Correlation of uric acid levels and parameters of metabolic syndrome

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Short title: Correlation of uric acid and metabolic syndrome

Summary

Aim: Hyperuricemia has been described as associated with the risk of development metabolic syndrome, however the relationship between the uric acid level and particular parameters of metabolic syndrome remained unclear.

Methods: We performed a cross-sectional study on a cohort of 833 dyslipidemic patients and correlated their levels of uric acid with parameters of insulin resistance, lipid metabolism, C-reactive protein, anthropometric parameters. We also defined patients with hypertriglyceridemic waist phenotype and compered their uric acid levels with those without this phenotype.

Results: We found that levels of uric acid are associated with parameters of metabolic syndrome. Specifically, dyslipidemia characteristic for metabolic syndrome (low HDL-cholesterol and high triglycerides) correlates better with uric acid levels than parameters of insulin resistance. Also waist circumference correlates better with uric acid levels than body mass index. Patients with hypertriglyceridemic waist phenotype had higher levels of uric acid when compared with patients without this phenotype.

Conclusion: Serum uric acid levels are even in low levels linearly correlated with parameters of metabolic syndrome (better with typical lipid characteristics than with parameters of insulin resistance) and could be associated with higher cardiovascular risk. cdss

Key words

Metabolic syndrome, uric acid, hypertriglyceridemic waist, lipid metabolism, insulin resistance

Introduction

Metabolic syndrome has been defined as cluster of different cardiovascular risk factors, including visceral obesity, hypertension, dyslipidemia, and glucose intolerance. In 1999, the World Health Organization, proposed for the first time some diagnostic criteria for metabolic syndrome (Alberti *et al*. 1998). Afterward, the National Cholesterol Education Program´s Adult Treatment Panel III (NCEP/ATP III) (Grundy *et al.* 2004) and the International Diabetes Federation (IDF) (Alberti *et al.* 2006) updated both metabolic syndrome diagnosis and definition. However, uric acid levels are not a part of any of provided metabolic syndrome definition, although the incidence of metabolic syndrome and hyperuricemia become higher (Tang *et al.* 2015, Sun *et al.* 2015). Whether hyperuricemia contributes to development of metabolic syndrome or is merely a by-product of other processes that cause this disorder has not been resolved. There are some experimental data providing evidence that hyperuricemia per se could have deleterious metabolic sequelae (DeBosh *et al*. 2015). Facchini *et al*. also demonstrated that pathophysiological mechanism responsible for this association is insulin resistance (Facchini *et al*. 1991).

Recently, Carbone et al. (Carbone *et al*. 2013) have described the results from four longitudinal and 12 cross-sectional published studies (although these results could be subject to bias) regarding the association between uric acid levels and the metabolic syndrome risk. However, the strength and the consistency of the quantitative relationship between the uric acid level and metabolic syndrome remain unclear and inconclusive (Yuan *et al*. 2015).

To address this issue, we have performed a cross-sectional study on dyslipidemic patients to identify relationships between laboratory and anthropometric parameters connected to metabolic syndrome and uric acid levels.

Methods

Study design and subjects

The study was carried out as a cross sectional study on asymptomatic dyslipidemic subjects. 833 patients (402 men and 431 women) of the Lipid Center at the University Hospital Olomouc who came for their first visit because of hyperlipidemia (total cholesterol ≥ 5 mmol/l and/or triacylglyceroles (TAG) ≥ 1.7 mmol/l) between January 2005 and December 2015 were included in the study. Detailed medical history was obtained and physical examination performed. All subjects were tested for secondary hyperlipidemia, particularly diabetes mellitus, hypothyroidism, hepatic or renal failure. Exclusion criteria were as follows: lipid lowering therapy in previous 6 weeks, use of allopurinol, the presence of diabetes mellitus or other secondary hyperlipidemias, acute infection or trauma, acute cardiovascular event in the last 3 months, and heart failure NYHA III and IV. Patients were asked about their smoking cessation and divided into smokers (19.9%) and non-smokers (80.1%), whereas an ex-smoker was recorded as a non-smoker when he quit at a young age or had not smoked for a substantial time period - according to generally accepted definition (Králíková *et al*. 2015).

The study was reviewed and approved by the Institutional Ethics Committee of the Medical Faculty and University Hospital and informed consent was obtained from all participants.

Anthropometric and laboratory measurements

The waist circumference was measured in the standing position, at the middle point between the anterior iliac crest and the lower border of the ribs. The body mass index (BMI) was determined as body weight (in kilograms)/ body high (in meters) ^{2}. The hypertriglyceridemic waist phenotype was defined as waist ≥ 90 cm and TAG ≥ 2.0 mmol/l in men and waist ≥ 85 cm and TAG ≥ 1.5 mmol/l in women (Arsenault *et al*. 2010).

Biochemical analyses

Venous blood samples were drawn after a 12 hours of overnight fast. Total cholesterol (TC) concentrations were measured by enzymatic method CHOD-POD, standardized according to Abell-

Kendall and ID/MS (set CHOL2, Roche Diagnostics GmbH, Mannheim, Germany). TAG results were obtained by enzymatic method GPO-POD, standardized according to ID/MS (set TRIGL, Roche Diagnostics GmbH, Mannheim, Germany). HDL-C was measured by enzymatic colorimetric test, standardized according to CDC reference method (set HDLC3, Diagnostics GmbH, Mannheim, Germany). LDL-C levels were calculated according to Friedewald formula. AIP (atherogenic index of plasma) was calculated as a log (TAG/HDL-C) (Frohlich *et al*. 2003) and non HDL-C as TC – HDL-C. Concentrations of apolipoprotein B (apoB) and apolipoprotein A1 (apoA1) were determined immunoturbidimetrically according to IFCC reference standards on COBASc8000 analyzer (sets APOBT and APOAT, all Roche Diagnostics GmbH, Mannheim, Germany). Glycaemia was determined using the enzyme based Glucose hexokinase kit, standardized according to ID/MS (set GLUC3, Roche Diagnostics GmbH, Mannheim, Germany). C-reactive protein (hs-CRP) was assessed by means of an ultra-sensitive latex imunoturbidimetric method traceable to CRM 470 standard (set CRPL3, all Roche Diagnostics GmbH, Mannheim, Germany). Uric acid level was determined using enzymatic (uricase) colorimetric test standardized according to ID/MS (set UA2, Roche Diagnostics GmbH, Mannheim, Germany). All these assays were performed in a COBAS c8000 biochemical analyzer from Roche.

Insulin was determined using Insuline kit (Immunotech, Marseille, France) with specific antibodies by IRMA method. The result obtained were then used for calculation of HOMA-IR (homeostatis model assessment: fasting glycaemia*fasting insulin/22.5) (Matthews *et al.* 1985). C-peptide was determined using the commercially available kit (Immunotech, Marseille, France) using specific anti-bodies by IRMA method.

Statistical analyses

Parameters with normal distribution, which was only patients´ age (normality tested with Shapiro-Wilk test) were compared with Student´s t-test and expressed as mean ± standard deviation. Parameters with skewed distribution (BMI, waist circumference, total cholesterol, TAG, HDL-C, LDL-C, ApoB, glycaemia, insulin, HOMA-IR, C-peptide, CRP, UA) were analyzed with Mann-Whitney U-tests and expressed as median (1st-3rd quartile). Spearman´s correlation and partial

correlation coefficient was used in order to determine the association among parameters of insulin resistance and lipid metabolism. Fisher´s r-to-z transformation was applied to assess the significance of the difference between two correlation coefficients. Two paired t-test was used to compare patients with and without hypertriglyceridemic waist. Probability values of $p < 0.05$ were considered statistically significant.

Results

The characteristics of the dyslipidemic subjects are summarized in Table 1 – both anthropometric and laboratory parameters are shown. Patients´ age was 45.5 ± 14.7 years (mean ± standard deviation). Other parameters had skewed distribution and are expressed as median (1st-3rd quartile).

Correlation between uric acid levels and lipid parameters, markers of insulin resistance and anthropometric parameters are displayed in Table 2.

Markers of lipid metabolism showed moderate correlations (correlation coefficient r = 0.4 – 0.6) with uric acid levels (positive correlation with TAG and AIP and negative with HDL cholesterol) whereas parameters of insulin resistance (glycaemia, insulin, C-peptide, HOMA-IR) demonstrated only low positive correlations (correlation coefficient r = 0.1 – 0.3) with uric acid levels. In our study, we have not found any significant differences between smokers and non-smokers regarding correlations with uric acid levels.

Both studied anthropometric parameters - BMI and waist circumference – proved moderate correlations with uric acid levels, but the correlation was stronger with waist circumference (r = 0.535) than with BMI (r = 0,422) and the difference was statistically significant (p = 0.005).

We have selected patients with hypertriglyceridemic waist phenotype (as defined by Arsenault *et al*. 2010) and compared them with those without it. Patients with hypertriglyceridemic waist (n=218) had significantly higher levels of uric acid when compared with patients without hypertriglyceridemic (n=488) waist ($p < 0.0001$) as shown in graph 1.

Multiple linear regression with stepwise elimination procedure was used to select significant predictors for uric acid levels. The model includes only those predictors whose contribution to the predicted variance (uric acid level) was statistically significant. Waist circumference, HDL cholesterol, C-peptide and insulin were found to be significant predictors of uric acid levels, see table 3.

Discussion

In this cross-sectional study on a cohort of dyslipidemic patients, we found that levels of uric acid were associated with parameters of metabolic syndrome. Specifically, dyslipidemia characteristic for metabolic syndrome (low HDL-cholesterol and high TAG) correlates better with uric acid levels than parameters of insulin resistance. Also atherogenic index of plasma (AIP) proved correlations with uric acid levels. This parameter correlates well with parameters of insulin resistance (Cibickova *et al*. 2014). AIP is taking into account not only HDL cholesterol levels but also plasma TAG, that play the role of a regulator of lipoprotein interactions and not the role of an independent risk marker. High TAG and low HDL-C concentrations induce both an increase in small HDL particle and an increase in small, dense LDL particles (Dobiasova 2004), which is especially important in patients with metabolic syndrome. Our data provide confirmation of recent findings on relationship between serum uric acid and metabolic syndrome, as summarized and quantified by Yuan *et al*. - they have found significant positive linear relationship between serum uric acid levels and the risk of metabolic syndrome in a meta-analysis of prospective studies (Yuan *et al*. 2015).

The underlying cause of metabolic syndrome is visceral obesity, which can be measured by waist circumference. Several lines of evidence, both epidemiologic and clinical, point to a close interrelation between hyperuricemia and obesity – for example Masuo and coworkers have demonstrated that serum uric acid concentrations predict subsequent weight gain (Masuo *et al*. 2003). Sautin *et al.* suggest that hyperuricemia induces redox-dependent signaling and oxidative stress in adipocytes (Sautin *et al*. 2007). Since oxidative stress in the adipose tissue has recently been recognized as a major cause of insulin resistance and cardiovascular disease, hyperuricemia-induced

alterations in oxidative homeostasis in the adipose tissue might play an important role in these derangements (Sautin *et al*. 2007). In agreement with other authors (Guerra 2015, Ciarla *et al*. 2015) we found positive correlation of uric acid levels with waist circumference. Moreover, waist circumference correlated better with uric acid levels than BMI. Our study provides support for importance of measurement waist circumference rather than only assessing BMI. He have newly find out, that also patients with hypertriglyceridemic waist phenotype had higher levels of uric acid. This finding is in agreement with Arsenaut *et al.*, who proposed assessing of hypertriglyceridemic waist phenotype as a combination of increased waist circumference and hypertriglyceridemia. It has been proposed as an inexpensive approach to identify patients with excess intra-abdominal adiposity and associated metabolic abnormalities and was associated with a deteriorated cardiometabolic risk profile and an increased risk for coronary artery disease (Arsenault *et al*. 2010).

In contrast to lipid and anthropometric parameters of metabolic syndrome, the relationship between uric acid levels and parameters of insulin resistance and diabetes are not clearly established yet. We have also found only weak correlations of parameters of insulin resistance (glycaemia, insulin, C-peptide, HOMA-IR) with uric acid levels. Also the biological mechanisms underlying the association between serum uric acid levels and development of diabetes remain a matter of debate. Hyperuricemia may lead to endothelial dysfunction and nitric oxide inhibition, which in turn contribute to insulin resistance and thus, diabetes (Nakagawa *et al*. 2005). This is supported by experimental findings that showed how fructose-induced hyperuricemia in rats leads to insulin resistance along with components of metabolic syndrome, and how these conditions are improved by decreasing uric acid levels (Nakagawa *et al*. 2005; Hallfrish, 1990). Magnitude of insulin resistance and serum uric acid concentration were significantly related in healthy, nondiabetic, individuals (Facchini *et al*. 1991). Prospective data from 2 generations of the Framingham Heart Study provide evidence that individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes independent of other known risk factors (Bhole *et al.* 2010). These data were confirmed by a 15-year follow-up which found higher incidence rates of diabetes and prediabetes among persons with greater serum urate concentrations (Kirshan *et al*. 2012). On the other hand, in a shorter 10-year longitudinal

study in adolescents, uric acid levels did not affect the occurrence of type 2 diabetes in both genders (Sun *et al*. 2015). In a smaller study, Ciara *et al*. showed that even low levels of uric acid were linearly correlated with BMI, waist circumference, glucose and insulin levels, triglycerides and hs-CRP levels (Ciarla *et al*. 2015). On a larger group of patients we have confirmed these data whereas median of uric acid levels in our study was also in normal range.

Besides of lipid parameters and parameters of insulin resistance we have also studied relationship of uric acid levels to hs-CRP. CRP, as a hepatic biomarker associated with metabolic syndrome might be particularly useful to better manage and prevent the atherothrombotic risk (Carbone *et al*. 2013).

One pathophysiological model proposes that the oxidative stress associated with hyperuricemia leads to lipid oxidation that in turn becomes antigenic, triggering an immune response and systemic vascular inflammation (Kanellis *et al*. 2005). A recent study on 80 patients with acute coronary syndrome and on 36 healthy individuals showed correlation between hs-CRP and uric acid levels which indicates a possible role of uric acid as a marker of low-grade inflammation and its potential in risk assessment in cardiovascular diseases (Spahic *et al*. 2015). Another smaller study on patients with metabolic syndrome demonstrated that hs-CRP and serum uric acid are associated with metabolic syndrome components and the combined rise of hs-CRP and uric acid is associated with the increase in severity of metabolic syndrome (Sah *et al*. 2016). In our study on a larger cohort of dyslipidemic patients we observed association of hs-CRP with serum uric acid level which is similar to above mentioned studies.

We have hot studied relationship between uric acid levels and blood pressure, which is one of the main risk factors of metabolic syndrome. Although blood pressure was measured in all patients, it has been often influenced by various antihypertensive drugs and that is why we have decided not to analyze it.

In summary, this study supports relationship between serum urate concentration and parameters of metabolic syndrome. Specifically, dyslipidemia characteristic for metabolic syndrome (low HDL-cholesterol and high triglycerides, AIP) correlates better with uric acid levels than parameters of insulin resistance. Also waist circumference correlates better with uric acid levels than BMI. Patients

with hypertriglyceridemic waist phenotype had higher levels of uric acid when compared with patients without this phenotype. Moreover we have found linear association of uric acid levels and hs-CRP. Therefore, increasing serum uric acid levels could be associated with higher cardiovascular risk.

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Graph 1: Patients with / without hypertriglyceridemic waist phenotype and their correlation with uric acid levels.

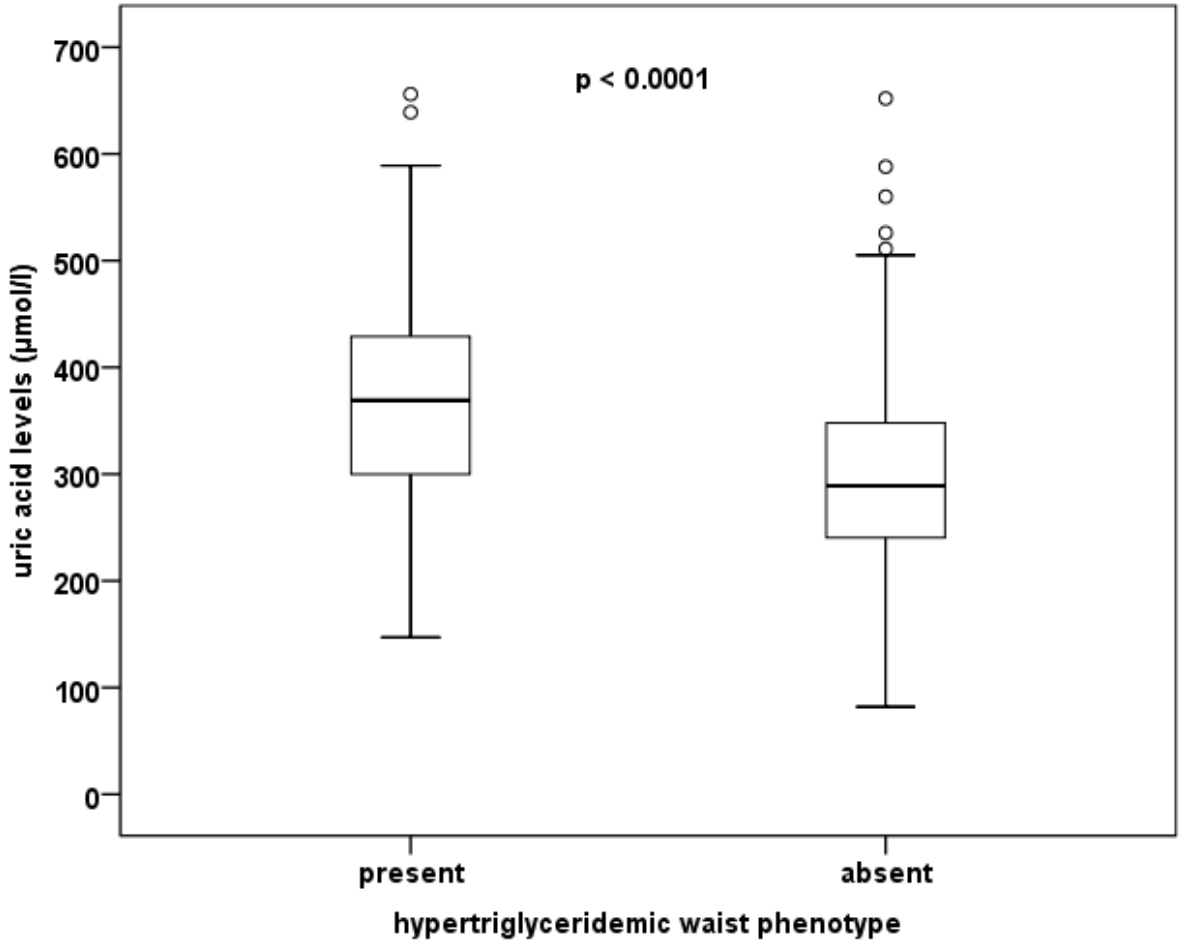

Table 1: Characteristics of the dyslipidemic subjects.

	1st quartile	Median	3rd quartile
hs-CRP (mg/l)	0.7	1.4	3.2
TC (mmol/l)	5.2	6.3	7.4
TAG (mmol/l)	1.2	1.7	2.7
AIP: log (TAG/HDL-C)	-0.14	0.07	0.35
nonHDL (mmol/l)	3.7	4.8	5.8
HDL-C (mmol/l)	1.1	1.4	1.7
LDL-C (mmol/l)	2.9	3.8	4.7
ApoA1 (g/l)	1.34	1.52	1.74
ApoB (g/l)	0.95	1.14	1.39
Uric acid levels (µmol/l)	254.0	307.0	370.0
Glucose (mmol/l)	4.6	5.0	5.5
Insulin (mIU/l)	5.3	7.7	11.0
HOMA-IR	1.04	1.66	2.51
C-peptide (mg/l)	1.6	2.3	3.3
BMI (kg/m^2)	23.1	25.7	28.6
Waist circumference (cm)	78.0	88.0	97.0

Table 2: Correlation between uric acid levels and lipid parameters, markers of insulin resistance and anthropometric parameters. Spearmans´ correlation coefficient for the whole group and separately for non-smokers and smokers. Bonefoni correction for multiple testing was used.

Correlation with uric acid levels			Whole group	Non-smokers	Smokers
Spearman's rho	Age	Correlation Coefficient	0.109	0.115	0.127
		p	0.046	0.088	1.000
	hs-CRP	Correlation Coefficient	0.134	0.136	0.153
		p	0.005	0.020	1.000
	Total cholesterol	Correlation Coefficient	0.085	0.053	0.118
		p	0.236	1.000	1.000
	TAG	Correlation Coefficient	0.442	0.412	0.453
		p	<0.0001	<0.0001	<0.0001
	AIP	Correlation Coefficient	0.478	0.471	0.445
		p	<0.0001	<0.0001	<0.0001
	nonHDL	Correlation Coefficient	0.200	0.178	0.190
		p	<0.0001	0.0001	0.255
	HDL cholesterol	Correlation Coefficient	-0.403	-0.409	-0.324
		p	<0.0001	<0.0001	0.0004
	LDL cholesterol	Correlation Coefficient	-0.029	-0.010	-0.136
		p	1.000	1.000	1.000
	ApoA1	Correlation Coefficient	-0.312	-0.319	-0.269
		p	<0.0001	<0.0001	0.019
	ApoB	Correlation Coefficient	0.126	0.114	0.096
		p	0.005	0.063	1.000
	Glucose	Correlation Coefficient	0.273	0.272	0.240
		p	<0.0001	<0.0001	0.034
	Insulin	Correlation Coefficient	0.174	0.177	0.187
		p	<0.0001	0.0002	0.380
	HOMA	Correlation Coefficient	0.182	0.196	0.146
		p	<0.0001	<0.0001	1.000
	C-peptide	Correlation Coefficient	0.307	0.312	0.244
		p	<0.0001	<0.0001	0.047
	BMI	Correlation Coefficient	0.422	0.441	0.370
		p	<0.0001	<0.0001	<0.0001
	Waist circumference	Correlation Coefficient	0.535	0.544	0.481
		p	<0.0001	<0.0001	<0.0001

Table 3: Multiple linear regression with stepwise elimination procedure for waist circumference, HDL cholesterol, C-peptide and insulin.

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	78.526	28.431		2.762	0.006
Waist circumference	2.968	0.278	0.434	10.679	<0.0001
HDL cholesterol	-26.736	7.267	-0.138	-3.679	0.0003
C-peptide	16.418	3.546	0.218	4.630	<0.0001
Insulin	-2.602	0.754	-0.155	-3.453	0.0006

R = 0,575, R Square = 0,331