Tohoku J. Exp. Med., 2007, **211**, 369-377

Independent Association of High Serum Uric Acid Concentration with Angiographically Defined Coronary Artery Disease

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Jelić-Ivanović, Z., Memon, L., Spasojević-Kalimanovska, V., Bogavac-Stanojević, N. and Spasić, S. *Independent Association of High Serum Uric Acid Concentration with Angiographically Defined Coronary Artery Disease*. Tohoku J. Exp. Med., 2007, **211** (4), 369-377 —— Epidemiological studies have shown that a high serum uric acid concentration is a risk factor for coronary artery disease (CAD). However, the issue of whether it is an independent cardiovascular risk factor or simply a marker of co-existing conditions is a matter of controversy. In the present case-controlled study, we explored the association between serum uric acid and angiographically defined CAD in middle-aged subjects (356 CAD patients and 350 healthy individuals). Serum uric acid in CAD patients was significantly higher than that in healthy individuals (359 ± 88.7 and 289 ± 79.3 μmol/l, respectively, $p < 0.01$) and remained significantly higher after adjusting for confounding factors ($F = 79.77$, $p < 0.01$). The association between uric acid and CAD was not limited to the hyperuricemic range of values, but was also found in the high-normal range ($p < 0.01$). An unadjusted odds ratio (OR) of 5.0 was obtained in both genders ($p < 0.01$). Female patients with > 50% stenosis (clinically significant CAD), regardless of the number of diseased vessels, had higher uric acid concentrations than those with < 50% stenosis even after adjusting for confounders ($F = 3.79$, $p = 0.01$). In conclusion, we have demonstrated that high serum uric acid is independently associated with CAD and that uric acid determination could be useful as one of the markers of clinically significant CAD. ———— angiography; atherosclerosis; coronary heart disease; risk factors; uric acid.

Uric acid, generated from xanthine by the enzyme xanthine oxidase, is the final product of purine degradation in humans. The association between high serum uric acid and incidence of coronary artery disease (CAD) was reported more than fifty years ago (Gertler et al. 1951). Since then, numerous clinical and epidemiological studies have explored the association more precisely. Such studies confirmed that elevated uric acid was a predictor of cardiovascular disease. However, a great controversy arose as to whether elevated uric acid was an independent risk factor for CAD or it was merely a marker of co-existing conditions such as hypertension, abdominal obe-

Received November 13, 2006; revision accepted for publication March 2, 2007.
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sity, diabetes mellitus, hyperlipidemia, inflammation, impaired renal function and diuretic treatment. The contradictory data obtained in the studies have been analysed and reviewed by independent research groups (Johnson and Tuttle 2000; Rich 2000; Alderman 2002; Johnson et al. 2003; Baker at al. 2005). Although different potential mechanisms explaining the association between high serum uric acid and CAD have been proposed (Alderman 2002; Johnson et al. 2003; Hayden et al. 2004; Mercuro et al. 2004; Baker at al. 2005), a well-established pathophysiological link is still missing.

The concentration of uric acid, as well as other risk factors for the development of CAD, is strongly influenced by different genetic factors and lifestyle habits. Therefore, studies that explore the association between a high uric acid concentration and CAD should be conducted in populations with different genetic and environmental backgrounds. To date, no such studies have been conducted within populations living in Southeastern European countries such as Serbia. In 2004, the coronary heart disease mortality rate in Serbia was 732.5/100,000 (Vukumirovic 2005) whereas a lower rate was recorded in Eastern European countries (671/100,000) (World Health Organization 2002). At the same time, improvement in primary prevention caused a steady decline in the overall cardiovascular mortality rate in Western Europe over the last 15 years.

The aims of this case-controlled study were the following: Firstly to investigate the association of high serum uric acid with the angiographically assessed CAD in middle-aged Serbian males and females, and secondly to explore whether there was an independent association between uric acid and CAD when adjusting for different confounding factors such as gender, obesity, waist/hip ratio, smoking status, hypertension, hyperlipidemia, diabetes mellitus, concentration of high-sensitivity C-reactive protein (hs-CRP), and diuretic treatment.

Materials and Methods

Study populations

A total of 356 patients (223 males and 133 females, mean age 56.1 ± 9.0 years) attending the Institute of Cardiovascular Disease at the Clinical Centre of Serbia in Belgrade were included in the study. Their presenting diagnosis was stable angina (112), unstable angina (41) or previous myocardial infarction (135). The rest of the patients had polymorphic complaints (usually atypical chest pain) with a positive family history of CAD. Patients with a recent myocardial infarction, congestive heart failure, impaired renal function (serum creatinine levels > 106 μmol/l in males and > 80 μmol/l in the females), gout symptoms, as well as patients taking medications targeted to lower uric acid levels, were not included in the study.

All patients were divided into four groups based on the extent of their CAD as assessed by coronary angiography. Patients with a lesion of less than 50% luminal narrowing were defined as having sub-clinical coronary atherosclerosis (group 0). Luminal narrowing of 50% or more was defined as a significant lesion. Such patients were defined as having single-, double- or triple-vessel disease. Triple-vessel disease was defined as having a significant lesion in all three vessels (the left main or left anterior descending artery, the left circumflex artery and right coronary artery [group 3]). If two of the major branches were involved then the patient was defined as having double-vessel disease (group 2). If only one of the branches was involved, then the patient was defined as having single-vessel disease (group 1). In addition to body weight and height, waist and hip circumference the presence of the following factors was recorded: (1) smoking at the time of angiography or at the time when the first symptoms appeared; (2) hypertension (HT) indicated by a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure of ≥ 90 mm Hg or prescribed antihypertensive medication; (3) diabetes requiring dietary or medical treatment; (4) hyperlipidemia (LDL-cholesterol > 4.13 mmol/l and/or triglycerides > 2.25 mmol/l) and (5) diuretic treatment. As coronary angiography is an aggressive method it was not possible to recruit a group of stenosis-free subjects for comparison. Instead, a group consisting of 350 apparently healthy, age-matched subjects with normal ECGs and exercise test results was included in the study.

The study was planned according to the ethical guidelines following the declaration of Helsinki. All subjects involved in the study gave written informed consent prior to study entry and the Ethics Committee at the Faculty of Pharmacy, University of Belgrade approved this study.

Apparatus, reagents and procedures

Blood samples were collected after a 12-hr fasting period, and multiple aliquots of plasma and serum samples were stored at –80°C. The samples were thawed immediately before analyses. All the assays were performed blindly.

Lipid status parameters were measured in EDTA plasma samples. Total cholesterol, HDL-cholesterol, triglycerides, apolipoprotein A-I and apolipoprotein B were assayed by standard laboratory procedures. The concentration of low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula (Friedewald 1972). Serum hs-CRP was quantitated using a latex-enhanced immunoturbidimetric method employing a Quantex hs-CRP kit (BIOKIT, Barcelona, Spain). Uric acid was measured in serum using a standard enzymatic assay (Randox, Antrim, UK). Intra- and inter-assay coefficients of variation peaked at 0.56% and 1.62%, respectively.

Statistical methods

Statistical differences were evaluated according to the Student *t*-test for continuous variables, whereas proportions were compared using chi-square test for contingency tables, or *t*-test for proportions. A comparison of uric acid concentrations obtained in patients with differing degrees of luminal narrowing was performed by ANOVA and significant differences among a group of means were tested by the Tukey HSD *post-hoc* test. Adjusted mean levels of uric acid were estimated by analysis of covariance. Uric acid concentrations in patients and controls were compared while adjusting for known confounders: gender, obesity (body mass index [BMI] > 28 kg/m^2), waist-to-hip ratio, smoking status (current smoker or non-smoker), hyperlipidemia, diabetes, hypertension, inflammation (log hs-CRP concentration), and diuretic treatment. The effect of age was taken into account via the study design, as healthy controls were age-matched with the patients. However, as older age was associated with a greater extent of CAD, the mean levels of uric acid obtained in patients groups 0, 1, 2 and 3 were also adjusted for age. Logistic regression analysis was used to investigate the association between serum uric acid concentration and CAD development, both unadjusted and after adjustment for other CAD risk factors. Statistical analysis was performed using STATGRAPHIC R software, version 4.2. Group differences with $p < 0.05$ were considered statistically significant.

Results

The demographic characteristics and laboratory data of both study populations are shown in Table 1. The patient population had a significantly higher BMI, waist/hip ratio, systolic and diastolic blood pressure and elevated triglyceride, apolipoprotein B and hs-CRP concentrations. Furthermore, the patient population had a higher prevalence of diabetes mellitus, hyperlipidemia, current smokers and subjects receiving diuretics. In contrast, HDL-cholesterol and apolipoprotein A-I concentrations were significantly lower in patients when compared with healthy controls.

Serum uric acid in CAD patients was significantly higher than that in healthy individuals (Table 2). Gender-specific serum uric acid concentration was also investigated. For both males and females serum uric acid in the patient population was significantly higher than that in healthy individuals. The prevalence of hyperuricemia (males: uric acid > 420 μmol/l; females: > 360 μmol/l) was also markedly higher in the patient population of both genders compared with healthy controls. To explore whether the association between serum uric acid and CAD was confounded by other factors, the concentration of uric acid in individuals belonging to both study populations was compared after adjusting for gender, obesity, waist-to-hip ratio, smoking status, hyperlipidemia, diabetes, hypertension, log hs-CRP concentration and diuretic treatment. The adjusted serum uric acid concentrations in the CAD patient population were significantly higher than the corresponding values in the healthy population ($F = 79.77$, $p < 0.01$).

To explore the association between high-normal uric acid levels and CAD, we partitioned the measured uric acid concentrations in the normouricemic healthy population into tertiles and compared the frequencies of patients having uric acid concentrations within the corresponding tertiles (Fig. 1). A significantly higher percentage of CAD patients (both males and females) had serum uric acid concentrations in the range corresponding to tertile 3. No significant difference was found between tertiles 1 and 2.

TABLE 1. Demographic characteristics and laboratory data of both study populations.

	Controls (n = 350)	Patients (n = 356)	p[a]
Age (years)	55.7 ± 10.5	56.1 ± 9.0	0.52
Male gender (%)	55.7	62.6	0.06
BMI (kg/m^2)	26.4 ± 3.6	28.0 ± 3.7	< 0.01
Waist/hip ratio	0.89 ± 0.11	0.91 ± 0.09	< 0.01
Systolic blood pressure (mmHg)	135.1 ± 19.6	140.9 ± 24.7	< 0.01
Diastolic blood pressure (mmHg)	86.2 ± 10.8	89.0 ± 14.5	< 0.01
Diabetes mellitus (%)	0	16.5	< 0.01
Current smoking (%)	32.5	51.1	< 0.01
Diuretic treatment (%)	5.7	24.5	< 0.01
Hyperlipidemia (%)	35	54	< 0.01
Triglycerides (mmol/l)	1.54 ± 0.82	2.27 ± 1.08	< 0.01[b]
Total cholesterol (mmol/l)	5.43 ± 0.99	5.41 ± 1.08	0.88
HDL-cholesterol (mmol/l)	1.17 ± 0.32	0.82 ± 0.21	< 0.01
LDL-cholesterol (mmol/l)	3.60 ± 0.93	3.73 ± 1.05	0.08
Apolipoprotein A-I (g/l)	1.84 ± 0.42	1.38 ± 0.29	< 0.01
Apolipoprotein B (g/l)	1.32 ± 0.31	1.39 ± 0.36	< 0.01
hs-CRP (mg/l)	1.95 ± 1.97	3.46 ± 2.83	< 0.01[b]
Creatinine (μmol/l)	62.31 ± 16.91	64.26 ± 18.04	0.14

Values are expressed as means ± S.D. or percentages.

[a] According to the Student t- test for continuous variables or the χ^2 test for contingency tables for proportions.

[b] Values were compared after logarithmic transformation.

TABLE 2. Serum uric acid concentrations (μmol/l) and prevalence of hyperuricemia (males: > 420 μmol/l; females: > 360 μmol/l) in both study populations.

	Variable	Controls	Patients	p
All subjects	Uric acid (μmol/l)	289 ± 79.3	359 ± 88.7	< 0.01[a]
	Hyperuricemic (%)	10.3	25.0	< 0.01[b]
	n	350	356	
Males	Uric acid (μmol/l)	327 ± 76.8	383 ± 74.5	< 0.01[a]
	Hyperuricemic (%)	14.4	27.4	< 0.01[b]
	n	195	223	
Females	Uric acid (μmol/l)	244 ± 54.5	318 ± 95.6	< 0.01[a]
	Hyperuricemic (%)	5.2	21.8	< 0.01[b]
	n	155	133	

Uric acid concentrations are expressed as means ± S.D.

The prevalence of hyperuricemia is expressed as the percentage of hyperuricemic subjects.

[a] According to the Student t-test.

[b] According to the χ^2-test.

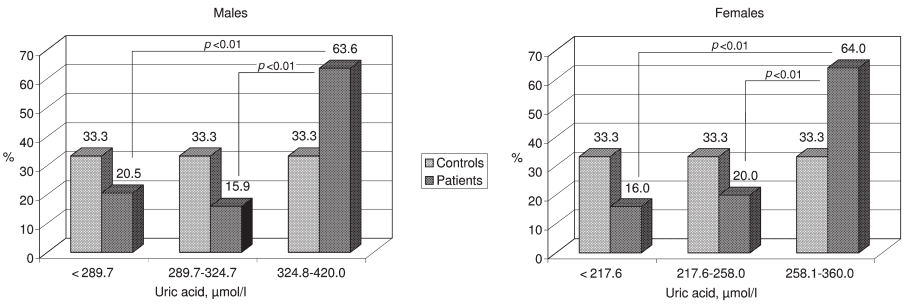

Fig. 1. Frequencies (expressed as %) of normouricemic CAD patients and healthy controls within tertiles (defined by partitioning the range found in normouricemic healthy controls into 3 tertiles).

To confirm and further explore the observed association of serum uric acid in the high-normal (tertile 3) and hyperuricemic range of concentrations, we calculated gender-specific ORs. Males with uric acid > 324.7 μmol/l were 5.0 times more likely to have CAD than males with lower uric acid (OR = 5.0, CI = 2.928 - 8.612, $p < 0.01$). Similar results were obtained for females having uric acid > 258.0 μmol/l compared with females with lower uric acid (OR = 5.0, CI = 2.61 - 9.64, $p < 0.01$). Table 3 shows that uric acid remained significantly associated with CAD after adjustment for traditional risk factors, lipid parameters, hs-CRP and creatinine.

Because a minority of CAD patients (25%) had elevated uric acid levels, we explored the test characteristics as a diagnostic correlate of CAD. When the uric acid reference limits were used as cut-off values (420.1 μmol/l in males, and 360.1 μmol/l in females), the following sensitivities (Se), specificities (Sp), positive predictive values (PPV) and negative predictive values (NPV) were obtained: Se = 0.274, Sp = 0.856, PPV = 0.685, NPV = 0.508 for males, and Se = 0.218, Sp = 0.948, PPV = 0.784 and NPV = 0.586 for females. When the limits of high-normal ranges were used as cut-off values (males - 324.8 μmol/l; females - 258.1 μmol/l), the calculated parameters were: Se = 0.735, Sp = 0.569, PPV = 0.648, NPV = 0.653 in the males, and Se = 0.714, Sp = 0.632, PPV = 0.625, NPV = 0.721 in the females.

Finally, we explored the association of high serum uric acid with the extent of CAD. We found statistically significant differences among patients with a different number of significantly stenosed vessels (Table 4). A comparison of gender-specific values revealed that a significant association existed only for females. According to the Tukey HSD *post-hoc* test, the uric acid concentrations in females with single-, double- and triple-vessel disease were significantly higher than the corresponding values in females with

TABLE 3. Odds ratios for uric acid: Impact on disease development.

	Males		Females	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Unadjusted OR	5.0 (2.928-8.612)	< 0.01	5.0 (2.612-9.636)	< 0.01
Model 1	4.35 (2.725-6.939)	< 0.01	4.45 (2.247-8.800)	< 0.01
Model 2	4.13 (2.399-7.124)	< 0.01	3.18 (1.649-6.140)	< 0.01
Model 3	3.71 (2.093-6.563)	< 0.01	2.80 (1.462-5.350)	< 0.01
Model 4	3.48 (1.948-6.206)	< 0.01	2.35 (1.050-5.260)	0.04

Model 1: age, BMI, HT, waist/hip ratio, smoking, DM, diuretic treatment; Model 2: total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apoA-I, apoB; Model 3: model 2, hs-CRP and creatinine, Model 4; all the parameters.

TABLE 4. Unadjusted serum uric acid concentrations (μmol/l) and prevalence of hyperuricemia (males: > 420 μmol/l; females: > 360 μmol/l) in patients with different extent of CAD (0, < 50% stenosis; 1, single-vessel disease; 2, double-vessel disease; 3, triple-vessel disease).

	Variable	0	1	2	3	*p*
All patients	Uric acid (μmol/l)	320 ± 86.02	367 ± 82.6	363 ± 82.8	382 ± 83.1	< 0.01[a]
	Hyperuricemic (%)	12.4	25.8	28.6	34	< 0.01[b]
	n	89	93	77	97	
Males	Uric acid (μmol/l)	367 ± 64.0	384 ± 71.0	374 ± 73.8	397 ± 82.7	0.17[a]
	Hyperuricemic (%)	18.6	25.4	28.6	33.8	0.35[b]
	n	43	67	42	71	
Females	Uric acid (μmol/l)	277 ± 81.0	323 ± 95.3	350 ± 111.3	343 ± 72.0	< 0.01[a]
	Hyperuricemic (%)	6.5	27	28.6	34.6	< 0.02[b]
	n	46	26	35	26	

Uric acid concentrations are expressed as means ± S.D., and the prevalence of hyperuricemia as the percentage of hyperuricemic subjects.

[a] According to ANOVA.

[b] According to the χ^2-test.

sub-clinical CAD (< 50% stenosis). However, no statistically significant differences within the female patient groups with clinically significant stenosis (single-, double- and triple-vessel disease) were found. The prevalence of hyperuricemia was also related to the degree of CAD only in female patients in which the percentage of hyperuricemic individuals with single-, double- and triple-vessel disease was significantly higher than the percentage of female patients with < 50% stenosis. Once again, no significant differences between the three patient groups with luminal narrowing ≥ 50% were found. The observed difference between the serum uric acid concentrations found in females with sub-clinical and clinically significant CAD also remained statistically significant after adjusting for confounding factors including age ($F = 3.79$, $p = 0.01$).

DISCUSSION

We report three main findings from the present study. First, serum uric acid concentrations > 324.7 μmol/l in males and > 258.0 μmol/l in females are positively associated with CAD. Second, serum uric acid is associated with the degree of CAD only in females. Third, the observed associations are independent of other atherogenic risk factors.

The association between elevated serum uric acid and CAD has been observed in numerous studies. Despite this, there is still no agreement on whether uric acid is a cause, a consequence or just a marker of cardiovascular disease (Alderman 2002; Johnson et al. 2003; Alderman et al. 2004; Baker et al. 2005). In our study both gender-specific serum uric acid and the prevalence of hyperuricemia were significantly higher in patients compared with the healthy population (Table 2). The observed association between uric acid and CAD was not limited to the hyperuricemic range, but rather it extended into the upper-normal range of values (males: > 324.7 μmol/l, OR = 5.1; females: > 258.0 μmol/l, OR = 5.0; Figure 1, Table 3). This is in agreement with the results of other authors (Niskanen et al. 2004; Madsen et al. 2005) who showed that uric acid concentrations within the high-normal range could also be considered as high risk.

The serum uric acid concentration and the prevalence of hyperuricemia significantly increased with the extent of CAD (Table 4). However, when gender-specific values were taken into account a significant increase was only found in the female patient population. Although

numerous studies have investigated the association between serum uric acid and CAD, few have examined the relationship between uric acid and the extent of the disease assessed by coronary angiography. Hiyamuta et al. (1990) failed to demonstrate any relationship between serum uric acid and the extent of CAD, but the majority of their patients were males (87%) and gender-specific comparisons were not performed. Kotake et al. (1992) reported that the concentration of serum uric acid in 40 women correlated with the number of arteries exhibiting ≥ 50% stenosis, whereas no significant changes were seen in men. In the study of Tuttle et al. (2001), serum uric acid correlated linearly with CAD severity in 82 women. Generally, the relationship between serum uric acid and increased cardiovascular risk tends to be stronger in women than in men and more frequently independent of other risk factors (Kotake et al. 1992; Culleton et al. 1999; Fang and Alderman 2000; Moriarity et al. 2000; Aboa Eboule et al. 2001; Tuttle et al. 2001; Alderman 2002; Hoieggen et al. 2004; Baker et al. 2005). In our current study both serum uric acid and prevalence of hyperuricemia in female patients with clinically significant stenosis were significantly higher when compared with female patients with sub-clinical coronary atherosclerosis. No significant differences were observed among the female patient groups with different extents of clinically significant disease (single-, double- and triple-vessel disease). This finding could have been due to the fact that some patients with severe CAD and high uric acid levels could have been excluded from the study because of a recent myocardial infarction, congestive heart failure, impaired renal function, or because they did not survive such conditions.

Elevated serum uric acid has been found to be closely associated with dyslipidemia, obesity, hypertension, waist-to-hip ratio, renal disease, diabetes, diuretic treatment, smoking and inflammation. The issue of whether serum uric acid is an independent cardiovascular risk factor or only a marker of co-existing conditions is a matter of controversy (Kotake et al. 1992; Johnson and Tuttle 2000; Moriarity et al. 2000; Rich 2000; Alderman 2002; Johnson et al. 2003; Alderman and Redfern 2004; Niskanen et al. 2004; Baker et al. 2005; Madsen et al. 2005; Yang et al. 2005; Simon et al. 2006). We compared the levels of uric acid found in patients and healthy controls after adjusting for known confounders. The observed association between uric acid and CAD, as well as the difference between the values obtained in the females with subclinical vs. clinically significant CAD, remained statistically significant. Therefore, the results of our study add to the body of evidence that serum uric acid is independently associated with the development of CAD.

The serum concentration of uric acid is strongly influenced by genetic backgrounds and lifestyle habits (Alderman 2002; Johnson et al. 2003; Baker et al. 2005; Yang et al. 2005). Likewise, it is well known that other cardiovascular risk factors are also affected by many inherited and environmental factors. Therefore, studies that explore the association of high serum uric acid with CAD should be conducted within populations living in different regions throughout the world. To date no such studies have been conducted in Southeastern European countries such as Serbia. The results reported herein, together with our previous reports considering other risk factors within the Serbian population (Bogavac-Stanojevic 2003; Bogavac-Stanojevic 2005; Memon et al. 2006), represent important pieces in the overall puzzle representing population-based relationships between lipid and non-lipid risk factors and the development of CAD. To minimise the effect of interfering factors it would have been optimal if we could have compared the values obtained in CAD patients with the corresponding values found in a population of stenosis-free patients with the same characteristics instead of the healthy control population. However, as coronary angiography is an aggressive method it is never performed without good reason and therefore it was not possible to recruit such a group of patients. Among the patients involved in our current study individuals with the lowest extent of CAD were classified as group 0. This group consisted of 89 individuals with less than 50% lumi-

nal narrowing. Only three of which were without any stenosis, too few to perform any meaningful statistical analyses.

In conclusion, we have demonstrated that serum uric acid concentrations within the high-normal and hyperuricemic range are independently associated with angiographically defined CAD. The issue of whether uric acid is a cause, a consequence or just a marker of cardiovascular disease still remains to be elucidated. Nevertheless, the serum uric acid assay is simple and inexpensive to perform and we can advocate its measurement as one of the markers for CAD risk assessment.

Acknowledgments

The work was financially supported by the Ministry of Science and Environmental Protection of the Republic of Serbia (project No. 145036). We are grateful to Prof. Dr. Dimitra Kalimanovska-Oštrić (Institute for Cardiovascular Diseases, Clinical Centre of Serbia, Belgrade, Serbia) for providing clinical data and biological samples.

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