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Association between serum uric acid and the Adult Treatment Panel III–defined metabolic syndrome: Results from a single hospital database

Young Hee Rho, Jin-Hyun Woo, Seong Jae Choi, Young Ho Lee, Jong Dae Ji, Gwan Gyu Song*

Division of Rheumatology, Department of Internal Medicine, Korea University Medical School, Seoul 152-703, South Korea

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Abstract

Hyperuricemia is known to be associated with various metabolic abnormalities of the metabolic syndrome, but its precise contribution is not well defined. We have investigated the effects of serum uric acid on the metabolic syndrome as defined by the Adult Treatment Panel (ATP) III criteria and tested its independent association. This was a cross-sectional study consisting of 1686 Korean subjects (821 men and 865 women) from a health promotion center. Clinical data and the presence of the metabolic syndrome were assessed, and serum uric acid was tested for its independent contribution to the metabolic syndrome using 2 multiple logistic regression models. The metabolic syndrome was defined by the original ATP III criteria and the modified ATP III criteria that include a reduced waist circumference. The general age-adjusted prevalence of the metabolic syndrome was 4.4% in men and 6.8% in women; hyperuricemic subjects tended to have a higher prevalence of the metabolic syndrome and more metabolic abnormalities than normouricemic subjects. The prevalence of the metabolic syndrome increased as normouricemia (2.9%) progressed to hyperuricemia (8.9%) and to gout (43.6%) in men. Multivariate analysis showed that serum uric acid was a significant factor for the development of the metabolic syndrome as defined by the original ATP III criteria only in one model for women (odds ratio, 1.51; 95% confidence interval, 1.11-2.05; $P = .009$). Serum uric acid is closely linked to and may even be independently associated with the metabolic syndrome as defined by the ATP III criteria, but only in women.

1. Introduction

Metabolic syndrome is a cluster of disorders characterized by insulin resistance and comprising high blood pressure, hyperglycemia, dyslipidemia, and abdominal obesity [1]. Since the recommendations for screening and treatment of metabolic syndrome from the Adult Treatment Panel (ATP) III guidelines appeared [2], this disease has gained much attention and is acknowledged as an important cardiovascular risk factor. Gout, which is an inflammatory arthritis resulting from chronic hyperuricemia, is also related to the components of the metabolic syndrome [3]; and we have recently reported that gout is related to the metabolic syndrome as defined by the ATP III criteria [4]. The relationship of gout to metabolic syndrome raises the question of whether hyperuricemia itself may be associated with metabolic syndrome. Although there are many studies indicating the association between insulin resistance and hyperuricemia [5-8], there are few studies directly investigating the relationship between hyperuricemia and metabolic syndrome as defined by the ATP III criteria. Therefore, we sought to make a more generalized study using a larger sample size.

2. Methods and materials

This study was a cross-sectional study consisting of 1686 subjects (821 men and 865 women) who were considered to be healthy and had visited a health center (Korea University Anam Hospital Health Promotion Center) for health screening. The subjects were selected from the health center database during the period from May to September 2004. The main research objective was to determine whether serum uric acid is related to metabolic

* Corresponding author. Division of Rheumatology, Department of Internal Medicine, Korea University Guro Hospital, Seoul 152-703, South Korea. Tel.: +82 2 818 6667.
E-mail address: gsong@kumc.or.kr (G.G. Song).

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syndrome as defined by the ATP III criteria and, if so, whether it is an independent contributing factor to the development of the metabolic syndrome.

The subjects were divided into male and female groups, and clinical data were collected and analyzed. Demographics such as age, height, weight, waist circumference, and clinical data relevant to insulin resistance and the occurrence of hyperuricemia (such as blood pressure, serum lipids, glucose, and creatinine) were checked. Insulin resistance was included as a composite index (homeostasis model assessment of insulin resistance [HOMA-IR]) [9]. Alcohol consumption, which is an important factor in hyperuricemia, was coded as nondrinkers, average consumption ≤30 g/d, and average consumption >30 g/d. Although not used as a representative variable for serum uric acid for fear of information loss from categorization, hyperuricemia was defined as >7 mg/dL in men and >6 mg/dL in women [10]. Before conducting the analysis, we excluded outlying samples that were deemed to be non-normal on the basis of other variables not used in the analysis. The arbitrary cutoff values were as follows: aspartate aminotransferase or alanine aminotransferase ≥100 IU/L, total bilirubin ≥2 mg/dL, hemoglobin ≤10 g/dL, white blood cell count ≥12 000/μL, platelet count ≤100 000/μL, free thyroxine ≥2.5 ng/dL, and thyroid-stimulating hormone ≥5 μIU/mL. This resulted in a 9.75% exclusion rate. There were 22 samples that had missing values and that were deleted. The final sample size was 1686.

The occurrence of metabolic syndrome was defined as in the ATP III guidelines [2], and the prevalence in the 2 sex groups was obtained. The prevalence was age-adjusted using the population value from the year 2000 Population Projection for Korea [11] as the standard population. In addition, a modified definition of metabolic syndrome was used using waist circumference criteria defined by the World Health Organization Asia-Pacific Obesity Criteria (men, ≥90 cm; women, ≥80 cm) [12]. The results were compared with 2 studies on metabolic syndrome in the general Korean population, the Korea National Health and Nutrition Examination Survey (KNHANES) study [13], which is a national survey, and the study of Lee et al [14], which provides data from another hospital's health promotion center, for assessing the representative nature of the study data pool. The significance of serum uric acid was assessed by sequential logistic regression from univariate to increasingly multivariate models using the presence of metabolic syndrome as the dependent variable. Because serum uric acid levels are also associated with the components of metabolic syndrome, multivariate correction seemed essential for appropriate assessment. We used 2 models: one used only the components of metabolic syndrome (serum glucose, high-density lipoprotein [HDL]), triglycerides [TG], systolic blood pressure [SBP], diastolic blood pressure [DBP], and waist circumference); and the other used all possible variables associated with serum uric acid including the components of the first model plus serum creatinine, alcohol consumption, simplifying blood pressure variables into a single mean blood pressure (MBP) variable (defined as [SBP + 2*DBP]/3), and replacing glucose into a composite index (HOMA-IR). The first model assessed whether serum uric acid might stand as an independent criterion for metabolic syndrome in addition to the original ATP III criteria, and the second model was constructed to be more complete by assessing the effects of all possible factors related to insulin resistance and the development of hyperuricemia while considering statistically parsimonious modeling. Both analyses were age-adjusted and carried out with separate sex groups because of the known difference in serum uric acid distribution between sexes and the possibility of statistical interaction. Multivariate results were described as odds ratios (ORs) with 95% confidence intervals (CIs). Descriptive data were expressed as the mean ± SD. Variable comparisons were accomplished by t tests (interval data) and χ^2 tests (categorical data) when required. Statistical analysis was performed with SPSS 10.0 for Windows (SPSS, Chicago, IL), and significance was determined when $P < .05$.

3. Results

The descriptive data for the 2 sex groups are shown in Table 1. Age-adjusted percentages of fulfillment for the individual criteria according to the ATP III are shown in Table 2. When these results were divided into hyperuricemic and normouricemic subjects, the hyperuricemic subjects tended to have higher proportions of criteria fulfillment compared with the normouricemic subjects regardless of criterion type or sex group. The age-adjusted percentages of simultaneous fulfillment of multiple ATP III criteria are shown in Table 3. In addition, when the modified ATP III criteria were applied, the percentages were ≥1, 51.7%; ≥2, 27.2%; ≥3, 10.4%; ≥4, 2.6%; and =5, 0.3% in men (total)

Table 1
Descriptive clinical data of the study population

Factor	Men (n = 821)	Women (n = 865)
Age (y)	48.8 ± 11.9	49.1 ± 12.3
Waist (cm)	85.2 ± 7.2	78.9 ± 9.3
Body mass index (kg/m^2)	24.4 ± 2.7	23.5 ± 3.2
SBP (mm Hg)	122.5 ± 9.8	118.5 ± 13.6
DBP (mm Hg)	78.7 ± 8.9	75.7 ± 10.9
MBP (mm Hg)	93.3 ± 8.8	90.0 ± 11.4
Total cholesterol (mg/dL)	193.8 ± 33.1	194.6 ± 34.6
HDL (mg/dL)	48.7 ± 10.9	56.0 ± 12.6
TG (mg/dL)	157.8 ± 97.9	114.6 ± 68.2
Glucose (mg/dL)	97.7 ± 23.4	92.4 ± 19.3
Insulin (μIU/L)	10.0 ± 3.7	9.9 ± 3.7
HOMA-IR	2.40 ± 1.1	2.27 ± 1.1
Uric acid (mg/dL)	6.2 ± 1.27	4.5 ± 0.97
Hyperuricemia	206 (23.8%)	55 (6.7%)
Creatinine (mg/dL)	1.01 ± 0.1	0.78 ± 0.1
Alcohol consumption[a]	342/252/271	730/64/27

[a] Nondrinkers/≤30g/d/>30g/d.

Table 2
Age-adjusted proportions of fulfillment of individual ATP III criteria

Criterion	Men			Women		
	Total	Normouricemia	Hyperuricemia	Total	Normouricemia	Hyperuricemia
Waist	0.8%	0.5%	1.8%	9.9%	8.9%	23.4%
Circumference	19.2%[a]	15.1%[a]	30.5%[a]	27.7%[a]	27.5%[a]	27.3%[a]
HDL	15.4%	13.3%	21.1%	23.9%	23.2%	37.9%
TG	29.9%	24.6%	44.8%	13.4%	12.3%	32.5%
SBP/DBP	20.9%	20.9%	20.8%	12.6%	12.2%	22.2%
Glucose	6.8%	6.3%	7.9%	3.6%	3.3%	5.5%

[a] Modified waist circumference according to the World Health Organization Asia-Pacific Criteria for Obesity is used.

and ≥1, 45.6%; ≥2, 22.2%; ≥3, 10.4%; ≥4, 2.9%; and =5, 0.3% in women (total). These results are lower than those in the KNHANES study [13], but are relatively similar to the results of Lee et al [14]. The percentages among normouricemic and hyperuricemic subjects showed a generally higher number of fulfilled criteria in the hyperuricemic subjects, especially in the female group.

The prevalence of metabolic syndrome within the study population is shown in Table 4. Again, the age-adjusted prevalence was smaller when compared with the KNHANES study [13] (men, 22.1%; women, 27.8%; modified ATP III) but very similar to that of Lee et al [14] (men, 5.2% and 9.8%; women, 9.0% and 12.4%; ATP III and modified ATP III, respectively). Because the data source for the latter study was also from a health promotion center, our results appear to represent characteristics of a population that visits such a center. Once again, the hyperuricemic group showed a larger proportion of subjects with metabolic syndrome than the normouricemic group for both men and women (Table 4).

The effects of serum uric acid on the presence of metabolic syndrome are described in Fig. 1. The univariate analysis showed that uric acid is a significant factor in the development of metabolic syndrome; the effects appear to be more pronounced in women. The multivariate analysis showed that when testing the independence over the ATP III criteria, uric acid maintained significance only in the female group (OR, 1.51; 95% CI, 1.11-2.05; P = .009). When considering the extended multivariate model that used all relevant variables associated with hyperuricemia and insulin resistance, uric acid was marginally insignificant in the female group as defined by the ATP III classification (OR, 1.34; 95% CI, 0.98-1.82; P = .064). When the presence of hyperuricemia is used instead of the serum uric acid variable, only the first multivariate model (female, ATP III) showed the significance of the hyperuricemia variable (OR, 2.49; 95% CI, 1.04-5.99; P = .042). This was similar to the results of the continuous serum uric acid models.

4. Discussion

The importance of serum uric acid as a contributing metabolic factor to cardiovascular mortality is still a topic of ongoing debate [15]. Most views regard hyperuricemia as a secondary phenomenon to other metabolic diseases or renal insufficiency [16], with no direct effects on cardiovascular disease; however, research results are conflicting [10,17-20]. We attempted to expand our previous study on the relationship between gout and metabolic syndrome [4] into a more generalized and representative form by testing the association of serum uric acid and the metabolic syndrome. The results were mixed; serum uric acid itself was associated with metabolic syndrome and also may be an independent contributing factor for the development of metabolic syndrome, but only in certain situations. As hyperuricemia is clinically more relevant to men than women, it was somewhat unexpected to find that serum uric acid (or hyperuricemia) was more significant in women than in men for the development of metabolic syndrome. We do not actually know why there was such a difference. However, similar trends for women have been found in previous studies [10,18,21] that investigated the contribution of serum uric acid to cardiovascular mortality. Recently, a Japanese study [22] also noted that serum uric acid is associated with metabolic syndrome only in women, although the study used a Japanese definition of metabolic syndrome that is different

Table 3
Age-adjusted percentages of simultaneous fulfillment of multiple ATP III criteria

Number	Men			Women		
	Total	Normouricemia	Hyperuricemia	Total	Normouricemia	Hyperuricemia
≥1	48.8%	43.6%	54.9%	37.7%	36.9%	52.8%
≥2	19.9%	15.9%	30.9%	16.8%	15.8%	32.6%
≥3	4.4%	2.9%	8.9%	6.8%	5.6%	24.8%
≥4	0.7%	0.5%	1.3%	2.0%	1.5%	10.9%
5	0.1%	0.0%	0.5%	0.1%	0.1%	0.5%

Table 4
Age-adjusted prevalence of the metabolic syndrome in the study patients

Classification	Men			Women		
	Total	Normouricemia	Hyperuricemia	Total	Normouricemia	Hyperuricemia
ATP III	4.4%	2.9%	8.9%	6.8%	5.6%	24.8%
Modified ATP III	10.4%	7.4%	18.8%	10.4%	9.3%	26.2%

from the original ATP III criteria. There is also a Turkish study [23] showing that hyperuricemia is associated with metabolic syndrome in women more than men. This study, too, used modified criteria that differ slightly from those of the original ATP III. These findings suggest that there may be some metabolic differences between sexes.

The possibility that the study population might be nonrepresentative is an unlikely explanation because the prevalence data do not deviate much from those of previous large-scale studies. Actually, it was intriguing that the prevalence of the metabolic syndrome was quite similar to that in a study from another health promotion center, which may indicate that people who visit health promotion centers may have some common characteristics. Both studies are from large university-based hospitals in Seoul, Korea; so both may represent urban subpopulations, such as the middle or upper classes, which are more likely to take an interest in health maintenance. The slightly lower values in this study are thought to have occurred because of the exclusion of subjects who were likely to have additional metabolic abnormalities. When exploring the results statistically, the loss of significance of serum uric acid when the modified ATP III criteria (which lower the obesity threshold) were applied suggests that uric acid has much influence from obesity. Indeed, obesity is an important factor that contributes to the development of metabolic syndrome in patients with gout [3,4]; and the association with genes linked to obesity such as the Trp64Arg polymorphism of the β-3 adrenergic receptor [24,25] indicates the close association compared with other metabolic abnormalities. This is also shown in the previous Turkish study [23] where uric acid had lower significance when controlled by waist circumference. Alternatively, it may reflect that the modified ATP III criteria may be a better fit for insulin resistance and metabolic abnormalities in Korean (which are also Asian) populations than the original ATP III criteria, which seem to match Western populations better [13,26,27]. This assumes that hyperuricemia is a secondary phenomenon to other diseases or that serum uric acid may instead indirectly contribute by inflicting metabolic disorders such as hypertension [28].

The rationale for constructing 2 multivariate models was to determine whether uric acid might stand as an independent criterion in the diagnosis of metabolic syndrome in addition to the original ATP III criteria and whether uric acid is truly independent in the development of metabolic syndrome

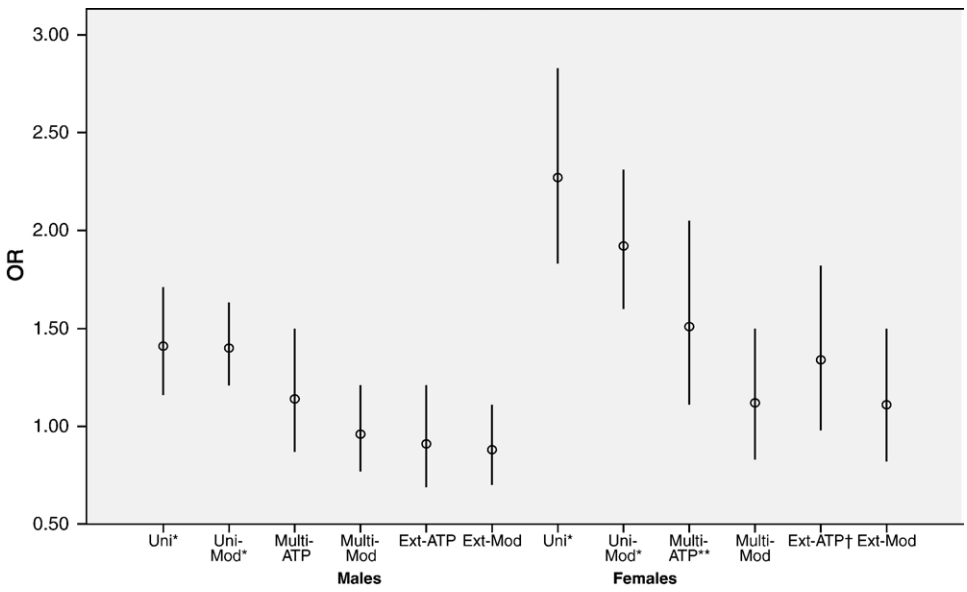

Fig. 1. Odds ratios of serum uric acid in the occurrence of the metabolic syndrome. Systolic blood pressure and DBP are collapsed into a single MBP variable. *$P \leq .001$, **$P = .009$, †$P = .064$. Uni indicates univariate analysis; Multi; multivariate analysis with age, waist circumference, HDL, TG, SBP, DBP, and serum glucose; Ext, extended model using multivariate model + HOMA-IR, amount of alcohol consumption, and serum creatinine; ATP, metabolic syndrome according to the original ATP III criteria; Mod, metabolic syndrome with waist circumference adjustment.

using all relevant variables. The HOMA-IR was used because it may explain insulin resistance better than serum glucose itself, and the MBP variable was used because SBP and DBP are correlated and may induce statistical difficulties. Alcohol is a verified risk factor for the development of hyperuricemia and gout [29,30], and serum creatinine is essential for inclusion considering the importance of the kidney in uric acid balance. Such variables were needed for further statistical control and precise assessment.

However, in either case, the results were not uniform, leaving possibilities but not definite conclusions. One may object to using the same variables to define metabolic syndrome because they are highly likely to be significant and thus the analysis would be meaningless. However, serum uric acid (including hyperuricemia) is well known to be associated with these variables; and controlling was required anyway.

This study is unique because it provides the first epidemiological evidence for the contribution of serum uric acid to the development of metabolic syndrome as defined by the ATP III criteria in a Korean population. It also gives additional data for comparison by adding a modified waist circumference criterion, which suggests 2 possibilities: the degree of obesity may differ between Western and Asian populations, and serum uric acid has much influence from obesity.

It was also interesting to find that there was a relationship among normouricemia, hyperuricemia, and gout that was similar to a dose dependency. We had recently found that the prevalence of metabolic syndrome in patients with gout is 43.6% in men [4], whereas the present results showed that it was 8.9% and 2.9% in hyperuricemic and normouricemic men, respectively (all results using original ATP III criteria). As gout usually occurs after chronic hyperuricemia, we hypothesize that patients with gout accumulate more “doses” of metabolic abnormalities than asymptomatic hyperuricemic subjects and that asymptomatic hyperuricemic subjects accumulate more than normouricemic subjects. Whether these occur because of the metabolic abnormalities themselves or the independent effects of uric acid remains to be determined.

In conclusion, serum uric acid is associated with metabolic syndrome as defined by the ATP III criteria and may even be an independent criterion, but only in women. The explanation for these findings needs further investigation.

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