

Original paper

Is the increase of uric acid associated with the components of the metabolic syndrome?

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Summary

Objectives: There is increasing evidence that metabolic syndrome (MetS) may be associated with increased uric acid levels. Previous studies indicate that hyperuricaemia is an independent risk factor for cardiovascular disorders. We sought to determine the association of serum uric acid (SUA) with MetS components and other cardiovascular risk factors among middle aged Lithuanians with MetS.

Design and methods: A cross-sectional study was conducted in 2018. A total of 705 subjects aged 40 to 65 years with MetS diagnosed using NCEP ATP III criteria were included. None of the participants had previously diagnosed cardiovascular, cerebrovascular, peripheral artery or end-stage oncological disease. Blood tests and all anthropometric measurements were obtained using standard methods. Subjects were divided into 2 groups: with hyperuricaemia and without hyperuricaemia.

Results: Hyperuricaemia was found in 33.3% of subjects. Mean serum uric acid level increased as the number of metabolic factors increased. Participants with hyperuricaemia had abnormal waist circumference ($p < 0.001$), higher systolic ($p = 0.001$) and diastolic blood pressure ($p = 0.003$), higher levels of triglycerides and, lower levels of high-density lipoprotein cholesterol ($p < 0.001$). Subjects in hyperuricaemia group were more likely to be alcohol users ($p = 0.034$), to have diabetes ($p = 0.02$) and higher body mass index ($p < 0.001$). Their creatinine levels were statistically significantly higher ($p < 0.001$).

Conclusions: Our analysis showed that serum uric acid is associated with MetS and other cardiovascular risk factors. The study found a statistically significant association with the four out of five components of the MetS (excluding plasma glucose) as well as with alcohol consumption, and renal function indicators (creatinine, eGFR).

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Keywords: metabolic syndrome, cardiovascular risk factors, hyperuricaemia, uric acid

Introduction

Metabolic syndrome (MetS) is a group of inter-related metabolic disorders that include impaired glucose tolerance, insulin resistance, abdominal

obesity, dyslipidaemia and arterial hypertension [1]. In the last decade, there is increasing evidence that metabolic syndrome may be associated with increased serum uric acid (SUA) levels. Previously it has been considered that elevated SUA is clinically insignificant, but hyperuricaemia was defined as an independent risk factor for cardiovascular diseases since 2018 [2], which is also associated with a risk of metabolic syndrome and increased cardiovascular mortality, as well as vascular diseases, especially in postmenopausal women. Hyperuricaemia can be caused by obe-

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sity, moderate to high alcohol consumption, high blood pressure (BP), impaired renal function, and also dyslipidaemia. Some medications and diseases also increase the amount of SUA. Renal function was found to be associated with both cardiovascular diseases and metabolic syndrome, and we decided to investigate the relationship with uric acid in our studied population [3]. Therefore, the aim of our study was to examine the association of SUA with the presence of MetS components and other cardiovascular risk factors such as smoking, alcohol consumption, and renal function markers among middle-aged Lithuanians with MetS.

Materials and methods

Subjects and study design

A total of 705 (53.6 ± 6.6 years old, 62.3% female) subjects were recruited from May 2018 to November 2018 being participants of ongoing Lithuanian High Cardiovascular Risk primary prevention program (LitHiR) [4]. Written informed consent was obtained from each participant. The investigation conforms with the principles outlined in the Declaration of Helsinki and approved by the local ethics committee (No. 158200-18/4-1006-521). The involvement criteria were as follows: age for men 40–55 years, for women – 50–65 years, MetS diagnosed according to the NCEP ATP III definition (3 or more of the following factors present: hypertension or pre-hypertension (systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg), waist circumference (WC) of ≥ 102 cm for men or ≥ 88 cm for women, serum triglycerides (TG) of ≥ 1.7 mmol/L, serum high-density lipoprotein cholesterol (HDL-C) of < 1.03 mmol/l for men or < 1.29 mmol/l for women, plasma glucose ≥ 5.6 mmol/L). The exclusion criteria were: previously diagnosed cardiovascular disease, cerebrovascular disease, peripheral artery disease or end-stage oncological disease. Prescribed reimbursable medications were not discontinued.

Anthropometric and blood pressure measurement

BP was measured twice on the right upper arm using an oscillometric semiautomatic device, validated according to a standardized mercury sphygmomanometer, while the patient was seated and had been resting for at least 10 minutes. WC was measured horizontally at the umbilical level using a metal tape while the patient was standing. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Height and weight were measured while

the patient was without shoes and had only light indoor clothes on. Use of tobacco or alcohol was noted if reported by patients.

Laboratory measurements

Venous blood samples for laboratory measurement of SUA, lipid panel, plasma glucose, and creatinine levels were taken from the subjects in the morning after an overnight fast. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.

Statistical analysis

All analyses were performed using STATISTICA (version 10) and R (version 3.6.1). Descriptive statistics were computed for demographic information. Data were expressed as mean $\pm$ standard deviation for continuous variables and as absolute and percentage values for categorical variables. Continuous variables were analysed using Student's t-test or Mann–Whitney U test, categorical variables with Pearson's chi-square test. Logistic regression was performed to assess risk factors for hyperuricaemia. Odds ratios were calculated from multivariable models adjusted for age and sex. For all tests, *p*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

All 705 subjects were middle-aged individuals (53.6 ± 6.6 years, median 54 years), 62.3% of them were female. Summarized baseline anthropometric, clinical, and biochemical characteristics of subjects with hyperuricaemia and without hyperuricaemia are presented in Table 1.

Among the whole study population, 33.3% had hyperuricaemia and 63.8% ($n = 150$) of all subjects were female. According to hospital normal laboratory values, hyperuricaemia was considered when SUA was > 357 $\mu\text{mol/l}$ for women and > 428 $\mu\text{mol/l}$ for men. Mean values of SUA were 422.08 ± 58.16 $\mu\text{mol/l}$ ($p < 0.001$) and 492.00 ± 46.66 $\mu\text{mol/l}$ ($p < 0.001$) of females and males from hyperuricaemia group accordingly.

Subjects with hyperuricaemia had statistically significantly higher WC ($p < 0.001$), as well as their systolic and diastolic BP values were higher. SUA positively correlated with TG, and negatively associated with HDL-C. The same results and association with TG and HDL-C were observed even after adjustment of the lipids and recalculation for participants who did not take statins during the study (Table 2). Subjects of this group had other cardiovascular risk factors. Participants with SUA levels above the normal more

Table 1.
Baseline characteristic of the study population stratified by uric acid levels

Characteristic	Total (N = 705)	Without hyperuricaemia (N = 470)	With hyperuricaemia (N = 235)	p-value*	OR	p-value**
SUA, $\mu\text{mol/l}$	359.04 $\pm$ 86.63	314 $\pm$ 58.05	447.37 $\pm$ 63.79	<0.001	–	–
Age, years	53.6 $\pm$ 6.6	53.7 $\pm$ 6.4	53.4 $\pm$ 7.0	0.740	0.955	0.103
Smoker, N (%)	152 (21.6)	108 (23.0)	44 (18.7)	0.191	0.770	0.175
Alcohol user, N (%)	393 (57.3)	250 (54.5)	143 (63.0)	0.034	1.423	0.028
AH, N (%)	609 (86.4)	400 (85.1)	209 (88.9)	0.162	1.407	0.175
Diabetes, N (%)	142 (20.1)	83 (17.7)	59 (25.1)	0.020	1.563	0.018
Dyslipidaemia, N (%)	685 (97.2)	457 (97.2)	228 (97.0)	0.873	0.927	0.906
Weight, kg	91.86 $\pm$ 15.78	89.17 $\pm$ 15.36	97.26 $\pm$ 15.26	<0.001	1.707	<0.001
BMI, kg/m^2	31.68 $\pm$ 4.50	30.75 $\pm$ 4.16	33.53 $\pm$ 4.58	<0.001	1.930	<0.001
WC, cm	102.79 $\pm$ 10.39	101.10 $\pm$ 10.29	106.17 $\pm$ 9.77	<0.001	1.672	<0.001
SBP, mmHg	136.64 $\pm$ 14.85	135.28 $\pm$ 14.45	139.36 $\pm$ 15.29	0.001	1.316	<0.001
DBP, mmHg	82.08 $\pm$ 9.46	81.33 $\pm$ 9.27	83.55 $\pm$ 9.67	0.003	1.266	0.003
TC, mmol/l	6.05 $\pm$ 1.41	6.06 $\pm$ 1.45	6.04 $\pm$ 1.35	0.969	0.987	0.773
LDL-C, mmol/l	3.80 $\pm$ 1.15	3.83 $\pm$ 1.15	3.76 $\pm$ 1.14	0.482	0.950	0.444
HDL-C, mmol/l	1.25 $\pm$ 0.32	1.27 $\pm$ 0.32	1.21 $\pm$ 0.31	<0.001	0.809	0.003
TG, mmol/l	2.26 $\pm$ 2.94	2.22 $\pm$ 3.47	2.35 $\pm$ 1.36	<0.001	1.043	0.572
Plasma glucose, mmol/l	6.51 $\pm$ 1.79	6.50 $\pm$ 1.93	6.52 $\pm$ 1.47	0.063	1.008	0.885
Creatinine, $\mu\text{mol/l}$	71.96 $\pm$ 12.18	70.58 $\pm$ 11.53	74.69 $\pm$ 12.97	<0.001	1.396	<0.001
eGFR <90, N (%)	274 (38.9)	161 (34.3)	113 (48.1)	<0.001	1.778	<0.001

*Student's t-test, Mann–Whitney U test or Pearson's chi-square test as appropriate.

**adjusted for age and sex.

SUA – serum uric acid; AH – arterial hypertension; BMI – body mass index; WC – waist circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; eGFR – estimated glomerular filtration rate.

Table 2.
Lipidogram in participants not taking statins and stratified by uric acid levels

Characteristic	Without hyperuricaemia (N = 350)	With hyperuricaemia (N = 185)	p-value*	OR	p-value**
TC, mmol/l	6.29 $\pm$ 1.24	6.26 $\pm$ 1.30	0.771	0.820	0.826
LDL-C, mmol/l	4.07 $\pm$ 1.07	3.97 $\pm$ 1.08	0.241	0.757	0.290
HDL-C, mmol/l	1.28 $\pm$ 0.31	1.21 $\pm$ 0.31	0.004	0.617	0.009
TG, mmol/l	2.04 $\pm$ 1.58	2.41 $\pm$ 1.46	<0.001	1.062	0.010

*Student's t-test or Mann–Whitney U test as appropriate.

**adjusted for age and sex.

TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides.

often used alcohol, had higher BMI, as well as weight, and higher creatinine levels and eGFR. A graph illustrating the association between renal function, expressed as a derivate indicator (eGFR) and the levels of SUA is shown in Figure 1. Participants with hyperuricaemia also had a higher prevalence of diabetes and primary arterial hypertension (PAH) and therefore used more medications, especially angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), beta-adrenergic blocking agents (BAB), calcium channel blockers (CCB) and diuretics. A table of all medications used by participants

stratified by uric acid levels is given below (Table 3).

Distribution of MetS components

Assessing the distribution of MetS variables in the studied population, it was found that participants with three (33.7%) or four (33.1%) components predominated. Less than three components of MetS were present in 12.7% and all five in 20.5% of subjects. A statistically significant difference was obtained between patients without hyperuricaemia and with hyperuricaemia ($p < 0.001$). As expected, individuals with 3 or more MetS components were more likely to be in the

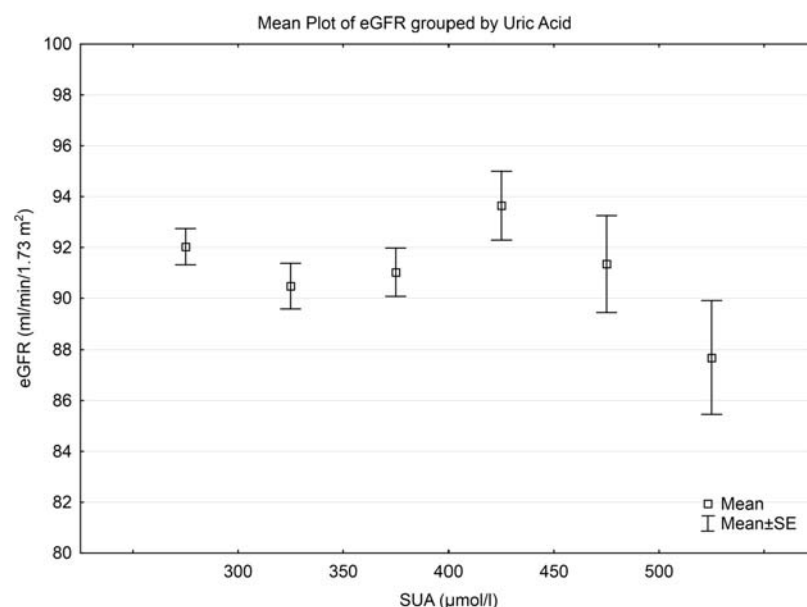


Figure 1. Correlation between the glomerular filtration rate and uric acid levels in study population.

Table 3.

Medications used by the study population stratified by uric acid levels

Medication	Total (N = 705)	Without hyperuricaemia (N = 470)	With hyperuricaemia (N = 235)	p-value*	OR	p-value**
ACE inhibitors or ARBs, N (%)	382 (54.3)	242 (51.6)	140 (59.6)	0.045	1.382	0.037
BAB, N (%)	245 (34.8)	152 (32.4)	93 (39.6)	0.060	1.366	0.068
CCB, N (%)	162 (23)	94 (20)	68 (28.9)	0.008	1.624	0.005
Diuretics, N (%)	145 (20.6)	72 (15.4)	73 (31.3)	<0.001	2.485	<0.001
Statins, N (%)	169 (24.0)	119 (25.4)	50 (21.3)	0.230	0.795	0.338

*Pearson's chi-square test.

**adjusted for age and sex.

ACE – angiotensin-converting enzymes; ARBs – angiotensin II receptor blockers; BAB – beta-adrenergic blocking agents; CCB – calcium channel blockers.

hyperuricaemia group, and with less than 3 components in the subjects without hyperuricaemia.

Discussion

In this study we approached to evaluate the association of SUA with MetS components and other cardiovascular risk factors such as smoking, alcohol consumption, and renal function (creatinine, eGFR).

The results of our study showed that serum uric acid was significantly associated with MetS and with four out of five its components. Higher SUA levels were present in subjects with abnormal WC, TG, HDL-C levels and BP. Similar results were observed in many other studies [5–9]. However, a number of studies found different associations with MetS components and higher SUA levels [10,11]. The main reason might be the different

study populations: some findings demonstrate that significant associations vary across gender [12–16] and age [13,15].

However, most studies [7,11,17] found, as we did, that SUA was higher with the increasing number of MetS components. Studies of prospective cohorts suggest that subjects with higher SUA at the baseline after a few years of follow-up had an increased risk of developing MetS [18–20]. This implies that SUA is a part of the MetS and could be one of MetS components. Nejatnamini et al. found that higher SUA level was associated with an increased odds ratio of MetS and is an independent risk factor of it [21]. On the other hand, the recent study of Wang et al. found no causal evidence to support that increased serum uric acid is a causal risk factor for MetS or its components [22].

Hyperuricaemia is commonly associated with arterial hypertension; thus, the BP component

was expected to be in statistically significant MetS combinations. However, we found no difference in groups with hyperuricaemia and without hyperuricaemia concerning prevalence of hypertension. Our results are in line with those of Wang et al. They found no association with hypertension [6]. The explanation to that could be the use of antihypertensive drugs that might affect the results and uric acid levels; therefore, it may be difficult to correctly assess the relationship between SUA and hypertension.

We have tried to find the relationship between the levels of SUA and the use of different groups of antihypertensive drugs. It is common knowledge that some antihypertensive drugs, especially diuretics are related to the level of SUA [23]. A study in 2019 analysed the relationship between the level of SUA and thiazide diuretics. Results showed that hyperuricaemia is a more common occurrence in thiazide diuretic users as compared to non-users. As the years of thiazide usage advanced, the number of hyperuricaemia participants also significantly increased [24]. The results of this study comply with the results of our study which also shows a statistically significant relationship between the levels of SUA and diuretic usage. Another study analysed the effect of perindopril and telmisartan treatment on anti-inflammatory cytokines in the hypertensive patients. Results showed that neither telmisartan nor perindopril affected circulating levels of uric acid [25]. Whereas our study showed a statistically significant relationship between ACE inhibitors and ARBs usage and the increased levels of SUA. It can be explained by the fact that our study included a bigger population, as well as the fact that we have analysed the drug groups instead of individual drugs. The study by Kansui et al. analysed the data of almost 4000 subjects and showed that SUA levels might be associated with the increase of BP because there is no relation between SUA and BP in the subjects treated with antihypertensive medications [26]. Further studies are required in order to find out the role of uric acid in BP increase.

A cross-sectional Japanese study investigated and found a strong association between SUA levels with both systolic and diastolic BP in healthy subjects who were not taking antihypertensive drugs [27].

Many studies show SUA correlation with dyslipidaemia [5,8]. However, we found no differences of distribution of diagnosed dyslipidaemia between our groups with hyperuricaemia and without hyperuricaemia. Lithuanians are more prone to have dyslipidaemia due to high LDL-C [28], the same was revealed by our results of the mean LDL-C. For this reason, we can assume why

dyslipidaemia was diagnosed in the majority of the studied population (97.2%) resulting in no differences between groups. On the other hand, we found statistically significant correlation of SUA with serum TG and HDL-C. Some other studies as well showed that serum TG correlates independently with SUA levels [7,29].

Interestingly, we found no association between higher SUA and higher plasma glucose as a separate MetS component. This might be due to the fact, that 79.2% of our subjects had higher plasma glucose (≥ 5.6 mmol/l). Thus, we found that subjects with hyperuricaemia had a higher prevalence of diabetes. At the beginning of the study, it was not clear whether diabetes was well controlled with medication, but from the mean plasma glucose, which was <7 mmol/l, we can assume that for most participants, diabetes was well controlled. A lot of studies have shown, that high SUA levels are associated with increased insulin resistance [7,30]. That could explain why there was no association between SUA levels and fasting glucose, but there was an association with diabetes.

WC as obesity indicator and BMI have a strong correlation with higher SUA levels in Western and Asian populations in different age groups [15,31,32]. Reflecting this, we found the same correlation among the middle-aged Lithuanian population.

Without the association of SUA and variables of MetS, a direct correlation between SUA and indicators of renal function (creatinine and eGFR) was also determined. The results showed an increasing trend in the mean serum creatinine concentration with a corresponding decreasing in eGFR. National Health and Nutrition Exam study (NHANES) [33] and German chronic kidney Disease (GCKD) study [34] are large and lengthy researches that showed an association of increased incidence of hyperuricaemia and decreased in eGFR. Al-Daghri et al. were the first ones who demonstrated the relation of SUA to creatinine levels with MetS and its components [35].

It is likely that some dietary factors may affect obesity and dyslipidaemia or directly SUA levels, also that alcohol consumption increases uric acid levels [36]. In this data analysis we did not investigate the dietary habits of participants, but it is planned to further examine dietary habits that could affect SUA concentration. However, we looked at smoking and alcohol consumption. Among our subjects smoking was found to have no association with hyperuricaemia, though there are some studies that found smoking was dominant in hyperuricaemia group with BMI ≥ 25 , but not in subjects with BMI < 25 [37]. Alcohol consumption in patients

with gout is contraindicated because it is known that alcohol is rich in purines and the final product of their metabolism is namely uric acid. Many studies, including results of this study, have demonstrated an association between alcohol and hyperuricaemia. What is interesting, despite the fact that Seki et al. confirmed that alcohol drinkers had significantly higher SUA levels, is that they also found a direct correlation of uric acid levels with BP and creatinine in this group [38]. There are several mechanisms of alcohol-induced hypertension and they are related to an imbalance of the central nervous system, increased sympathetic system activity, and stimulation of the renin-angiotensin system [39].

Conclusions

Our analysis showed the importance of uric acid in subjects with MetS – patients with hyperuricaemia had worse biochemical and anthropometric parameters. Subjects with hyperuricaemia had abdominal obesity, higher blood pressure, increased triglycerides and decreased high-density lipoprotein cholesterol levels. They consumed alcohol and had diabetes more often. Hyperuricaemia was also associated to worse renal function.

Conflicts of interest

The authors have no conflicts of interest to declare.

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