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The Association of Uric Acid with Glucose and Lipids in General Population: Croatian Cross-Sectional Study

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A B S T R A C T

Hyperuricemia may have an important role in metabolic syndrome, cardiovascular diseases and stroke. Elevated serum uric acid concentration has been shown to be the strong predictor of cardiovascular mortality in several recently published studies. Our aim was to determine the prevalence of hyperuricemia in general Croatian population and to investigate the association of serum uric acid with glucose and lipids. This was a retrospective cross-sectional study on 6,476 consecutive adults. Prevalence of hyperuricemia was 13.9% in general population and it was significantly higher in males, than in females (26% vs. 6%; p<0.001). Median uric acid concentration was higher in males than in females (343 vs. 238 μmol/L; p<0.001). Age, glucose and lipid parameters did not correlate with uric acid. In hyperuricemic subjects, increased concentrations of glucose (33.1% vs. 13.1%; p<0.001), triglycerides (46.9% vs. 17.6%; p<0.001), total cholesterol (69.6% vs. 51.9%; p<0.001), LDL-cholesterol (64.5% vs. 46.4%; p<0.001) and decreased concentration of HDL-cholesterol (24.3% vs. 13.0%; p<0.001) were more prevalent than in subjects with normal serum concentrations of uric acid. Hyperuricemia is highly prevalent in Croatian general population and it aggregates with hyperglycemia and dyslipidemia.

Key words: *uric acid, metabolic syndrome, lipids, hyperuricemia*

Introduction

The concentration of serum uric acid is controlled by many factors, including genetics, insulin resistance, renal function, obesity, diet and alcohol consumption[1,2]. Elevation of the serum uric acid level (i.e. hyperuricemia) more frequently occurs in males and overweight persons and its prevalence varies in different populations[3]. It has been reported that hyperuricemia may have an important role in several pathological conditions such as metabolic syndrome, cardiovascular diseases (CVD), chronic kidney disease, stroke, maternal complications in pre-eclampsia[4–7]. Elevated serum uric acid has been shown to be the strong predictor of cardiovascular mortality in several recently published studies[8–10], whereas some other publications were not able to confirm these findings[11].

Hyperuricemia has also been associated with certain metabolic abnormalities, such as impaired glucose metabolism and dyslipidemia and several investigators have studied this association[12,13]. However, these associations are not yet fully understood and results are still inconsistent.

We have, therefore, undertaken this study with the aim to: (i) determine the prevalence of hyperuricemia in general Croatian population and (ii) investigate the association of serum uric acid with glucose and lipid concentration.

Materials and Methods

Patients

This was a retrospective cross-sectional study on patient laboratory results retrieved from the laboratory information system (LIS). The study included laboratory

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results for 6,476 consecutive adults referred to medical biochemistry laboratory of Policlinic Bonifarm for routine blood testing, mainly as a part of the routine periodic health check-up between June 2007 and February 2009.

Policlinic Bonifarm is policlinic specialized in pharmacology and toxicology and medical biochemistry laboratory. Total number of samples admitted to the laboratory is 11,000 *per* year and the total yearly number of analyses is about 75,000.

Methods

Following data were retrieved from the LIS for every individual: age, gender, concentration of glucose, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and uric acid.

For all patients venous blood sampling was done in the morning, after an overnight fast. All laboratory tests were done immediately after sampling.

All biochemical parameters were measured by standard enzymatic methods on analyzer Cobas Integra 400 plus (Roche Diagnostics, Mannheim, Germany).

LDL-cholesterol was calculated using Friedwald equation. When triglyceride concentration was above 3 mmol/L, LDL-cholesterol was measured by direct method on Cobas Integra 400 plus (Roche Diagnostics, Mannheim, German).

Statistical analysis

Categorical data are presented as counts and percentages. Normality was tested using Kolmogorov-Smirnov test. All distributions were non-Gaussian. Median and interquartile range (IQR) were used to describe the data. Data were categorized into two subgroups: with (a) normal and (b) increased (decreased for HDL) concentrations of measured parameters. Cut-off values used for grouping were 5.5 mmol/L for glucose, 5.0 mmol/L for cholesterol, 1.7 mmol/L for triglycerides, 3.0 mmol/L for LDL cholesterol and 1.0 mmol/L and 1.2 mmol/L for HDL cholesterol for males and females respectively. Those values were chosen according to the recommended ATP III criteria[14]. Value for HDL in females was slightly modified according to national recommended value (Croatian Chamber of Medical Biochemists). As a cut-off value used for categorizing subjects respective to the concentration of uric acid, we used the upper limit of reference interval (URL) (403 μmol/L for males and 337 μmol/L for females).

The χ^2-test was used for comparing categorical variables and Mann-Whitney rank sum test for assessing differences between numerical variables. Spearman rank correlation analysis was used to assess the association between variables (uric acid, age, glucose, lipid parameters). The level of statistical significance was set at 0.001, due to the large sample size.

Statistical analysis was performed by using MedCalc 10.1.2.0 (Frank Schoonjans, Mariakerke, Belgium).

Results

The study included 6,476 patients. Patient demographic characteristics and biochemical parameters are presented in Table 1.

Hyperuricemia prevalence was 13.9% in general population and it was significantly higher in males, than in females (26% *vs.* 6%; $p<0.001$). Furthermore, median uric acid concentration, although within the reference interval, was higher in males than in females (343 *vs.* 238 μmol/L; $p<0.001$).

We have tested possible correlations of uric acid with age, glucose and lipid parameters. As of our result, age, glucose and lipid parameters did not correlate with uric acid in studied population (data not shown). Correlation was not present even when we analyzed the relationship of uric acid with age, glucose and lipids within the uric acid quartile subgroups (data not shown).

Study subjects with hyperuricemia were found to have higher prevalence of increased concentrations of glucose (33.1% *vs.* 13.1%; $p<0.001$), triglycerides (46.9% *vs.* 17.6%; $p<0.001$), total cholesterol (69.6% *vs.* 51.9%; $p<0.001$), LDL-cholesterol (64.5% *vs.* 46.4%; $p<0.001$) and decreased value HDL-cholesterol (24.3% *vs.* 13.0%; $p<0.001$) compared to subjects with serum uric acid levels within the reference interval (Table 2).

TABLE 1
PATIENT DEMOGRAPHIC CHARACTERISTICS AND BIOCHEMICAL PARAMETERS

	Male, N=2,827	Female, N=3,598	p
Age, years*	43 (34–52)	41 (33–50)	<0.001
Uric acid, μmol/L*	343 (300–391)	238 (204–276)	<0.001
Hyperuricemia, N (%)	1.683 (26%)	389 (6%)	<0.001
Glucose, mmol/L*	5.1 (4.8–5.5)	4.7 (4.5–5.1)	<0.001
Cholesterol, mmol/L*	5.3 (4.6–6.1)	5.0 (4.4–5.8)	<0.001
HDL-cholesterol, mmol/L*	1.3 (1.1–1.5)	1.7 (1.4–2.0)	<0.001
LDL-cholesterol, mmol/L*	2.8 (2.3–3.5)	3.3 (2.6–3.9)	<0.001
Triglycerides, mmol/L*	1.4 (0.9–2.0)	0.9 (0.7–1.3)	<0.001

*Data are presented as median and interquartile range

TABLE 2
PREVALENCE OF SUBJECTS WITH HYPERGLYCEMIA AND DYSLIPIDEMIA RESPECTIVE TO THE URIC ACID CONCENTRATION

	Uric acid within reference interval N=5,671 (87.8%)	Uric acid above URL N=787 (12.2%)	p
Glucose >5.5 mmol/L N=457 (15.6%)	746 (13.1%)	261 (33.1%)	<0.001
Cholesterol >5.0 mmol/L N=3,500 (54.0%)	2,947 (51.9%)	553 (69.6%)	<0.001
Triglycerides >1.7 mmol/L N=1,374 (21.2%)	1,001 (17.6%)	373 (46.9%)	<0.001
LDL cholesterol >3.0 mmol/L N=3,151 (48.7%)	2,638 (46.4%)	513 (64.5%)	<0.001
HDL cholesterol ≤1.0 (M) mmol/L HDL cholesterol ≤1.2 (F) mmol/L N=929 (14.3%)	736 (13.0%)	193 (24.3%)	<0.001

URL – upper limit of reference interval

Discussion

The prevalence of hyperuricemia in this study was 13.9% in general population and it was significantly more prevalent in males, than in females. Age, glucose and lipid parameters did not correlate with uric acid concentration in studied population. However, hyperuricemic subjects more often had increased concentrations of glucose, triglycerides, total cholesterol, LDL-cholesterol. HDL-cholesterol concentrations were more often decreased in our subjects with elevated uric acid concentration.

Eventhough the prevalence of hyperuricemia and its association with various biochemical parameters has been studied by many authors, the results are controversial and not yet conclusive. The overall prevalence of hyperuricemia in one recently published study on 132 subjects from western Turkey was 12.1%[3]. The cut-off values for uric acid in this study were >420 μmol/L for males and >360 μmol/L for females, what was comparable to cut-off values used in our study. Males had significantly higher uric acid concentrations than females (330±80 *vs*. 260±70 μmol/L, respectively; p=0.05). This gender dependent difference in uric acid concentrations may probably be explained by gonadal hormones[15].

Lippi et al.[12] have investigated the association between uric acid, fasting plasma glucose and triglycerides in the general population. The overall prevalence of hyperuricemia in 10,181 randomly selected individuals was 3.8%. It should be noted that cut-off values for uric acid were much higher than the ones used in our study (uric acid cut-off values were ≥506 μmol/L and ≥416 μmol/L, for males and females, respectively). This might explain the observed large difference between the prevalence in our and Italian population. The major finding of the study by Lippi et al. was that hypertriglyceridemic (triglycerides >1.7 mmol/L) and hyperglycemic (fasting plasma glucose >6.1 mmol/L) adults had increased prevalence of elevated serum uric acid concentrations, compared to subjects having normal lipid and glucose concentrations (11% *vs*. 3%, respectively; p=0.018). The authors conclude that this association raises the possibility of a potential pathogenic overlap between these states.

Hjortnaes et al.[16] have investigated the association between serum uric acid and components of metabolic syndrome in patients with manifest vascular disease. They observed higher average concentrations of serum uric acid in patients with, than in patients without metabolic syndrome (360±80 μmol/L *vs*. 329±90 μmol/L). Furthermore, their observation was that the patients who had more components of metabolic syndrome present, had also higher concentration of serum uric acid.

Rathmann[17] and his colleagues have published the results of the Cardia study with the 10-year follow-up on 1,249 male and 1,362 female young subjects. During the follow-up, they observed the significant increase of the mean serum uric acid concentration (p<0.01). They also observed a significant independent association of body mass index (BMI) and triglycerides with serum uric acid.

In the study published by Liou et al.[18], uric acid aggregated with BMI, waist circumference (WC), glucose, log value of triglycerides, and HDL cholesterol. However, their conclusion was that metabolic syndrome is not associated with hyperuricemia.

In one recently published cross-sectional study on 2,085 Taiwanese men and 1,557 women[19], hyperuricemia was significantly associated with increased risk for hypertriglyceridemia, low high-density lipoprotein cholesterol level, and high blood pressure in men and women. However, contrary to our results, the uric acid levels were inversely associated with hyperglycemia in Taiwanese men. In one other similar study on 470 subjects, who were also from Taiwan, serum uric acid was significantly related to risk factors of metabolic syndrome, with the exception of blood glucose which did not correlate with uric acid[20]. It may be that there are some racial and ethnic differences in metabolic interactions of the components of lipid and glucose metabolism. Furthermore, the observed difference in the association between glucose and uric acid may also be at least partially due to large

differences in diet and lifestyle between Western civilizations and Asian subjects[21].

So, although not confirmed by all, uric acid was mostly found to aggregate with disturbed metabolism of glucose and lipids. Uric acid is known to correlate with insulin resistance. The mechanism of this phenomenon is not fully understood. It has been postulated that insulin probably decreases the clearance of uric acid in the renal proximal tubule, resulting in a subsequent increase in serum uric acid levels in healthy individuals and asymptomatic hyperuricemic subjects[22].

As such, the measurement of uric acid might be advisable to those at increased risk of CVD[23]. However, there is a continuing debate about the relevance of the increased serum uric acid concentration and its role as an independent cardiovascular risk factor. The predictive value of uric acid concentration for cerebrovascular and cardiovascular mortality has been studied in several large prospective studies. In the prospective cohort study on 1,423 middle-aged Finnish men initially without CVD, published by Niskanen et al., serum uric acid was a strong predictor of cardiovascular mortality, independent of variables commonly associated with gout or the metabolic syndrome[8]. Elevated concentrations of uric acid were also associated with increased mortality in one Austrian cohort of 83,683 subjects[10]. However, one prospective cohort study on 22,698 Korean men, aged 30 to 77 years, with a 9-year of follow-up found that elevated serum uric acid was not an independent risk of cardiovascular mortality[11]. It is therefore clear that we still need some well designed prospective trials and monitored therapeutic interventions to further improve our understanding of the risk factors for metabolic syndrome and cardiovascular mortality[24].

Despite of the very intense research on this field, there is still much controversy on the role and significance of uric acid and its relation to some biological parameters. Such controversy may be due to the different cut-off used to define hyperuricemia, small sized studies and some ethnical differences, comorbidity and other differences in studied populations.

The present study has some limitations. The study population of outpatient adults from laboratory may not be completely representative sample of general population. Anthropometric measures, like BMI and some other important data on the comorbidity (like hypertension, cardiovascular disease, etc.), therapy, diet and other environmental factors would be very useful to further explore these complex associations. Unfortunately, none of the additional clinical information was available on this large cohort of outpatients.

Conclusion

Hyperuricemia is highly prevalent in Croatian general population and it aggregates with hyperglycemia and dyslipidemia. Males are more often hyperuricemic than females.

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POVEZANOST MOKRAĆNE KISELINE S GLUKOZOM I LIPIDIMA U OPĆOJ POPULACIJI: PRESJEČNO ISTRAŽIVANJE U HRVATSKOJ

S A Ž E T A K

Hiperuricemija može imati značajnu ulogu u metaboličkom sindromu, kardiovaskularnim bolestima i moždanom udaru. Novija istraživanja su pokazala da koncentracija mokraćne kiseline u serumu može biti snažan prediktor kardiovaskularne smrtnosti. Cilj ovog istraživanja bio je utvrditi prevalenciju hiperuricemije u općoj populaciji u Hrvatskoj i ispitati povezanost koncentracije mokraćne kiseline s koncentracijama glukoze i lipida. Ovo retrospektivno presječno istraživanje provedeno je na 6,476 uzastopnih odraslih ispitanika. Prevalencija hiperuricemije je bila 13,9% u općoj populaciji. Hiperuricemija je bila učestalija u muškaraca, nego u žena (26% prema 6%; p<0,001), a medijan koncentracije mokraćne kiseline je bio viši u muškaraca nego u žena (343 prema 238 μmol/L; p<0,001). Dob, koncentracija glukoze i lipidnih parametara nisu bili povezani s koncentracijom mokraćne kiseline. Ispitanici s hiperuricemijom imali su povišenu koncentraciju glukoze (16,5% prema 6,8%; p<0,001), triglicerida (46,9% prema 17,6%; p<0,001), ukupnog kolesterola (69,6% prema 51,9%; p<0,001), LDL-kolesterola (64,5% prema 46,4%; p<0,001) i sniženu koncentraciju HDL-kolesterola (24,3% prema 13,0%; p<0,001) češće nego ispitanici s normalnom koncentracijom mokraćne kiseline u serumu. Hiperuricemija ima visoku prevalenciju i povezana je s hiperglikemijom i dislipidemijom u općoj populaciji u Hrvatskoj.