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Relationship between hyperuricemia and metabolic syndrome*

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Abstract: Objective: To investigate the relationship between metabolic syndrome and hyperuricemia. Methods: A total of 2374 subjects who received health examination in our hospital from Jan. 2004 to Dec. 2006 were enrolled in our study. Hyperuricemia is defined as ≥7 mg/dl (in men) or ≥6.0 mg/dl (in women). Metabolic syndrome was defined using AHA/NHLBI (American Heart Association/National Heart, Lung, and Blood Institute) criteria. Results: (1) The overall prevalence of hyperuricemia was 13.10%. The condition was more common in men than in women (19.07% vs 3.42%). (2) Among men, uric acid concentration is statistically significantly positively correlated with waist circumference, blood pressure, and triglyceride. Uric acid is negatively correlated with serum high-density lipoprotein-cholesterol (HDL-C). Uric acid concentration is most strongly correlated with serum triglyceride (r=0.379) and waist circumference (r=0.297). Among women, statistically significant positive correlations were noted for the serum uric acid concentrations with waist circumference, triglyceride and fasting plasma glucose. Serum triglyceride (r=0.329) and waist circumference (r=0.234) are most strongly correlated with uric acid concentrations. (3) Men with hyperuricemia had a 1.634-fold increased risk of metabolic syndrome as compared with those without hyperuricemia [odds ratio (*OR*)=1.634, *P*=0.000]. Women with hyperuricemia had a 1.626-fold increased risk of metabolic syndrome (*OR*=1.626, *P*=0.000) as compared with those without hyperuricemia. Conclusion: Hyperuricemia is prevalent among Chinese population. Additionally, serum uric acid is positively associated with metabolic syndrome.

Key words: Hyperuricemia, Metabolic syndrome, Triglyceride
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INTRODUCTION

The prevalence of hyperuricemia has been increasing in recent years, not only in advanced countries but also in developing countries, along with the development of their economies. It has been suggested that hyperuricemia is associated with metabolic syndrome (Nakagawa *et al*., 2006; Conen *et al*., 2004). However, very little progress has been made in China. Little information is available concerning the prevalence of hyperuricemia and its association with metabolic syndrome. Our objective in this study was to estimate the prevalence of metabolic syndrome in patients with hyperuricemia and the association between uric acid levels and the various metabolic syndrome components in our country.

MATERIALS AND METHODS

Subject

The research covered 2374 persons (1468 men and 906 women) who received general health examination in our hospital from Jan. 2004 to Dec. 2006. Subjects who were taking antihypertensive or antidiabetic agents, lipid-lowering agents and hypouricemic agents were excluded. Participants were asked to take a vegetable diet in the three days before they received examination.

Measurement methods: To measure waist circumference, locating top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen

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at level of iliac crest. Before reading tape measure, ensure that the tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration (Grundy *et al*., 2005). Blood pressure was measured using a sphygmomanometer after the subjects had rested for more than 5 min. For those with a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg (defined as hypertension by the 2003 JNC-7), blood pressure was measured on a further 2 occasions after resting, and average values were then taken (Himmelmann *et al*., 2003).

Laboratory analyses: Participants provided an overnight fasting venous blood sample. Serum samples were used to determine participants' lipid profiles and fasting blood glucose using an automatic analyzer (Advia 1650, Bayer, Germany). Serum triglyceride concentration was determined by standardized enzymatic procedures using glycerol phosphate oxidase assay. High-density lipoprotein-cholesterol (HDL-C) was measured by a chemical precipitation technique using dextran sulfate. Fasting plasma glucose was measured using the hexakinase method. Serum uric acid concentrations were measured using the uricase EMST method (Hitachi 747 automatic analyzer, Hitachi, Japan).

Diagnosis criteria

1. Hyperuricemia is defined as serum uric acid level ≥7 mg/dl (in men) or ≥6.0 mg/dl (in women) (Hochberg *et al*., 2003).

2. We assessed metabolic syndrome according to AHA/NHLBI criteria. The presence of metabolic syndrome was defined as those patients having ≥3 of the following 5 items: (1) waist circumference ≥90 cm for males (≥80 cm for females); (2) serum triglyceride levels ≥150 mg/dl or on drug treatment for elevated triglycerides; (3) serum HDL-C levels <40 mg/dl for males (<50 mg/dl for females), or on drug treatment for reduced HDL-C; (4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension; (5) fasting blood glucose ≥110 mg/dl or on drug treatment for elevated glucose (Grundy *et al*., 2005).

Statistical analysis

Descriptive data is described as mean±*SD*, comparisons between the quantitative data were done by *t*-tests and categorical variables were done by chi-square tests. Analysis of variance (ANOVA) followed by multiple comparisons with the LSD test was used to evaluate the differences by age groups. Pearson's correlation coefficients were obtained for each of the metabolic syndrome components and the respective uric acid concentration. Fasting plasma glucose and triglyceride were skewed and were normalized by logarithmic transformation in all analyses. Logistic regression procedures were used to examine the risks of having metabolic syndrome. All analyses were completed separately for male and female patients. All reported *P* values are two tailed. Variables with *P* values of <0.05 were considered significant. Statistical analyses were performed using SPSS (V. 13.0) software.

RESULTS

Characteristics of study population according to hyperuricemia status

Some characteristics of the study population according to hyperuricemia status are shown in Table 1. Men (1468) and women (906) were enrolled in our research. Men with hyperuricemia, as compared with those without the condition, were more likely to have reported smoking (*P*=0.000) and exercising (*P*=0.015). Women with hyperuricemia as compared with their counterparts without the condition were likely to do exercise (*P*=0.000). The mean age and drinking status were not statistically significantly associated with hyperuricemia status in both men and women.

Prevalence of hyperuricemia by gender group

As shown in Table 2, the overall prevalence of hyperuricemia was 13.10%. Hyperuricemia was more common in men (19.07%) than in women (3.42%) (*P*=0.000).

Correlation between metabolic syndrome component and uric acid concentrations

As shown in Table 3, elevated waist circumference and high triglyceride were statistically significantly associated with higher uric acid concentration in both men and women. Men with high blood pressure and low HDL-C had higher uric acid concentra-

tions than those without such conditions, but this association was not evident among women. There was no statistical significance between elevated fasting glucose and uric acid concentration.

Table 4 summarizes Pearson's correlation coefficients between metabolic syndrome components and serum uric acid concentrations. Among men, uric acid concentrations were statistically significantly positively correlated with waist circumference, blood pressure, and log-transformed serum triglyceride concentrations. Uric acid was negatively correlated with serum HDL-C. Uric acid concentrations were most strongly correlated with serum triglyceride concentrations (r=0.379) and waist circumference (r=0.297). Among women, statistically significant positive correlations were noted for the serum uric acid concentrations with waist circumference, log-transformed triglyceride and log-transformed fasting plasma glucose concentrations. Serum triglyceride concentrations (r=0.329) and waist circumference (r=0.234) were most strongly correlated with uric acid concentrations.

Risk of metabolic syndrome according to uric acid concentration

We used binary logistic regression procedures to evaluate the relative risk of metabolic syndrome in relation to serum uric acid concentration in men and women, respectively. As shown in Table 5, we noted that men with hyperuricemia had a 1.634-fold increased risk of metabolic syndrome as compared with men without hyperuricemia [odds ratio (OR)=1.634, P=0.000]. Women with hyperuricemia had a 1.626-fold increased risk of metabolic syndrome (OR=1.626, P=0.000) as compared with those without hyperuricemia.

Table 1 Characteristics of study population according to hyperuricemia status

Characteristics	Men (n=1468)			Women (n=906)		
	Non-hyperuricemia (n=1188)	Hyperuricemia (n=280)	P value	Non-hyperuricemia (n=875)	Hyperuricemia (n=31)	P value
Age (years)	43.20±9.53	42.50±9.82	0.507	41.70±10.24	42.38±14.58	0.772
Drinking status			0.432			0.924
Never drinker	370 (31.14)	94 (33.57)		261 (29.83)	9 (29.03)	
Ever drinker	818 (68.86)	186 (66.43)		614 (70.17)	22 (70.97)	
Smoking status			0.000			0.724
Never smoker	690 (58.08)	118 (42.14)		338 (38.63)	11 (35.48)	
Ever smoker	498 (41.92)	162 (57.86)		537 (61.37)	20 (64.52)	
Exercise			0.015			0.000
Yes	480 (40.40)	91 (32.50)		536 (61.26)	9 (29.03)	
No	708 (59.60)	189 (67.50)		339 (38.74)	22 (70.97)	
WC (cm)	89.96±8.99	94.77±7.29	0.000	77.14±9.49	86.43±13.79	0.000
Hypertension	333 (28.03)	105 (37.50)	0.034	134 (15.31)	10 (32.26)	0.255
FPG (mg/dl)	97.98±25.12	96.31±10.10	0.525	94.31±16.11	101.15±12.27	0.062
TG (mg/dl)	193.53±138.14	269.10±146.46	0.003	100.53±51.33	152.63±75.59	0.000
HDL-C (mg/dl)	41.20±11.44	38.17±10.61	0.016	54.31±12.59	51.33±15.76	0.308

Note: The data are expressed as mean±SD or n (percentage). WC: Waist circumference; FPG: Fasting plasma glucose; TG: Triglyceride

Table 2 Prevalence of hyperuricemia by gender group

Groups	Hyperuricemia	Non-hyperuricemia	Total	Prevalence (%)	P value
Males	280 (90.03)	1188 (57.59)	1468	19.07	0.000
Females	31 (9.97)	875 (42.41)	906	3.42	
Total	311	2063	2374	13.10	

The data in the parentheses are percentage

Table 3 Means of uric acid (mg/dl) according to selected features of metabolic syndrome

	Men			Women		
	n	Uric acid (mg/dl)	*P* value	*n*	Uric acid (mg/dl)	*P* value
Waist circumference			0.000			0.000
≥90 cm (men)/≥80 cm (women)	861	5.92±1.26		336	3.88±0.99	
<90 cm (men)/<80 cm (women)	607	5.28±1.04		570	3.46±0.88	
Blood pressure			0.010			0.237
SBP≥130 mmHg/DBP≥85 mmHg	726	5.77±1.28		462	3.67±0.95	
SBP<130 mmHg/DBP<85 mmHg	742	5.54±1.14		444	3.56±0.93	
Fasting plasma glucose			0.238			0.881
≥110 mg/dl	164	5.51±1.14		86	3.64±1.14	
<110 mg/dl	1304	5.68±1.22		820	3.61±0.92	
Triglyceride			0.000			0.000
≥150 mg/dl	796	6.01±1.25		161	4.17±1.02	
<150 mg/dl	672	5.24±1.02		745	3.50±0.88	
HDL-C			0.000			0.339
<40 mg/dl (men)/<50 mg/dl (women)	792	5.83±1.14		349	3.67±0.97	
≥40 mg/dl (men)/≥50 mg/dl (women)	676	5.45±1.26		557	3.58±0.93	

Note: SBP: Systolic blood press; DBP: Diastolic blood press; HDL-C: High-density lipoprotein-cholesterol

Table 4 Pearson's correlation coefficients (*r*) for each component of metabolic syndrome in relation to uric acid concentrations (mg/dl)

	Men		Women	
	Pearson's correlation (*r*)	*P* value	Pearson's correlation (*r*)	*P* value
Waist circumference	0.297	0.000	0.234	0.000
Systolic blood pressure	0.077	0.037	0.052	0.265
Diastolic blood pressure	0.116	0.002	0.035	0.454
HDL-cholesterol	−0.159	0.000	0.015	0.746
Log-transformed triglyceride	0.379	0.000	0.329	0.000
Log-transformed fasting plasma glucose	−0.001	0.987	0.098	0.037

Table 5 Risk of metabolic syndrome according to uric acid concentration

	B	*S.E.*	Wald	*df*	Sig.	Exp(*B*)
Uric acid (men)	0.491	0.073	45.843	1	0.000	1.634
Uric acid (women)	0.486	0.108	20.179	1	0.000	1.626

DISCUSSION

Hyperuricemia is an increasingly common medical problem not only in the advanced countries, but also in the developing countries. It has been described that hyperuricemia is associated with metabolic syndrome components (Nakagawa *et al*., 2006; Conen *et al*., 2004; Schachter, 2005), such as obesity, dyslipidemia, hyperglycemia and hypertension. The incidence of hyperuricemia has rarely been investigated in China up to the time. The purpose of our study was to investigate the prevalence of hyperuricemia and the association between uric acid levels and the various metabolic syndrome components.

Obesity is one component of metabolic syndrome. Matsuura *et al*.(1998) and Bonora *et al*.(1996) reported that obesity and central body fat distribution were associated with hyperuricemia. In our study, we found elevated waist circumference to be at greater risk of having hyperuricemia, which is in line with Feig and Johnson (2003)'s research. Researchers conducted studies to evaluate the relationship be-

tween leptin (gene production of obesity) and the cluster of hyperuricemia in order to clarify the pathogenic mechanisms associating obesity with hyperuricemia. They found that the serum uric acid concentration is independently associated with the serum leptin concentration (Bedir *et al*., 2003; Fruehwald-Schultes *et al*., 1999). It was suggested that leptin could be a pathogenic factor responsible for hyperuricemia in obese patients.

In our research the data indicated that serum triglyceride was markedly associated with hyperuricemia. Conen *et al*.(2004) and Schachter (2005) showed the same results. Hyperuricemia and hypertriglyceridemia are suggested to be associated with insulin resistance syndrome (Tai *et al*., 1999; Bo *et al*., 2001; Bosello and Zamboni, 2000), and many investigators are studying the mechanisms of the emergence of this syndrome. The association between insulin resistance syndrome, hyperuricemia, and hypertriglyceridemia are complicated. This might be expected from the fact that uric acid production is linked to glycolysis and that glycolysis is controlled by insulin. Phosphoribosylpyrophosphate (PPRP) is an important metabolite in this respect. Its availability depends on ribose-5-phosphate (R-5-P), the production of which is governed by glycolytic flux. Diversion of glycolytic intermediates toward R-5-P, PPRP, and uric acid will follow if there is diminished activity of GA3PDH (glyceraldehyde-3-phosphate dehydrogenase), which is regulated by insulin. Serum triglyceride concentrations may also increase, as might be expected from accumulation of glycerol-3-phosphate. Thus, intrinsic defects in GA3PDH and a loss of its responsiveness to insulin, by causing accumulation of glycolytic intermediates, may explain the association between insulin resistance, hyperuricemia, and hypertriglyceridemia (Leyva *et al*., 1998).

It was shown in our study that uric acid was negatively correlated with serum HDL-C, but this association was not evident among women. This founding was consistent with Rho *et al*.(2005)'s research. The mechanisms of this condition may due to the relationship between decreased HDL-C levels and insulin resistance syndrome (Schmidt *et al*., 1996).

Serum uric acid concentration was found to independently correlate with hypertension (Yoo *et al*., 2005; Feig and Johnson, 2003). A study done by Krishnan *et al*.(2007) found that men with hyperuricemia had more risk for incident hypertension. Each unit increase in serum uric acid was associated with a 9% increase in the risk for incident hypertension. Although the mechanism by which uric acid plays a pathogenetic role in hypertension was unclear, hyperuricemia is associated with deleterious effects on endothelial function, platelet adhesion and aggregation, or oxidative metabolism (Alderman and Redfern, 2004). It has been suggested that uric acid may play a role in the pathogenesis of early-onset hypertension (Schachter, 2005). In our research, it was found that uric acid concentration was statistically significantly positively correlated with blood pressure among men, but this association did not evident among women.

Yoo *et al*.(2005) and Becker and Jolly (2006) reported that hyperglycemia was a remarkable risk factor for hyperuricemia. In a study of 3681 Japanese adult, it was found that an elevation of serum uric acid concentration in males increased the risk of type 2 diabetes (Nakanishi *et al*., 2003). It was concluded that hyperuricemia was positively associated with hyperglycemia. Insulin resistance may be the linking between them (Yoo *et al*., 2005), but we found there was not statistically significance between elevated fasting glucose and uric acid concentration. Statistically significant positive correlation was noted for serum uric acid concentration with log-transformed fasting plasma glucose only in women. The reasons have not been clearly defined. Further studies should be done in this area.

We found that the incidence of hyperuricemia in males was 19.07%, which is much higher than that in females (3.42%). This result was in line with Conen *et al*.(2004)'s research. The pathogenic mechanism may be due to estrogen promoting uric acid excretion (Sumino *et al*., 1999), so it may be more important for men to prevent hyperuricemia.

This study shows serum uric acid is markedly associated with metabolic syndrome and its components, in particular serum triglycerides and waist circumference. Considering the growing incidence of obesity and metabolic syndrome worldwide and the potential link to hyperuricemia, more emphasis should be put on the evolving morbidity prevalence of hyperuricemia in our country.

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