)	p value
Age (years)	39.47 ± 10.92	43.55 ± 10.41	<0.0001*
Male gender (%)	20.73	44.83	<0.0001*
BMI (kg/m²)	36.23 ± 4.96	37.69 ± 6.86	0.0084*
Uric acid (μmol/L)	295.27 ± 104.65	321.11 ± 85.04	0.0014*

UAL did not show significant correlation with any of other analyzed parameters which significantly differed between groups of obese subjects without and with diagnosed MS (age: r=-0.002491, P=0.9515; male gender: rho=0.0368, P=0.3681; BMI: r=0.004721, P=0.9082). Stepwise logistic regression showed independent association of all included parameters (age, male gender, BMI and UAL) with MS in obese subjects (Table 7)

Table 7. Results of stepwise logistic regression with MS as dependent variable and age, male gender, BMI and UAL as independent variables in the group of obese subjects

Parameter	p value	Odds ratio	95% confidence interval
Age	0.0078*	1.0251	1.0066-1.0440
Male gender	<0.0001*	4.4047	2.7452-7.0675
BMI	<0.0001*	1.1112	1.0695-1.1545
Uric acid	0.0007*	1.0035	1.0014-1.0056

Figure 2. Incidence of normal weight (NW), overweight (OW) and obesity (OB) in groups without and with diagnosed MS



NW-18.5 kg/m² ≤ BMI < 25 kg/m²; OW-25 kg/m² ≤ BMI < 30 kg/m²; OB-BMI ≥ 30 kg/m²

Discussion and Conclusion

It is widely known that obesity is associated with greater risk for developing MS. Association of hyperuricemia with obesity and MS was found by previous studies, as in adults[16] and, also, in children.[17] One of the population based studies reported that an increment of one standard deviation of serum UAL is associated with a 35% higher MS likelihood in both sexes, independent of ten risk factors related to MS.[18]

Similar to our results, previously conducted study showed that age and male gender are associated with greater risk for MS in adults.[19]

As far as for separate MS components, earlier publications showed association of abdominal obesity and UAL in patients with high cardiovascular risk and normal UAL.[20] Considering lipid and lipoprotein parameters, other investigators found association of triglycerides and HDL cholesterol with UAL in general population.[21] Interestingly, association was also found between triglycerides to HDL cholesterol ratio and UAL, even independently of obesity and MS in the study which enrolled subjects without previous history of cardiovascular diseases.[22] Follow-up study conducted by Finnish Diabetes Prevention Study Group showed that UAL and its changes during follow-up were related to corresponding changes in fasting and post load glucose and insulin levels in overweight and obese persons with impaired glucose tolerance.[23]. Cohort study which was performed in China reported that UAL is an independent predictor of blood pressure progression and incident hypertension in general population.[24]

UAL is significantly higher in subjects with diagnosed MS in both overall study group and in the group of obese subjects, but not in normal weight and overweight groups. Multivariate analysis showed independent association of UAL and the presence of MS in both overall study group and in the group of obese subjects. This leads to the conclusion that UAL could be used as a marker of "metabolically unhealthy" phenotype, mainly in obese person. Considering the present knowledge of pathophysiological mechanisms of association between the UAL and the components of MS, analysis of serum UAL could detect obese persons who are at greater risk for developing metabolic complications and MS. Meta-analysis which will include a great number of studies dealing with role of UA in MS development could define what exact values of UA are associated with greater risk of MS development.

The value of this study lays in the fact that it is conducted among subjects with different nutritional status, so it tested UAL in separate groups of normal weight, overweight and obese persons. The major limitation of this study is modest set of analyzed parameters and consequential lack of the data on other factors which are relevant for MS research.

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