Original Article

Hyperuricemia and the metabolic syndrome in Hangzhou

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The aim of this study was to investigate prevalences of hyperuricemia and the metabolic syndrome (MS) in the Hangzhou population, and the relationship between serum uric acid and the MS. A cross-sectional study was conducted among 4155 subjects (2614 men and 1541 women) aged 20-80 years, recruited through a health check program in Hangzhou, China. Biochemical and haematological parameters were measured by standard methods. The diagnosis of the MS is made when three or four of the following criteria are met: 1) body mess index (BMI) ≥ 25; 2) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; 3) fasting triacyglycerol ≥ 1.7 mmol/L (150 mg/dL), high density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (35 mg/dL) in men and <1.0 mmol/L (39 mg/dL) in women; 4) fasting glucose ≥ 6.1 mmol/L (109 mg/dL). Hyperuricemia is defined by cut-off values of > 420 μmol/L for men and > 360 μmol/L for women. Prevalences were 16.9% (N=702) for hyperuricemia and 8.4% (N=349) for the MS. Serum uric acid concentration was significantly higher in males than in females (p<0.0001), and significantly higher in subjects with obesity, dyslipidemia and hypertension compared with those without. In the partial correlation analysis, after controlling for gender, age and creatinine, serum uric acid concentration was significantly positively correlated with BMI (r=0.301, p<0.0001), systolic blood pressure (r=0.151, p<0.0001), diastolic blood pressure (r=0.168, p<0.0001), total cholesterol (r=0.144, p<0.0001) and triacyglycerol (r=0.234, p<0.0001). Results suggest that increased serum uric acid concentration is associated with an increased prevalence of metabolic disorders such as obesity, dyslipidemia and hypertension in the Hangzhou population.

Key Words: uric acid, the metabolic syndrome, correlation, Hangzhou, China

INTRODUCTION

The metabolic syndrome (MS) is characterized by a clustering of cardiovascular risk factors, including abdominal obesity, high blood pressure, increased glucose concentration, and dyslipidemia.[1] It has become a large public health issue worldwide, and its prevalence is increasing. Increased serum uric acid levels have been reported to be associated with hypertension,[2,3] diabetes,[4,5] obesity,[6,7] insulin resistance,[8] dyslipidemia,[9] cardiovascular diseases,[10-12] peripheral arterial disease,[13] markers of inflammation,[14] and oxidative stress.[15,16] Previous studies have examined the putative association between serum uric acid levels and the MS,[17-20] but have been limited by small sample sizes, inconsistent findings and lack of adjustment for important confounders. No studies on the association between serum uric acid level and the MS have been conducted in the Hangzhou population. The present study examined the association between serum uric acid level and the MS in a representative sample of Hangzhou adults participating in annual health examinations. We also sought to evaluate the extent to which serum uric acid concentrations were associated with several components of the MS.

MATERIALS AND METHODS

Design

A cross-sectional study was conducted among 4155 participants (2614 men and 1541 women) aged 20-80 years. The association between increased serum uric acid level and the MS in the Hangzhou population was examined. Each subject gave fasting blood, from which serum uric acid and other parameters of biochemistry and haematology were measured by standard methods, while other physiological parameters were also measured.

Subjects and diagnostic criterion

Subjects were recruited through a health check program during the period of October 2007 through April 2008 in Hangzhou, China. They visited the Health Examination

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Manuscript received 20 November 2008. Initial review completed 27 February 2009. Revision accepted 5 March 2009.

Centre, Hangzhou Convalescent Hospital, China, in the morning following an overnight fast. Subjects were allowed to sit relaxed for 10 min, and then venous blood was taken into vacutainers. Serum and plasma samples were prepared by centrifugation, aliquoted into separate tubes and stored at −20°C until analyses were performed.

None of the participants of the study had thyroid, renal, hepatic, gastrointestinal, or oncology disease or were receiving drugs for hypoglycemia, antioxidant vitamin supplementation, or drugs known to affect lipoprotein metabolism or uric acid metabolism. The study was approved by the Research Ethics Committee, School of Biosystem Engineering and Food Science, Zhejiang University, and all subjects gave written informed consent.

According to the Chinese Diabetes Society (CDS),[21] the diagnosis of the MS is made when three or four of the following criteria are met: 1) obesity, as body mess index (BMI) ≥ 25; 2) high blood pressure, as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; 3) dyslipidemia, as fasting triacyglycerol ≥ 1.7 mmol/L (150 mg/dL), high density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (35 mg/dL) in men and <1.0 mmol/L (39 mg/dL) in women; 4) impaired insulin tolerance, as fasting glucose ≥ 6.1 mmol/L (109 mg/dL).

Hyperuricemia is defined by cut-off values of > 420 μmol/L for men and > 360 μmol/L for women.[22]

Blood collection

Overnight fasting blood specimens were collected for measurement of serum uric acid, lipids and plasma glucose. All participants fasted for at lease 10 h before blood collection. Serum and plasma samples were prepared during the two hours after blood was drawn, and stored at -20^0C until laboratory assays.

Parameters measurements

Anthropometric and haematological parameters were measured by standard methods. Serum uric acid, triacylglycerol (TG) and total cholesterol (TC) concentrations were determined by standard enzymatic dipyridamole methods. High density lipoprotein cholesterol and low density lipoprotein cholesterol (LDL-C) were measured by differential antibody methods, and blood glucose was measured by hexokinase methods on an auto-biochemical analyzer (Olympus AV400, Japan). Lipid, lipoprotein and blood glucose concentrations were reported as mmol/L, while uric acid and creatinine concentrations as μmol/L.

Statistical analyses

Statistical analyses were performed using the SPSS software package version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were initially performed, given as mean and 95% confidence interval. Strata-specific differences were assessed using one-way Analysis of Variance (ANOVA). Prevalences of hyperuricemia, the MS and components of the MS were calculated by cross-tabulation and compared by Chi-square test for 2×2 tables for each pair. Bivariate correlation was initially employed to determine the relationship between serum uric acid concentrations and features of the MS. Partial correlation analyses were performed to assess associations between uric acid and features of the MS after adjustment for confounding factors (gender, age and serum creatinine concentration). The values were reported as mean±standard deviation. Two-tailed *p*-values were regarded as significant when $p<0.05$.

RESULTS

Prevalences of hyperuricemia were 0.9%, 14.8%, 53.0% and 31.3% in the ≤200, 201-300, 301-400 and >400 μmol/L groups in men, respectively, and were 15.1%, 65.5%, 17.5% and 1.9% in women (Figure 1). Men had higher serum uric acid concentration than women. Serum uric acid concentration was significantly higher in men than in women, with average levels of 371±75μmol/L and 257±59μmol/L ($p<0.0001$), respectively. Prevalences of hyperuricemia were 23.7% in men (N=620) and 5.3% in women (N=82) in this study population ($p<0.0001$). The overall prevalence of hyperuricemia was 16.9% (N=702).

The overall prevalence of the MS for this study population was 8.4%. The MS was more commonly seen in men than in women (12.2% versus 2.0%). According to the diagnostic criterion, the overall prevalences of each individual component of the MS were, in descending order, obesity 32.6%, dyslipidemia 28.0%, hypertension 17.7%, and diabetes 7.7%. There were obvious differences between the two gender groups in the prevalences of the MS and each individual component of the MS

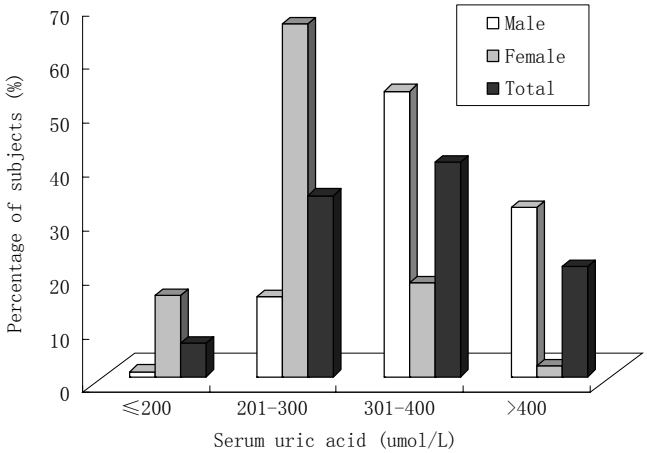

Figure 1. Serum uric acid distributions

Table 1. Prevalence of the metabolic syndrome and individual components of metabolic syndrome (%)*

	Obesity	Hypertension	Diabetes	Dyslipidemia	Metabolic Syndrome
All subjects	32.6 (N=1354)	17.7 (N=735)	7.7 (N=318)	28.0 (N=1163)	8.4 (N=349)
Males	42.5 (N=1110)	21.9 (N=573)	9.7 (N=253)	37.6 (N=984)	12.2 (N=318)
Females	15.8 (N=244)	10.5 (N=162)	4.2 (N=65)	11.6 (N=179)	2.0 (N=31)
p values (Males vs. Females)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*Metabolic syndrome and its components were diagnosed based on Chinese Diabetes Society (CDS) definition.[21]

Table 2. Bivariate analysis between serum uric acid and features of the metabolic syndrome

Correlates	All subjects (N=4155)		Males (N=2614)		Females (N=1541)	
	r	*p* values	r	*p* values	r	*p* values
Age (year)	0.178	<0.0001	0.073	<0.0001	0.223	<0.0001
BMI (kg/m^2)	0.446	<0.0001	0.349	<0.0001	0.262	<0.0001
Sys BP (mmHg)	0.259	<0.0001	0.170	<0.0001	0.223	<0.0001
Dias BP (mmHg)	0.333	<0.0001	0.202	<0.0001	0.172	<0.0001
Creatinine (μmol/L)	0.603	<0.0001	0.254	<0.0001	0.330	<0.0001
Glucose (mmol/L)	0.099	<0.0001	0.001	0.948	0.117	<0.0001
TC (mmol/L)	0.201	<0.0001	0.165	<0.0001	0.180	<0.0001
TG (mmol/L)	0.353	<0.0001	0.258	<0.0001	0.219	<0.0001
HDL-C (mmol/L)	-0.017	0.549	0.014	0.694	0.097	0.067
LDL-C (mmol/L)	-0.022	0.457	-0.030	0.391	0.183	0.001

BMI, body mass index; Sys BP, systolic blood pressure; Dias BP, diastolic blood pressure; TC, total cholesterol; TG, triacylglycerol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 3. Partial correlation analysis between serum uric acid and features of the metabolic syndrome, controlled for gender, age and creatinine

Correlates	Standardised coefficients	*p* values
BMI (kg/m^2)	0.292	<0.0001
Sys BP (mmHg)	0.139	<0.0001
Dias BP (mmHg)	0.160	<0.0001
Glucose (mmol/L)	-0.018	0.563
TC (mmol/L)	0.132	<0.0001
TG (mmol/L)	0.228	<0.0001
HDL-C (mmol/L)	0.003	0.913
LDL-C (mmol/L)	-0.091	0.761

BMI, body mass index; Sys BP, systolic blood pressure; Dias BP, diastolic blood pressure; TC, total cholesterol; TG, triacylglycerol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

(p<0.0001) (Table 1).

Serum uric acid concentration was significantly and positively correlated with age (r = 0.178, p<0.0001), BMI (r = 0.446, p<0.0001), systolic blood pressure (r = 0.259, p<0.0001), diastolic blood pressure (r = 0.333, p<0.0001), serum concentrations of creatinine (r = 0.603, p<0.0001), total cholesterol (r = 0.201, p<0.0001), and triacyglycerol (r = 0.353, p<0.0001). In the bivariate analysis for each gender, serum uric acid concentration was significantly and positively correlated with glucose (r = 0.117, p<0.0001) in women, but not in men. In the partial correlation analysis, after controlling for gender, age and creatinine, serum uric acid was significantly positively correlated with BMI (r = 0.292, p<0.0001), systolic blood pressure (r = 0.139, p<0.0001), diastolic blood pressure (r = 0.160, p<0.0001), total cholesterol (r = 0.132, p<0.0001), and triacylglycerol (r = 0.228, p<0.0001) (Table 3). However, no correlations between uric acid and glucose, HDL-C, or LDL-C were found (Table 2).

Table 4. Comparison of uric acid levels (μmol/L) between subjects with and without the metabolic syndrome

	Metabolic Syndrome (+)	Metabolic Syndrome (-)	*p* values
All subjects	446±81	317±81	<0.0001
Males	454±76	359±68	<0.0001
Females	362±93	255±56	<0.0001
	Obesity (+)	Obesity (-)	
All subjects	376±87	305±80	<0.0001
Males	287±69	251±55	<0.0001
Females	287±69	251±55	<0.0001
	Dyslipidemia (+)	Dyslipidemia (-)	
All subjects	381±84	308±82	<0.0001
Males	397±77	355±70	<0.0001
Females	293±70	252±55	<0.0001
	Hypertension (+)	Hypertension (-)	
All subjects	370±92	320±85	<0.0001
Males	392±85	365±71	<0.0001
Females	292±72	253±55	<0.0001
	Diabetes (+)	Diabetes (-)	
All subjects	355±84	326±89	<0.0001
Males	372±78	371±75	0.872
Females	293±77	255±57	<0.0001

Metabolic syndrome, obesity, dyslipidemia, hypertension and diabetes diagnosed based on Chinese Diabetes Society (CDS) definition.[21]

Table 4 shows the serum uric acid levels of subjects with and without MS, as well as the levels in subjects with and without each individual component of MS. Serum uric acid levels were significantly higher in subjects

Table 5. Prevalence of the metabolic syndrome by quartiles of serum uric acid concentration

Males			Females		
Uric acid (μmol/L)	N	%	Uric acid (μmol/L)	N	%
Quartile 1 (≤320)	20	3.0	Quartile 1 (≤218)	1	0.3
Quartile 2 (321-365)	15	2.3	Quartile 2 (219-250)	2	0.5
Quartile 3 (366-416)	23	3.5	Quartile 3 (251-287)	3	0.8
Quartile 4 (>416)	260	39.9	Quartile 4 (>287)	25	6.3
Total	318	12.2	Total	31	2.0

Metabolic syndrome was diagnosed based on Chinese Diabetes Society (CDS) definition.[21]

Table 6. Proportion of those with hyperuricemia with and without the metabolic syndrome‡ and vice versa.

	Metabolic Syndrome (+)	Metabolic Syndrome (-)	All
Hyperuricemia† (+)	278	424	702
Hyperuricemia† (-)	71	3382	3453
All	349	3806	4155

Metabolic syndrome was diagnosed based on Chinese Diabetes Society (CDS) definition.[21]
Hyperuricemia is difined by cut-off values of > 420 μmol/L for men and > 360 μmol/L for women.[22]

with MS, obesity, dyslipidemia and hypertension than in subjects without these conditions.

As shown in Table 5, the prevalence of MS increased across successive quartiles of serum uric acid concentrations (0.3%, 0.5%, 0.8% and 6.3% for successive quartiles) in women. However, no linear gradient of increased prevalence of MS across increasing quartiles of uric acid was observed in men from quartile 1 to quartile 3 (3.0%, 2.3% and 3.5% for the first three successive quartiles). There was a sharp increase in the prevalence of MS from quartile 3 to quartile 4, both in men (from 3.5% to 39.9%) and women (from 0.8% to 6.3%).

Some 39.6% of those with hyperuricemia (n = 702) have the MS (n = 278); vice versa, 80% of those with the MS (n = 349) have hyperuricemia (n = 278) (Table 6).

DISCUSSION

Overall, the prevalence of hyperuricemia in the present study population was 23.7% in men and 5.3% in women, respectively. In men, prevalence of hyperuricemia was higher than in the Thai population (18.4%),[17] Beijing urban population (15.4%) and Beijing rural population (11.3%).[23] However, in women, they were lower than in the Thai population (7.8%),[17] Beijing urban (11.0%) and rural populations (8.4%).[23] Higher serum uric acid concentration and higher prevalence of hyperuricemia in men than in women were consistent with a previous study in the Hangzhou population,[10] and from studies of various populations.[17,18,23,24] Hyperuricemia is consistently more common in men than in women.

Prevalence of MS for this study population (8.4%) was lower than that of the Beijing population (13.2%).[25] MS is more common in men than in women, 12.2% versus 2.0% in the present study, 15.7% versus 10.2% in the Beijing population.[25] Prevalence of MS was 16.4% (20.4% for men and 15.3% for women) in the Taiwanese from 1998 to 2002.[26] With regard to the lower prevalence of MS and hyeruricemia in women than in men, it is thought that estrogen's protective effects allow for a lower incidence of MS and hyperuricemia in women. This is further confirmed by the knowledge that some features of MS and cardiovascular diseases can be prevented or alleviated with soy or its traditional products, which provides a source of phyto-estrogens.[26,27]

The frequency of components of MS varies among different populations. In this study, obesity (prevalence 32.6%) and dyslipidemia (28.0%) were the main components of MS, followed by hypertension (17.7%) and diabetes (7.7%). In contrast, in Yang's study of the Taiwan population, the order is: diabetes (15.5%), dyslipidemia (11.0%), hypertension (10.0%) then obesity (6.2%),[26] and in Gu's study of the general Chinese population, hypertension (41.2%), dyslipidemia (33.9%), obesity (28.9%) then diabetes (12.7%).[28]

The positive correlation between serum uric acid and BMI, systolic blood pressure, diastolic blood pressure, serum concentrations of creatinine, total cholesterol, and triacyglycerol in the partial correlation analysis were generally similar to those reported by other investigators.[17] In this study, serum uric acid levels were significantly higher in subjects with the MS than that in healthy subjects. These findings are consistent with those in other populations.[17-20] Additionally, obesity, dyslipidemia and hypertension contribute in both gender groups to the development of hyperuricemia. Not only is serum uric acid correlated with individual cardiovascular disease and MS risk factors such as obesity, hypertension, and dyslipidemia, but hyperuricemia tends to cluster with these risk factors.[10,17] Although we were not able to evaluate the relation between serum uric acid and the incidence of cardiovascular disease, we found positive associations between the MS severity and quartiles of serum uric acid concentrations in men and women. Apart from adults, positive correlations between serum uric acid concentration and the MS have been found in both children and elderly Taiwanese.[29,30]

Many recent epidemiological, cross-sectional and case-control studies have found that increased serum uric acid level is a risk factor for the MS.[17-20] The present study compared serum uric acid levels in subjects with and without the MS using a criteria for the Chinese population. The positive correlation between serum uric acid concentration and BMI, blood pressure, serum concentration of TC, TG and creatinine are consistent with previous studies. However, we did not find correlations between serum uric acid concentration and glucose, HDL-C,

or LDL-C. A positive correlation between serum uric acid and serum LDL-C concentrations was reported in Thai populations,[17] and a negative correlation between serum uric acid and serum HDL-C concentrations was found in the Taiwanese.[11]

Female subjects with diabetes had higher concentrations of serum uric acid, but this was not the case in men. Serum uric acid has been found elevated in the non-diabetic range of fasting plasma glucose distribution, and reduced after the onset of diabetes.[5] Serum uric acid level decreases in diabetic subjects, particularly in diabetic men.[31,32] Normally, uric acid is totally filtered in the renal glomeruli and is almost completely reabsorbed in the proximal tubule, while glucose competitively inhibits uric acid reabsorption and enhances its excretion at the same anatomic position, given normal renal function.[32,33]

Hyperuricemia can be the consequence of increased uric acid production or decreased excretion.[34] The mechanism by which uric acid causes metabolic diseases may involve a reduction in the concentrations of endothelial nitric oxide (eNO). Uric acid potently reduces the concentrations of endothelial nitric oxide in vitro and in vivo in experimental animals. In turn, a reduction in endothelial nitric oxide predisposes animals to develop features of the metabolic syndrome. Hyperuricemia in humans is also strongly associated with endothelial dysfunction.[35] Several potential mechanisms may explain how an impaired production of endothelial nitric oxide results in features of the metabolic syndrome. The endothelium is an elegant symphony responsible for the synthesis and secretion of several biologically active molecules. It is responsible for regulation of vascular tone, inflammation, lipid metabolism, vessel growth, arterial vessel wall, and modulation of coagulation and fibrinolysis. The healthy endothelium is a net producer of endothelial nitric oxide (eNO). The activated, dysfunctional endothelium is a net producer of superoxide (O_2^-) associated with the MS, type 2 diabetes, and atherosclerosis.[34]

In conclusions, the present study indicates that an increased serum uric acid concentration is associated with a cluster of the MS components. Serum uric acid is significantly correlated with the components of the MS except for hyperglycaemia. Higher serum uric acid concentration is associated with the MS in the Hangzhou population.

AUTHOR DISCLOSURES

Zhenzhen Cai, Xiaofeng Xu, Xiangming Wu, Ciqin Zhou, Duo Li, have no conflicts of interest.

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Original Article

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杭州地区人群的高尿酸血症和代谢综合征

本研究主要探讨杭州地区人群的高尿酸血症和代谢综合征的发病率，以及两者之间的相关性。从杭州疗养院进行健康体检的人群中征集 4155 名体检者作为研究对象，其中包括 2614 名男性和 1541 名女性，年龄介于 20 至 80 岁。血液生化参数均以标准方法测定。以下 4 项指标中具备 3 项以上的，被诊断为代谢综合征：1）身体质量指数≥25；2）收缩压≥140 mmHg 或舒张压≥90 mmHg；3）三酸甘油酯≥1.7 mmol/L（150 mg/dL），高密度脂蛋白胆固醇在男性<0.9 mmol/L（35 mg/dL），女性<1.0 mmol/L（39 mg/dL）；4）空腹血糖≥6.1 mmol/L（109 mg/dL）。高尿酸血症的诊断标准为，男性血尿酸>420 μmol/L，女性>360 μmol/L。结果显示，高尿酸血症的发病率为 16.9%（702 例），代谢综合征的发病率为 8.4%（349 例）。男性的血尿酸浓度显著高于女性（p<0.0001），肥胖、血脂紊乱、高血压都可使血尿酸浓度显著升高。把性别、年龄和肌酸酐浓度作为控制变量的偏相关分析结果显示，血尿酸浓度和身体质量指数、收缩压、舒张压、总胆固醇浓度、三酸甘油酯浓度都呈显著正相关。本研究结果提示，杭州地区人群的血尿酸浓度升高，和肥胖、血脂紊乱、高血压等代谢性疾病相关。

关键词：尿酸、代谢综合征、相关性、杭州、中国