Original Article

Serum uric acid and appropriate cutoff value for prediction of metabolic syndrome among Chinese adults

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The relation between serum uric acid and metabolic syndrome is observed not only with frank hyperuricemia but also with serum uric acid levels within the normal range. The current "normal" range set for hyperuricemia often fails to identify patients with potential metabolic disorders. We investigate the association between serum uric acid within the normal range and incident metabolic syndrome risk, and further to determine the optimal cut-off value of serum uric acid for the diagnosis or prediction of metabolic syndrome. A total of 7399 Chinese adults (2957 men and 4442 women; ≥20 years) free of metabolic syndrome were followed for 3 years. During the 3-year follow-up, 1190 normouricemic individuals developed metabolic syndrome (16.1%). After adjusting the associated variables, the top quartile of serum uric acid levels was associated with higher metabolic syndrome development compared with the bottom quartile in men (hazard ratio (HR), 1.29; $p<0.05$) and women (HR, 1.62; $p<0.05$). ROC curve analysis indicated that the optimal cut-off values for serum uric acid to identify metabolic syndrome were 6.3 mg/dl in men and 4.9 mg/dl in women. Our results suggested that high baseline serum uric acid levels within the normal range predict future development of metabolic syndrome after 3 y of follow-up.

Key Words: **serum uric acid, cutoff value, metabolic syndrome, follow-up**

The metabolic syndrome (MetS) refers to a cluster of cardiovascular risk factors, including visceral obesity, dyslipidemia, hyperglycemia and hypertension, that has become one of the major public-health challenges worldwide.[1] The prevalence of MetS is becoming more prevalent[2,3] in developing country with changes in lifestyle and dietary habits. In China, the prevalence is estimated to be 13.7% (9.8% in men and 17.8% in women),[4] and in Tianjin, it is 25.56%.[5] MetS not only increases cardiovascular morbidity and mortality but also increases the risk of developing diabetes.[6] Hence, early identification of individuals at high-risk of MetS is of great importance to prevent the premature incidence of MetS.

A number of epidemiologic studies have reported that hyperuricemia is associated with MetS,[7–13] and proposed that hyperuricemia should be included in the definition of MetS.[14,15] Recently, the relation between serum uric acid (SUA) and MetS is observed not only with frank hyperuricemia but also with SUA levels considered to be in the normal range.[16] Higher levels of SUA still within the normal range also might reflect the presence of MetS,[17] and even "normal" levels of SUA are associated with the long-term development of metabolic disease.[18–20] Currently, few longitudinal studies have demonstrated SUA might be a risk factor for MetS.[21–23] However, to the best of our knowledge, no longitudinal study has specifically assessed the MetS risk associated with SUA within the normal range and the current "normal" range set for hyperuricemia often fail to identify patients with potential metabolic disorders, thus underestimating the risks of Type 2 diabetes and cardiovascular disease. Therefore, the aim of the present study was to examine the association between SUA within the normal range and incident MetS during the 3-year follow-up, and further to determine the optimal cut-off value of SUA for the detection of MetS based on a large sample of Chinese adults. In addition, we compared the sensitivity and specificity of the new SUA cut-off value for the diagnosis of MetS with those of SUA cut-off value for hyperuricemia to determine whether lowering of the current "normal" range of SUA would contribute to the early detection of metabolic disorder.

Materials and Methods

Study participants. A total of 9655 subjects (3664 men and 5991 women) aged ≥20 years were performed annual health check-up in Health Examination Center of Heping District, Tianjin, China in 2008. At baseline, 702 men and 1549 women with MetS and 5 men with low SUA level (<3.0 mg/dl in men and <2.0 mg/dl in women) were excluded from the enrollment. Totally, 7399 subjects (2957 men and 4442 women) were enrolled and they repeated the health check-up in 2011. The medical examination performed for subjects who visited the health examination voluntarily to promote public health through the early detection of chronic disease.

This study was performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of Tianjin Medical University. Informed consent was obtained from each participant.

Data collection and measurements. Baseline information on smoking status (yes/no), drinking status (yes/no), habit of regular exercise (yes/no) and past medical history of diabetes, dyslipidemia, hypertension or hyperuricemia were collected by self-reported questionnaire.

Anthropometric measurements were performed by trained health professional personnel using a standardized protocol. Body weight and height were measured without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was then calculated as weight (in kilograms)/height (in square meters). Waist circumference (WC) was measured midway between the lowest rib and the iliac to the nearest 0.1 cm. Blood pressure was measured by trained nurses with a mercury sphygmomanometer on the right arm of the participants in a comfortable sitting position after at least 5-min rest. Participants were asked to avoid

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vigorous exercise, drinking, and smoking for at least 30 min before the measurement.

Overnight fasting venous blood specimens were drawn. Triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), SUA and fasting plasma glucose (FPG) were measured enzymatically on a auto-Analyzer TBA-40 (Toshiba, Tokyo, Japan).

Definition of MetS. The International Diabetes Federation (IDF) criteria[24] was used to define MetS in the present study because this definition considers the ethnic difference for central obesity. According to the IDF criteria, participants are classified as having MetS if they have central obesity (waist circumference ≥90 cm for men and ≥80 cm for women) plus any other two abnormalities of those shown below: (1) Hypertension: systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg, or treatment of previously diagnosed hypertension; (2) Hypertriglyceridemia: TG ≥150 mg/dl or specific medical treatment for this lipid abnormality; (3) Low HDL-C: HDL-C <40 mg/dl for men or <50 mg/dl for women; (4) Hyperglycemia: fasting glucose ≥100 mg/dl or treatment of previously diagnosed diabetes.

Quartiles of SUA levels within the normal range stratified by gender. Hyperuricemia was defined as SUA >7.0 mg/dl in men and >6.0 mg/dl in women.[9] SUA concentration within the normal range (≤7.0 mg/dl in men and ≤6.0 mg/dl in women) was categorized into quartiles based on the cut-off points of the entire distribution for men and women separately (men: Q1, <5.3 mg/dl; Q2, 5.3–5.9 mg/dl; Q3, 6.0–6.6 mg/dl and Q4, 6.7–7.0 mg/dl; women: Q1, <4.1 mg/dl; Q2, 4.1–4.6 mg/dl; Q3, 4.7–5.2 mg/dl and Q4, 5.3–6.0 mg/dl).

Statistical analysis. Data were expressed as means ± standard deviation (SD) or number (%). Baseline characteristics between the groups with incident MetS and without incident MetS were assessed by Student's *t* test or chi-square test. Cox regression analysis was used to assess the relationship between 3-y development of MetS and quartile of SUA level within the normal range before and after adjustment for compound factors, including age, BMI, smoking status, drinking status, habit of regular exercise, SBP, LDL-C, TG, HDL-C and FPG.

Results are presented as hazard ratio (HR) and 95% confidence interval (CI). To compare the predictability of the baseline SUA on the future development of MetS, we plotted receiver operating characteristic (ROC) curves. The diagnostic cutoffs for future MetS by each component were defined by the values with the highest accuracy that maximized the Youden index (sensitivity + specificity-1).[25] Significance tests were 2-tailed and a $p<0.05$ considered as statistically significant. Statistical analyses were performed using the SPSS ver. 16.0 (SPSS, Chicago, IL). Furthermore, using the Medcalc 7.2 software with the method of DeLong *et al.*[26] to compare the areas under the curve (AUC) among SUA, BMI, WC, SBP, DBP, TG, HDL-C and FPG.

Results

The baseline characteristics in relation to the development of MetS by gender during 3 years were shown in Table 1. There were totally 7399 subjects (2957 men and 4442 women) without MetS at baseline who participated in the follow-up survey. Of these, 776 men and 749 women developed MetS during the 3-year follow-up. The accumulated incidence of MetS was 26.2% in men and 16.9% in women, respectively. Age, BMI, WC, SBP, DBP, TC, TG, LDL-C and FPG were statistically significantly greater in the MetS group; and HDL-C was statistically significantly lower. The habit of regular exercise was significantly different between MetS group and non-MetS group in men and women, whereas there were no significant differences in smoking status. In addition, drinking status was significantly different between MetS group and non-MetS group in men, not in women.

Table 2 displayed HRs for the risk of MetS in men and women before and after adjustment for compound factors, including age, BMI, smoking status, drinking status, habit of regular exercise, SBP, LDL-C, TG, HDL-C and FPG. Participants with hyperuricemia associated a 2.8- and 5.0-fold increase of the MetS risk in men and women, respectively. This association remained significant after adjustment for compound factors including age, BMI, smoking status, drinking status, habit of regular exercise, SBP, LDL-C, TG, HDL-C and FPG. Among participants without hyperuricemia, 630 men and 560 women developed MetS during the 3-year follow-up and the accumulated incidence of MetS was 21.3% in men and 12.6% in women, respectively. We performed a subgroup analysis by gender among participants without hyperuricemia to elucidate the association between SUA level within the normal range and MetS. Overall, a higher SUA concentration significantly increased the risk for MetS and this trend was increased for MetS in both genders. In normouricemic men, Q2, Q3 and Q4 showed higher risks (with unadjusted HR of 1.59, 1.78

Table 1. Baseline characteristics of study population stratified for the absence and presence of MetS by gender

	Men			Women		
	MetS	Non-MetS	*p*	MetS	Non-MetS	*p*
No. of subjects	776	2181		749	3693	
Age (years)	54.2 ± 13.4	51.1 ± 14.6	<0.001	57.2 ± 12.0	46.1 ± 14.0	<0.001
BMI (kg/m^2)	26.7 ± 2.2	23.6 ± 2.7	<0.001	25.7 ± 2.7	22.1 ± 2.7	<0.001
WC (cm)	87.1 ± 5.7	79.4 ± 7.3	<0.001	82.9 ± 7.2	73.0 ± 6.8	<0.001
SBP (mmHg)	130.0 ± 16.5	123.1 ± 16.2	<0.001	126.7 ± 17.7	114.3 ± 15.9	<0.001
DBP (mmHg)	84.2 ± 9.5	79.8 ± 9.6	<0.001	79.6 ± 10.0	73.8 ± 9.6	<0.001
TC (mg/dl)	187.9 ± 28.6	184.0 ± 30.6	0.002	198.9 ± 33.4	182.4 ± 31.5	<0.001
LDL-C (mg/dl)	111.9 ± 25.4	107.3 ± 26.0	<0.001	118.0 ± 26.6	102.2 ± 26.9	<0.001
HDL-C (mg/dl)	45.0 ± 11.7	49.6 ± 13.0	<0.001	53.5 ± 13.6	55.6 ± 13.4	<0.001
TG (mg/dl)	167.0 ± 104.5	132.6 ± 96.3	<0.001	124.6 ± 62.7	91.9 ± 56.4	<0.001
FPG (mg/dl)	104.2 ± 24.5	99.8 ± 21.9	<0.001	97.6 ± 16.5	93.3 ± 24.5	<0.001
SUA (mg/dl)	6.5 ± 1.4	6.0 ± 1.1	<0.001	5.4 ± 1.0	4.8 ± 1.0	<0.001
Smoking	375 (48.3)	1013 (46.4)	0.368	20 (2.7)	67 (1.8)	0.123
Drinking	402 (51.8)	1037 (47.5)	0.042	42 (5.6)	152 (4.1)	0.069
Regular exercise*	317 (40.9)	1206 (55.3)	<0.001	340 (45.4)	2175 (58.9)	<0.001

Data are means ± standard deviation (SD) or number (%). MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; SUA, serum uric acid. *At least once a week.

Table 2. Hazard ratios of 3-y incident MetS according to quartiles of SUA within the normal range before and after adjustment for baseline confounding factors in men and women

	Quartiles of SUA within the normal range				Hyperuricemia	*p-trend*
	Q1	Q2	Q3	Q4		
Men						
SUA quartile (mg/dl)	<5.3	5.3–5.9	6.0–6.6	6.7–7.0	>7.0	
No. of subjects	635	642	699	627	354	
No. of incident MetS (%)	101 (15.9)	157 (24.5)	189 (27.0)	183 (29.2)	146 (41.2)	
Crude HR (95% CI)	1.00 (reference)	1.59 (1.24–2.04)	1.78 (1.40–2.26)	1.92 (1.50–2.44)	2.84 (2.20–3.66)	<0.001
Adjusted HR* (95% CI)	1.00 (reference)	1.34 (1.04–1.72)	1.55 (1.21–1.98)	1.29 (1.01–1.67)	1.78 (1.35–2.34)	0.001
Women						
SUA quartile (mg/dl)	<4.1	4.1–4.6	4.7–5.2	5.3–6.0	>6.0	
No. of subjects	940	931	1069	942	560	
No. of incident MetS (%)	75 (8.0)	92 (9.9)	177 (16.6)	216 (22.9)	189 (33.8)	
Crude HR (95% CI)	1.00 (reference)	1.24 (0.91–1.68)	2.13 (1.63–2.80)	3.00 (2.31–3.90)	4.57 (3.49–5.97)	<0.001
Adjusted HR* (95% CI)	1.00 (reference)	0.94 (0.69–1.28)	1.41 (1.07–1.86)	1.62 (1.24–2.11)	1.55 (1.17–2.06)	<0.001

*Adjusted for age, body mass index, smoking status, drinking status, habit of regular exercise, systolic blood pressure, low-density lipoprotein cholesterol, triglyceride, high-density lipoprotein cholesterol and fasting plasma glucose. MetS, metabolic syndrome; SUA, serum uric acid; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 3. Optimal cut-off points of risk factors defined by maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve in men and women

	SUA (mg/dl)	BMI (kg/m^2)	WC (cm)	SBP (mmHg)	DBP (mmHg)	FPG (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)
Men								
Cut-off point	6.3	25.0	82.5	123.0	87.0	97.4	114.6	46.2
Sensitivity (%)	55.5	82.6	86.5	59.9	37.9	54.5	66.1	43.7
Specificity (%)	58.5	70.0	65.6	59.0	79.2	54.9	53.3	42.2
AUC	0.601$^{\#,\$}$	0.824*	0.815*	0.623$^{\#,\$}$	0.624$^{\#,\$}$	0.573$^{\#,\$}$	0.636$^{*,\#,\$}$	0.395$^{*,\#,\$}$
95% CI	0.578–0.624	0.808–0.840	0.799–0.830	0.601–0.646	0.602–0.647	0.549–0.596	0.613–0.658	0.373–0.418
Women								
Cut-off point	4.9	22.6	76.5	117.0	79.0	89.5	90.7	56.3
Sensitivity (%)	65.2	90.3	85.8	71.8	67.8	70.9	72.9	40.3
Specificity (%)	57.4	61.1	72.2	58.4	58.5	43.5	60.8	56.3
AUC	0.666$^{\#,\$}$	0.844*	0.861*	0.702$^{*,\#,\$}$	0.662$^{\#,\$}$	0.593$^{*,\#,\$}$	0.711$^{*,\#,\$}$	0.469$^{*,\#,\$}$
95% CI	0.645–0.687	0.830–0.857	0.849–0.874	0.682–0.722	0.641–0.683	0.572–0.615	0.692–0.729	0.477–0.492

AUC, areas under the curve; 95% CI, 95% confidence interval. Refer to the legends of Table 1 for other abbreviations. *p<0.05, compared with SUA. $^{\#}p$<0.05, compared with BMI. $^{\$}p$<0.05, compared with WC.

and 1.92, respectively) relative to Q1. After adjusting for age, BMI, smoking status, drinking status, habit of regular exercise, SBP, LDL-C, TG, HDL-C and FPG, the HR was significantly higher in Q4 (1.29, p<0.05) than in Q1. In normouricemic women, the high-SUA group (Q4) had a higher unadjusted risk than did the low-SUA group (Q1) (HR, 3.00; p<0.05). And the risk was remained statistically significant after adjustment for compound factors (HR, 1.62; p<0.05).

Table 3 shows the baseline risk factors of MetS predicted future development of MetS obtained with a ROC curve. The maximal sensitivity and specificity for the predictable cut-off points of BMI, WC, SBP and TG concentrations for future development of MetS, exceeded 55%. The optimal cut-off point of SUA as an optional component of MetS was 6.3 mg/dl in men and 4.9 mg/dl in women. When the AUCs for each component with the maximal sensitivity and specificity to predict future MetS were calculated, the AUCs of SUA was significantly larger than that of FPG or HDL-C (p<0.01), and smaller than that of BMI, TG, SBP and DBP in both gender (p<0.01). BMI or WC was shown as the best predictor for future development of MetS (p<0.01).

The sensitivity and specificity of the new SUA cut-off values for the diagnosis of MetS was evaluated (Table 4). Compared with the traditional "normal" limits for the diagnosis of hyperuricemia, the new SUA cut-off values identified approximately 40% more patients with MetS.

Discussion

Previously, evidences from cross-sectional studies[5,7,20] and cohort studies[21–23] have demonstrated SUA might be a risk factor for MetS. Our present study differed in several respects. We found this association not only frank hyperuricemia but also SUA levels within the normal range. The four quartiles in our study were divided by the distribution of SUA level confined to the normal range (SUA level ≤7.0 mg/dl in men and ≤6.0 mg/dl in women). Results from the current follow-up study are compatible with existing data on SUA as a predictor of the development of MetS.[27] We are of the opinion that SUA level might be considered as a marker to detect the early dysmetabolism, especially the SUA level approaches to the critical value for clinical physician.

Large epidemiologic studies have established a close link between elevated SUA levels and the increasing prevalence of the MetS components, including blood pressure, levels of fasting plasma glucose, insulin, triglycerides, and inversely correlated with HDL-C levels in both adolescents and adults.[12,28–31] This raises the possibility that SUA levels could also be included in

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Table 4. Sensitivity and specificity of new serum uric acid cut-off value for the diagnosis of MetS compared with traditional serum uric acid upper limits of normal

	SUA (mg/dl)	MetS (+)	MetS (–)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Men	>6.3	405/776	1325/2181	52.2	60.8	32.1	78.1
	>7.0	146/776	1973/2181	18.8	90.5	41.2	75.8
Women	>4.9	484/749	2180/3693	64.6	59.0	24.2	89.2
	>6.0	189/749	3322/3693	25.2	90.0	33.8	85.6

MetS, metabolic syndrome; SUA, serum uric acid; PPV, positive predictive value; NPV, negative predictive value.

the definition of the MetS. Improvement of the insulin resistance status and endothelial dysfunction related to hyperuricemia are probably the common underlying condition triggering the development of the above metabolic abnormalities.[32] SUA has been shown to inhibit nitric oxide bioavailability, which is known to be necessary for insulin action in the promotion of glucose uptake.[33] Another mechanism related to hyperuricemia and the development of MetS may involve oxidative stress. SUA as an antioxidant in the extracellular environment can induce oxidative stress in a variety of cells, as demonstrated in adipocytes,[34] and these inflammatory and oxidative changes in adipocytes cause the MetS in obese mice.[35] It seems reasonable to suppose that the ability of hyperuricemia to promote MetS, or at least to worsen insulin resistance states. On the other hand, recent studies also have called attention to another perspective on hyperuricemia, indicating that it may be not only a consequence of insulin resistance states but also a significant predictor of the development of MetS.[27] The strongest evidence of the role of SUA in the development of MetS has been provided by experimental studies in animal models showing that a decrease in SUA levels can reverse features of the MetS.[36] Although researchers have proposed that the hyperuricemia should be included in the definition of MetS, no studies have conducted the optimal cut-off values of SUA as an optional component of MetS for the detection of MetS. It should be noted that, on the basis of results from the present study, elevated SUA even within current normal range could reflect the presence of MetS. Therefore, the traditional cut-off value that was used for diagnosis of hyperuricemia was not appropriate for the identification of patients with MetS. The "normal range" can be altered depending on certain conditions. Our study indicated that the optimal cut-off values for SUA to identify MetS were 6.3 mg/dl in men and 4.9 mg/dl in women. Although they were poor in their MetS discriminatory power (AUC, 0.601 in men and 0.666 in women, respectively), the AUC of SUA to predict future MetS was larger than the AUCs of FPG or HDL-C. Therefore, the SUA level might be a better index combination with BMI, WC and TG for the diagnosis of MetS.

It has previously been reported that using SUA ≥7.0 mg/dl as a cut-off point for the diagnosis of the MetS, the sensitivity would be 58.0% and the specificity would be 55.3% in men.[37] However, we used the traditional cut-off value that was used for diagnosis of hyperuricemia to detect the MetS, the sensitivity and specificity were both lower in our study. Compared with the traditional "normal" limits for the diagnosis of hyperuricemia, the new SUA cut-off values identified approximately 40% more patients with MetS. Thus, the new SUA cut-off value that was determined in our study was much more sensitive and effective in detecting MetS than traditional SUA cut-off values for the diagnosis of hyperuricemia. We suggest that the meaning of increased SUA within the normal range should be evaluated from the metabolic aspect and that lowering the definition of normal SUA range would be advantageous for the early detection of potential MetS.

The current "normal" SUA range for the diagnosis of hyperuricemia was not appropriate for the identification of patients with metabolic disorders. A lowering of normal SUA limits is advisable for the early detection of MetS in "healthy" patients who currently have elevated SUA levels within normal range.

This study has a few limitations. Our study has several limitations such as short period of follow-up years and sampling size. And information on life style and dietary intake was not available, further longitude study will be conducted included these confound factors. In addition, the participants of this study were a group of relatively homogeneous characters, which is a follow-up cohort of annual health check-up program in a single health promotion center in China, and not the representatives of other ethnic group. Thus, the results derived from our research are not applicable to other ethnics. Large prospective study is needed for the evaluation of predictability of SUA concentrations for future risk of MetS in various ethnic groups. Despite these limitations, our study is the first longitudinal cohort study on the relationship between SUA within the normal range and the development of MetS, and determining an optimal cut-off value of SUA to predict MetS in China.

In conclusion, in this large prospective study in China, higher SUA concentrations within the normal range predicted future development of MetS during a 3-year follow-up.

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Abbreviations

AUC	areas under the curve
BMI	body mass index
95% CI	95% confidence interval
DBP	diastolic blood pressure
FPG	fasting plasma glucose
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IDF	International Diabetes Federation
LDL-C	low-density lipoprotein cholesterol
MetS	metabolic syndrome
NPV	negative predictive value
PPV	positive predictive value
ROC	receiver operating characteristic
SBP	systolic blood pressure
SD	standard deviation
SUA	serum uric acid
TC	total cholesterol
TG	triglyceride
WC	waist circumference

Conflict of Interest

No potential conflicts of interest were disclosed.

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