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Original Article

Serum Uric Acid Level and Metabolic Syndrome in Patients Undergoing Coronary Angiography

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ABSTRACT

Background and Objectives: The association between metabolic syndrome (MetS) and hyperuricemia has been formerly studied mostly in healthy people in western countries. We tried to examine the relationship between hyperuricemia and MetS in an Iranian population undergoing coronary angiography.

Materials and Methods: From March 2008 to September 2008, we studied 465 patients (260 men, 55.9%) undergoing elective coronary angiography due to symptoms related to coronary artery disease. The MetS was defined according to the adapted Adult Treatment Panel III (ATP-III A), and hyperuricemia was defined as serum uric acid concentrations ≥ 7.0 mg/dl in men and ≥ 6.0 mg/dl in women. For the statistical analysis, the statistical software SPSS version 13.0 and the statistical package SAS version 9.1 were applied

Results: The mean age of the study population was 59.66 ± 10.04, ranging from 31 to 85 years. Hyperuricemia was detected in 231 (49.7%) of total population, in 126 (54.5%) of men, and in 105 (45.5%) of women. In the multivariable adjusted model, subjects with MetS and subjects with 5 components of the MetS compared to those without any components of the MetS, had 1.56-fold and 4.19-fold increased odds of hyperuricemia, respectively. Hyperuricemia was significantly associated with elevated BP and low level of HDL-cholesterol but not with other components of MetS.

Conclusions: Our study demonstrated that hyperuricemia was strongly associated with the prevalence of MetS according to adapted ATP III guidelines in an Iranian sample of patients undergoing coronary angiography.

Keywords: Metabolic Syndrome X, Hyperuricemia, Coronary Angiographies

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Introduction

The recent increase in the prevalence of hyperuricemia is potentially attributed to recent shifts in diet and lifestyle, improved medical care, and increased longevity. But it may partly be also attributable to the metabolic syndrome (MetS) both in adults and children (1-4), a clinical entity that associated with obesity and is mediated principally by insulin resistance.

In the present study, the MetS is defined by the adapted ATP-III guidelines proposed by American Heart Association/ National Heart, Lung, and Blood Institute, AHA/ NHLBI(5) which better predict the clinical cardiovascular events in patients undergoing coronary angiography (6), and is more useful in clinical practice (7).

Previous studies have suggested that an increase in serum uric acid levels is associated with MetS (8-11). However, little data is available concerning this issue in Iran. More specifically, there have been very little if any studies on population subgroups with more cardiovascular risk factors, particularly coronary artery disease (CAD) suspected subjects with MetS.

The aim of this study was first to examine the association of serum uric acid levels with MetS, and secondly to assess the relationship between hyperuricemia and various components of MetS in an Iranian sample who were candidates for coronary angiography because of suspected CAD.

Materials and Methods

Study population

The study consisted of 465 patients (260 men, 55.9%) who from March 2008 to September 2008 underwent coronary angiography at our institution due to symptoms related to CAD. Patients with the history of renal failure, rheumatic disease particularly gout, and malignancy as well as those receiving hypouricemic agents were excluded. The study protocol was approved by the local Ethics Committee. Written informed consent were obtained from all patients, who approved the collection of blood samples for scientific research.

Anthropometric indices, physical examination, and laboratory tests

Qualified trained staff measured height, waist circumference, and weight to the nearest 0.1cm, and 0.1 kg, respectively. Waist circumference was measured at the midpoint between the lower part of the last rib and the iliac crest while participants were at minimal respiration. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). For measuring the blood pressure, the participants remained at rest for at least 10 min then the same staff measured blood pressure using standard calibrated mercury sphygmomanometers. For each patient two measurements were performed with at least 1 min interval and the mean of two measurements recorded as the patient's blood pressure.

Peripheral venous blood specimens were collected from an antecubital vein after 10 h overnight fasting of participants. Biochemical measurements such as total cholesterol, HDL- cholesterol, triglycerides, and fasting blood sugar (FBS) levels were done by an auto analyzer (Beckman Synchron CX4, Beckman Coulter Inc., Fullerton, CA, USA) using standard methods and commercial kits. Low-density lipoprotein cholesterol (LDL-cholesterol) was estimated based on Friedewald formula (12). LDL- cholesterol was not calculated if the serum triglyceride

level was more than 400 mg/dl. Assay performance was monitored every 50 tests, using the lipid control serum commercial kit (Pars Azmon Inc., Tehran, Iran). Quality control data were plotted on Levey-Jennings chart and Westgard rules applied to control whether the results from the samples when the control was done can be released, or if they need to be rerun. The uric acid concentration was measured in milligrams per deciliter by an enzymatic colorimetric method using uricase and peroxidase.

Definitions

Patients with hyperuricemia, defined as serum uric acid concentrations ≥ 7.0 mg/dl in men and ≥ 6.0 mg/dl in women .The MetS was defined based on adapted NCEP ATP-III criteria (5) as the presence of at least three of the following characteristics: abdominal obesity (WC> 102 cm in men and >88 cm in women), high BP (BP≥ 130/85mmHg or the use of antihypertensive medication), high FBS level (≥ 100 mg/dl), hypertriglyceridemia (triglyceride level≥ 150 mg/dl), and low level of HDL cholesterol (< 40 mg/dl in men and < 50 mg/dl in women).

Diabetes mellitus was defined as FBS level of> 126 mg/dl, or random BS> 200 mg/dl or pharmacological therapy for diabetes. Current smoking was defined as history of smoking (cigarette, cigar, and other tobacco products like pipe, water pipe, etc) any time during the past one month.

Statistical methods

Numerical variables were presented as mean ± SD, while categorical variables presented by absolute frequencies and percentages. Continuous variables were compared using the Student's *t* test, and categorical variables compared by the chi-square test. Multivariable logistic regression models were established to evaluate the relationship between hyperuricemia and components of metabolic syndrome adjusted for other components of MetS. Associations were expressed as odds ratio (OR) with 95% confidence interval (CI). For the statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were applied. All *P*-values were 2-tailed; statistical significance defined as $P \leq 0.05$.

Results

The clinical and demographic characteristics of the study population based on hyperuricemia status are listed in Table1. The average age of the study population was 59.66 ± 10.04 yr, ranging from 31 to 85 yr. Overall, hyperuricemia was detected in 231 (49.7%) of participants, in 126 (54.5%) of men, and in 105 (45.5%) of women. Similar in age, participants with hyperuricemia were heavier, had more central adiposity with higher waist circumference and had higher BMI compared with participants without hyperuricemia. In addition, 66.7% of individuals with hyperuricemia had metabolic syndrome compared with 56.0% of individuals without this condition ($P = 0.018$). Patients with hyperuricemia, as compared to those without the condition, were similar regarding the cardiovascular risk factors except that the prevalence of hypertension was higher in those with hyperuricemia (55.0% vs. 41.9%; $P= 0.005$). Moreover, HDL-cholesterol showed a trend to be lower in subjects with hyperuricemia than those with normouricemia but the difference was not of the statistical significance.

Table1- Baseline characteristics of the study population according to uricemia status

	Normouricemia (n= 234)	**Hyperuricemia (n= 231)**	***P-value***
Age (yr)	59.72 ± 9.70	59.61 ± 10.43	0.906
Male gender	134 (57.3)	126 (54.5)	0.555
Metabolic syndrome	131 (56.0)	154 (66.7)	0.018
Diabetes	76 (32.5)	71 (30.7)	0.686
Hypertension	98 (41.9)	127 (55.0)	0.005
Current smoker	45 (19.2)	38 (16.5)	0.434
Family history of CAD	76 (32.5)	78 (33.8)	0.768
Weight (Kg)	73.86 ± 12.23	77.07 ± 13.74	0.008
Height (cm)	163.57 ± 9.39	162.45 ± 10.06	0.215
Body mass index (Kg/m^2)	27.69 ± 4.03	29.33 ± 5.12	<0.001
Waist circumference (cm)	97.14 ± 11.14	101.36 ± 10.45	<0.001
Fasting glucose (mg/dl)	122.25 ± 48.21	118.32 ± 41.14	0.345
Gensini score, mean ± SE	21.99 ± 2.04	23.16 ± 2.22	0.672
Triglyceride (mg/dl)	187.21 ± 96.58	201.88 ± 109.02	0.125
HDL* cholesterol (mg/dl)	43.70 ± 10.34	41.85 ±11.56	0.070
LDL **cholesterol (mg/dl)	110.68 ± 39.60	107.65 ± 40.34	0.414
Total cholesterol (mg/dl)	191.48 ± 43.59	193.50 ± 93.77	0.766
Uric acid (mg/dl)	5.23 ± 1.00	8.03 ± 1.28	<0.001

Data are presented as n (%) or mean ± SD unless otherwise noted.

*High Density Lipoprotein

** low Density Lipoprotein

Mean serum uric acid concentrations according to each component of the Mets stratified by gender, are summarized in Table 2. As shown in this table, women with elevated FBS and low HDL-cholesterol had higher uric acid concentrations than those without these components of MetS but this association was not evident among men. On the other hand, men but not women with high blood pressure, as compared to their counterparts, showed an increased level of plasma uric acid. There were no statistical significant relation between elevated waist circumference and high triglyceride level with uric acid concentrations.

Table 2- Mean serum uric acid concentrations according to each component of the Mets stratified by gender

	All (n= 465)	Men (n= 260)	Women (n=205)
Fasting plasma glucose (mg/dl)			
≥ 100	6.73 ± 1.82	6.95 ± 1.76	6.49 ± 1.85
< 100	6.48 ± 1.80	6.85 ± 1.87	5.86 ± 1.51
P value	0.141	0.673	0.009
Waist circumference (cm)			
> 102 in men & >88 in women	6.51 ± 1.78	7.02 ± 1.82	6.28 ± 1.72
≤ 102 in men & ≤88 in women	6.77 ± 1.85	6.85 ± 1.80	6.15 ± 2.08
P value	0.132	0.472	0.746
HDL-cholesterol (mg/dl)			
< 40 in men & < 50 in women	6.78 ± 1.79	7.10 ± 1.78	6.45 ± 1.75
≥ 40 in men & ≥ 50 in women	6.41 ± 1.83	6.69 ± 1.82	5.94 ± 1.75
P value	0.027	0.068	0.047
Blood pressure (mmHg)			
> 130/85	6.84 ± 1.78	7.44 ± 1.74	6.39 ± 1.67
≤ 130/85	6.42 ± 1.83	6.59 ± 1.78	6.06 ± 1.89
P value	0.012	<0.001	0.204
Triglyceride (mg/dl)			
≥ 150	6.68 ± 1.86	6.93 ± 1.91	6.39 ± 1.75
< 150	6.52 ± 1.73	6.87 ± 1.63	6.03 ± 1.76
P value	0.343	0.813	0.161

Data are presented as n (%) or mean ± SD unless otherwise noted.

Table 3 demonstrates the multivariable-adjusted odds ratios for hyperuricemia for individual components of MetS. After simultaneously controlling for the other components of MetS, in total, and in male gender, the association between hyperuricemia and elevated BP remained statistically significant. Among subjects with elevated BP, the adjusted OR (95% CI) of having hyperuricemia was 1.64 (1.12-2.40) in total, and 2.23 (1.31-3.79) in men. A low level of HDL-cholesterol was also independently associated with an increased OR of hyperuricemia in total, but not in men or in women. Women with high plasma glucose showed 2-fold increase in odds of hyperuricemia compared to those without high FBS. Hyperuricemia was not significantly associated with other components of MetS in total, in women, or in men.

Table3- Adjusted odds ratios of hyperuricemia by components of the metabolic syndrome

	All participants		**Women**		**Men**	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
High FBS*	1.16 (0.79-1.69)	0.4498	2.00 (1.11-3.61)	0.0217	0.78 (0.47-1.29)	0.3293
High BP**	1.64 (1.12-2.40)	0.0115	1.20 (0.67-2.14)	0.5480	2.23 (1.31-3.79)	0.0031
High TG***	0.97 (0.65-1.44)	0.8907	1.07 (0.58-1.97)	0.8256	0.89 (0.52-1.52)	0.6730
Large waist	1.05 (0.71-1.55)	0.8040	1.24 (0.49-3.10)	0.6531	1.07 (0.62-1.84)	0.8175
Low HDL****	1.58 (1.08-2.33)	0.0192	1.72 (0.95-3.12)	0.0755	1.55 (0.92-2.61)	0.0978

OR, Odds ratio adjusted for all other components of metabolic syndrome

* fasting glucose; ** blood pressure;

*** triglyceride; **** high-density lipoprotein cholesterol

The prevalence of 0, 1, 2, 3, 4, or 5 components of MetS was 4.3%, 10.8%, 23.7%, 27.5%, 23.2%, and 10.5%, respectively. The multivariable age- and sex-adjusted OR of hyperuricemia associated with the number of MetS components are presented in Table 4. In the adjusted model, subjects with MetS had 1.56-fold increased odds of hyperuricemia compared to those without any components of the MetS. In addition, subjects with 5 components of the MetS had increased odds of 4.19.

Table 4- Multivariable adjusted odds ratios of hyperuricemia by the number of metabolic syndrome components

	Odds ratio	95% CI	*P*-value
0 component	1*		-
1 component	1.09	0.28-1.70	0.8721
2 components	1.08	0.42-2.48	0.8842
3 components	1.40	0.71-4.02	0.5073
4 components	1.55	1.46-8.76	0.4004
5 components	4.19	3.16-25.61	0.0145
MetS	1.56	1.04-2.32	0.0298

* Reference group.Odds ratio adjusted for age and gender.
CI, confidence interval; CAD, coronary artery disease; MetS, metabolic syndrome.

Discussion

In the present study we found that patients with MetS compared to subjects without any components of the MetS had 1.56-fold increased odds of hyperuricemia. In addition, those with 5 components of the MetS had increased odds of 4.19. Hyperuricemia was significantly related to high BP and low level of HDL-cholesterol but not with other components of MetS.

Previous studies demonstrated that there is an association between hyperuricemia with MetS and its components, such as obesity, dyslipidemia, high BP, and high FBS (13, 14). Epidemiologic studies revealed that the prevalence of MetS being increased according to serum uric acid level (3, 10, 15). On the other hand, there is evidence that uric acid may not be a consequence of MetS, but it may actually induce or worsen MetS (9). We aimed to estimate the prevalence of hyperuricemia and to examine the relationship between uric acid levels and the various components of MetS in an Iranian sample of patients undergoing coronary angiography.

The 49.7% prevalence of hyperuricemia in our study population is higher than reports from other studies using the same criteria for definition (16-18). One reason for that may be the fact that we studied a population at risk of atherosclerosis with high average of age and frequent cardiovascular risk factors. We also found that the prevalence of hyperuricemia was 54.5% in men vs. 45.5% in women. This may be because due to estrogen inducing uric acid excretion indicating that it is probably more essential for men to prevent hyperuricemia (19).

The association of high BP and hyperuricemia has been established for more than a century, and several possible mechanisms have been suggested, including rise in urate reabsorption, or confounding with antihypertensive drugs (20). In our study, hypertension had had a stronger association with increasing serum uric acid level than all other components. Significant relationship between hyperuricemia and elevated BP in our multivariable analyses is consistent with a growing large body of literature linking uric acid concentrations to the

development of hypertension (4, 15, 21).

Our study Showed that hyperuricemia was negatively associated with serum HDL-cholesterol in total population, but this association was not evident among women and men separately. This finding was similar to Chen *et al.* results who found that uric acid was reversely correlated with serum HDL- cholesterol in men but not in women (22).

Central obesity, as one of the components of MetS, has been reported to be associated with hyperuricemia (23, 24). In our study, BMI and waist circumference were related to high serum uric acid levels in univariable analyses; however, by multivariable analyses adjusting for other components of MetS, hyperuricemia did not show an association with MetS.

An association of serum uric acid levels with triglyceride levels has been previously established in cross-sectional and longitudinal studies (25, 26). This relationship could have been justified by confounding factors, particularly by BMI. In our study, we failed to find an association between hypertriglyceridemia, as a component of MetS, and hyperuricemia which is difficult to be explained. But one plausible reason may be relatively small sample size and the fact that we were also unable to show an association between obesity and hyperuricemia in multivariable analyses.

Previous investigators reported that hyperglycemia was a significant risk factor for hyperuricemia (15, 27). Nakanishi *et al.*, in a study among 2310 Japanese male office workers over a 6-year follow-up found that an increased level of serum uric acid was closely associated with an increased risk for Type 2 diabetes, and concluded that hyperuricemia was positively associated with hyperglycemia (28). However, in our multivariable adjusted analyses, significant association was found for hyperuricemia with high FBS only in women which is in line with Chen *et al.* (22) study. Further studies are needed to clearly define this issue.

Another important finding of this study was that the ORs of hyperuricemia for those patients who had three or more (MetS definition by ATP III A), and five components of MetS were 1.56 and 4.19, respectively. In a cross-sectional study, Onat *et al.* also suggested an independent association between serum uric acid levels and MetS in which the upper 10% of uric acid levels in both sexes had approximately 2-fold higher risk of MetS comparing to the lower 10% (29).

Limitations

First, our study had cross-sectional study design possibly restricting us to identify and analyze all potential confounding factors. Second, our analyses are based on a single measurement of uric acid rather than serial uric acid levels checking over time which likely to be more accurate. Third, our control group composed individuals having suspected CAD on clinical evaluation; this study group may not be considered as representative of general population or individuals without CAD who lack clinical features triggering a plan to perform coronary angiography.

Conclusion

Hyperuricemia was strongly associated with the prevalence of MetS as defined by adapted ATP III guidelines in an Iranian sample of patients undergoing coronary angiography. Much remains to be discovered including whether the association between hyperuricemia and Mets is causative and the possible specific mechanisms by which higher serum uric acid increase the risk of MetS development.

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conflict of interests.

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