Serum Uric Acid Is Independently Associated with Metabolic Syndrome in Subjects with and without a Low Estimated Glomerular Filtration Rate

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ABSTRACT. Objective. The relationship among serum uric acid (SUA), metabolic syndrome, and chronic kidney disease (CKD) is unclear. We examined whether SUA level is an independent risk factor for chronic kidney disease and whether the association between SUA and metabolic syndrome is affected by kidney function.

Methods. We analyzed 28,745 subjects (17,478 men, 11,267 women, age 20–49 yrs) who underwent health examinations at this hospital between 2000 and 2007. Hyperuricemia was defined as SUA level > 7.7 mg/dl in men or > 6.6 mg/dl in women. Kidney function was assessed by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study equation modified for Chinese subjects. Impaired renal function with low GFR was defined as eGFR < 90 ml/min/1.73 m². The UA-low GFR groups were defined according to the observed combination of hyperuricemia and low GFR: Group A (absence of both hyperuricemia and low GFR); Group B (presence of low GFR but no hyperuricemia); Group C (presence of hyperuricemia but not low GFR); and Group D (presence of both hyperuricemia and low GFR).

Results. The prevalence of hyperuricemia, metabolic syndrome, and impaired kidney function with low GFR was 20.3% (27.6% in men, 8.9% in women), 7.6% (10.6% in men, 3.0% in women), and 9.9% (11.6% in men, 7.1% in women), respectively. The Pearson correlation between SUA and eGFR was only –0.26 (–0.21 in men, –0.22 in women; p < 0.001). In men, the age-adjusted odds ratio (OR) of metabolic syndrome was 1.41 (Group B), 2.45 (Group C), and 2.58 (Group D) in comparison with Group A. In women, the age-adjusted OR of metabolic syndrome was 0.83 (Group B), 5.47 (Group C), and 3.31 (Group D) in comparison with Group A.

Conclusion. Hyperuricemia is prevalent in the Taiwan population. Hyperuricemia is only weakly associated with renal function, but is strongly associated with metabolic syndrome with or without a low eGFR. (First Release June 15, 2009; J Rheumatol 2009;36:1691–8; doi:10.3899/jrheum.081199)

Key Indexing Terms: URIC ACID HYPERURICEMIA METABOLIC SYNDROME CHRONIC KIDNEY DISEASE
uricemia\textsuperscript{4,5} and metabolic syndrome\textsuperscript{14} confer an increased susceptibility to CKD.

To clarify the relationship of SUA, kidney function, and metabolic syndrome, we analyzed health examination data from the period 2000-2007 at this hospital. To avoid medication effect on the serum biochemical data measurement, only data for subjects aged 20-49 years were analyzed. Kidney function was assessed by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study equation\textsuperscript{15-17} modified for Chinese subjects\textsuperscript{16}.

**MATERIALS AND METHODS**

**Study population.** From 2000 to 2007, 89,449 subjects received health examinations at this facility. Mean age for men was 53.0 ± 12.9 years and for women 54.2 ± 13.0 years. Only data for those aged 20 to 49 years with health examinations at our hospital were used. Demographic and laboratory data were collected for all participants. The study was approved by the Institutional Review Board at this facility.

**Clinical and laboratory data.** Uric acid, creatinine, and other biochemical data were measured using a Hitachi 7470 autoanalyzer (Hitachi Co., Tokyo, Japan). The uricase differential spectrophotometric method was used for uric acid measurement\textsuperscript{18}, and the Jaffe method was used for creatinine measurement\textsuperscript{19}. SUA values were reported in mg/dl, to convert to micro moles per liter, values were multiplied by 59.45. The coefficient of variation of repetitive determinations of SUA of known samples throughout the year at the hospital laboratory was 1.8% or less. External quality control was provided by participation in 2 programs: the international program run by the College of American Pathologists and the National Quality-Control Program conducted by the Taiwan government. Internal and external quality-control procedures yielded consistently satisfactory results. Body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) was recorded for all subjects. Hyperuricemia was defined as SUA level > 7.7 mg/dl in men or > 6.6 mg/dl in women\textsuperscript{20,21}.

Gglomerular filtration rate (eGFR), the traditional measure of kidney function, was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation\textsuperscript{17}. The eGFR-MDRD equation was $170 \times \frac{\text{sCr}^{0.999}}{\text{age}^{0.176}} \times \frac{\text{blood urea nitrogen (BUN)}^{0.170}}{\text{alb}^{0.318}} \times 0.762$ (if female). We applied the modified MDRD equation corrected for Chinese\textsuperscript{16} as follows: $	ext{eGFR-MDRDc} = 170 \times \frac{\text{sCr}^{0.999}}{\text{age}^{0.176}} \times \frac{\text{BUN}^{0.170}}{\text{alb}^{0.318}} \times 0.762$ (if female) $\times 1.211$ (Chinese). The equations have been validated in Chinese patients with CKD\textsuperscript{16}. Further, different stages of kidney function were defined according to Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines\textsuperscript{15}. Impaired renal function with low GFR\textsuperscript{15,16} was defined as eGFR < 90 ml/min/1.73 m$^2$ using the MDRD equation corrected for Chinese subjects\textsuperscript{16}. The UA-low GFR groups were defined according to the observed combination of hyperuricemia and low GFR: Group A (absence of both hyperuricemia and low GFR); Group B (presence of low GFR but no hyperuricemia); Group C (presence of hyperuricemia but not low GFR); and Group D (presence of both hyperuricemia and low GFR).

Metabolic syndrome was defined by the original ATP III criteria and the modified ATP III criteria, which reduce the waist circumference criteria for Asian populations\textsuperscript{22}. The original ATP III definition of metabolic syndrome requires 3 or more of the following: waist circumference ≥ 102 cm (male) or ≥ 88 cm (female); blood pressure ≥ 130/85 mm Hg; high density lipoprotein (HDL)-cholesterol < 40 mg/dl (1.04 mmol/l); male) or < 50 mg/dl (1.30 mmol/l; female); triglycerides ≥ 150 mg/dl (1.70 mmol/l); and fasting glucose ≥ 110 mg/dl (6.1 mmol/l). Central obesity was defined by waist circumference and differs between ethnic groups, with limits of 94 and 80 cm for white European subjects but 90 and 80 cm for South Asian and Chinese subjects\textsuperscript{22,23}. In this study BMI was used\textsuperscript{23} instead of the waist circumference, which is not measured in the health examination program. For individual component analysis, blood pressure was categorized as hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) or normotension (systolic blood pressure < 140 mm Hg, diastolic blood pressure < 90 mm Hg)\textsuperscript{24}.

**Statistical analysis.** All data are expressed as mean ± standard deviation (SD) or percentage. Chi-square test was used for group comparisons of categorical data. Analysis of variance (ANOVA) was used to compare continuous data among groups. Multiple logistic regression was performed to obtain unadjusted or adjusted odds ratio (OR) of metabolic syndrome for the UA-CKD group. A 2-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

**RESULTS**

We analyzed 28,745 subjects (aged 20-49 yrs) who had received health examinations at this hospital in the period 2000-2007. Men accounted for 17,478 (60.8%) subjects, women 11,267 (39.2%). Mean age was 40.8 ± 6.3 years (men 41.0 ± 6.2 yrs, women 40.4 ± 6.6 yrs). Mean eGFR-MDRDc was 109.1 ± 16.7 ml/min/1.73 m$^2$; 107.0 ± 15.6 ml/min/1.73 m$^2$ in men and 112.3 ± 17.7 ml/min/1.73 m$^2$ in women. The mean SUA level was 6.1 ± 1.6 mg/dl: 6.9 ± 1.4 mg/dl in men (range 1.0 to 15.3 mg/dl) and 4.9 ± 1.1 mg/dl in women (range 1.2 to 11.3 mg/dl). The prevalence of hyperuricemia was 20.3% (5,822 of 28,745): 27.6% in men (4,824 of 17,478) and 8.9% in women (998 of 11,267). The prevalence of renal function impairment with low GFR (eGFR-MDRDc < 90 ml/min/1.73 m$^2$) was 9.9% (2,833 of 28,745) in the overall population. Prevalence was 11.6% (2,033 of 17,478) in men and 7.1% (800 of 11,267) in women.

Table 1 shows the study population grouped according to e-GFR with CKD stage, in accord with the K/DOQI guidelines\textsuperscript{15}. The distribution of eGFR-MDRDc in the sample was as follows: 0.2% (n = 66, stage III-V = eGFR < 60 ml/min/1.73 m$^2$); 9.6% (n = 2,767, stage II = eGFR 60–89 ml/min/1.73 m$^2$); and 90.1% (n = 25,912, stage I = eGFR ≥ 90 ml/min/1.73 m$^2$). SUA levels in subjects grouped according to the presence of K/DOQI stages I through V were 6.1 ± 1.6, 7.0 ± 1.7, 8.6 ± 2.1, 8.3 ± 2.3, and 7.7 ± 2.4 mg/dl, respectively, revealing a statistically significant trend (p < 0.0001). The prevalence of hyperuricemia was significantly greater in patients with a low GFR. Overall, 18.3% (4,734 of 25,912) of patients with eGFR-MDRDc ≥ 90 ml/min/1.73 m$^2$ had an elevated uric acid level, compared with 37.6% (1,040 of 2,767) of patients with eGFR-MDRDc of 60 to 89 ml/min/1.73 m$^2$ and 72.7% (48 of 66) with eGFR-MDRDc < 60 ml/min/1.73 m$^2$ (p < 0.0001; Table 1). The mean ages of subjects in K/DOQI renal function stages I through V were 40.5 ± 6.4, 43.9 ± 4.9, 40.9 ± 5.8, 43.7 ± 5.4, and 43.1 ± 4.4 years, respectively, a statistically significant trend (p < 0.0001). BMI values were higher across different stages of kidney function (p < 0.0001). Participants who had eGFR-MDRDc < 60 ml/min/1.73 m$^2$ (i.e., CKD stage III-IV) comprised 0.2% of the participants and were there-
fore analyzed as a separate group. In the group with decreased eGFR-MDRDc < 60 ml/min/1.73 m², the mean age was older (41.8 ± 5.5 vs 43.9 ± 4.9 vs 40.5 ± 6.4 yrs; p < 0.0001), the BMI was higher (24.9 ± 4.8 vs 24.9 ± 3.5 vs 23.6 ± 3.7 kg/m²; p < 0.0001), systolic blood pressure was higher (143.3 ± 29.1 vs 122.2 ± 17.7 vs 119.6 ± 16.9 mm Hg; p<0.0001), the prevalence of metabolic syndrome was higher (31.8% vs 11.2% vs 7.2%; p < 0.0001), the prevalence of hypertension was higher (42.4% vs 10.2% vs 7.1%; p < 0.0001), and the prevalence of hyperuricemia was higher (72.7% vs 37.6% vs 18.3%; p < 0.0001) compared with the stage II and stage I subjects, respectively. The Pearson correlation between SUA and eGFR-MDRDc was only –0.26 (–0.21 in men and –0.22 in women; p < 0.001); and the Spearman correlation between hyperuricemia and CKD was only –0.26 (–0.21 in men and –0.22 in women; p < 0.001).

Based on the presence or absence of hyperuricemia and low e-GFR, subjects were divided into the following 4 groups: Group A, subjects with normouricemia (normal SUA level) and eGFR-MDRDc ≥ 90 ml/min/1.73 m² (men, n = 11,532; women, n = 9,646); Group B, subjects with normouricemia but eGFR-MDRDc < 90 ml/min/1.73 m² (men, n = 1,122; women, n = 623); Group C, subjects with hyperuricemia but eGFR-MDRDc ≥ 90 ml/min/1.73 m² (men, n = 3,913; women, n = 821); and Group D, subjects with both hyperuricemia and eGFR-MDRDc < 90 ml/min/1.73 m² (men, n = 911; women, n = 177). The analysis also stratified risk factors according to component of metabolic syndrome (i.e., BMI ≥ 27 kg/m², triglycerides ≥ 150 mg/dl, HDL-cholesterol < 40 mg/dl in men or < 50 mg/dl in women, LDL-cholesterol ≥ 130 mg/dl, or fasting plasma glucose ≥ 110 mg/dl).
regression analysis, the corresponding adjusted OR of individual metabolic risk factor profiles in male subjects were as follows (Table 2): BMI, 1.14 (CI 1.04–1.34), 2.50 (CI 2.32–2.69), and 2.20 (CI 1.92–2.52) (< 0.0001); MBP, 1.48 (CI 1.39–1.57), 1.85 (CI 1.73–2.00), and 1.98 (CI 1.82–2.16) (< 0.0001); Glucose, 1.04 (CI 0.96–1.12), 1.09 (CI 1.00–1.18), and 1.03 (CI 0.94–1.13) (p = 0.4786); Hyperglycemia, 1.01 (CI 0.98–1.04), 1.07 (CI 1.04–1.10), and 1.10 (CI 1.07–1.13) (p = 0.2675). In women, the adjusted OR had a trend similar to that in men (Table 3). Men in Groups C and D were at higher risk for most components of metabolic syndrome than men in Groups A and B. In men with hyperuricemia (with or without low eGFR-MDRDc, Groups C and D) adjusted OR for metabolic syndrome was more than 2.5-fold that in men with eGFR-MDRDc ≥ 90 ml/min/1.73 m² (Table 3).
Group A. Further, patients with normouricemia (with or without low eGFR-MDRDc, Groups A and B) had a similar risk for metabolic syndrome. Similar trends were observed when CKD with renal function impairment was defined as eGFR-MDRDc < 60 ml/min/1.73 m², when hyperuricemia was defined as > 7.0 mg/dl for men and > 6.0 mg/dl for women, and when hyperuricemia was defined as > 7.0 or 6.8 mg/dl for both sexes (data not shown). The data for each year were also analyzed separately, and the statistical results were similar (data not shown).

**DISCUSSION**

We found a low association between SUA and eGFR. We also found that the association of hyperuricemia and metabolic syndrome existed in subjects with and without CKD (eGFR-MDRDc < 60 ml/min/1.73 m²) or a low eGFR (defined as eGFR-MDRDc < 90 ml/min/1.73 m²).

**High prevalence of hyperuricemia.** Uric acid is the final oxidation product of purine metabolism in humans. Hyperuricemia is usually caused by inadequate renal excretion of uric acid.1,2 In the last 4 decades, SUA has increased...
in populations in the United States and other countries\textsuperscript{25-32}. Mean SUA levels have risen in men from $<3.5$ mg/dl in the 1920s\textsuperscript{27} to approximately $5.0$ mg/dl in the 1950s\textsuperscript{28} and to $6.0-6.5$ mg/dl in the 1970s\textsuperscript{29}. In a recent nationwide epidemiological study in Taiwan, the mean SUA level in men was $6.14 \pm 1.43$ mg/dl\textsuperscript{30}, similar to that observed in the present study ($6.1 \pm 1.6$ mg/dl). This serum urate level is higher than reported in the Framingham study ($5.12 \pm 1.11$)\textsuperscript{28}, in the Tecumseh study ($4.90 \pm 1.40$)\textsuperscript{31}, and in data from Taiwan ($4.99 \pm 0.91$)\textsuperscript{32} in the 1960s. In our study, the prevalence of hyperuricemia was $20.3\% - 27.6\%$ in men and $8.9\%$ in women. The high prevalence of hyperuricemia is related to the predominance of male subjects in this study. When hyperuricemia was defined as $>7.0$ mg/dl in men and $>6.0$ mg/dl in women, the prevalence increased further (overall $34.4\%$, men $45.5\%$, women $17.3\%$).

**Weak association between SUA and eGFR.** The association between severity of chronic kidney disease and hyperuricemia has not been well defined. Some studies report that elevated SUA (hyperuricemia) is common in patients with CKD\textsuperscript{1,2}. Others suggest that uric acid is elevated as a consequence of renal function impairment, and uric acid itself may therefore predict renal function deterioration\textsuperscript{3,5,33}. Our study revealed a weak association (Pearson correlation coefficient $-0.26$, $p < 0.0001$) between SUA and eGFR in a large population of young adults.

**SUA, but not CKD or low GFR, is associated with metabolic syndrome.** Hyperuricemia is reportedly associated with cardiovascular events, hypertension, and metabolic syndrome\textsuperscript{6,25,26}. Traditionally, SUA has been viewed merely as a marker of obesity, hyperinsulinemia, hyperlipidemia, hypertension, and renal disease\textsuperscript{1,2}. However, our findings suggest that metabolic syndrome is significantly higher in subjects with hyperuricemia than in those without hyperuricemia, and is independent of a high or low eGFR. We found an adjusted odds ratio of metabolic syndrome that was similar in Groups C and D and was higher in Groups C and D than in Group A.

Hyperuricemia is commonly associated with insulin resistance, glucose intolerance, hypertension, and dyslipidemia, which characterize the metabolic syndrome\textsuperscript{6,13}. In previous studies, the SUA level was positively correlated with the risk factors of metabolic syndrome and the number of metabolic syndrome components increases as SUA level increases\textsuperscript{10-13}; this association apparently applies to adolescents and children as well\textsuperscript{12}. Moreover, even those with SUA level within the normal range showed an increased risk of metabolic syndrome as SUA level increases\textsuperscript{13}. The underlying mechanisms and reasons why hyperuricemia is more commonly associated with metabolic syndrome than with CKD are still unknown. However, there are 2 possible explanations for this pattern. First, insulin resistance is widely recognized as a major risk factor for kidney disease and is also common in subjects with hyperuricemia and metabolic syndrome. In humans, renal clearance of urate is inversely related to insulin resistance\textsuperscript{34}. Although uric acid is often considered secondary to hyperinsulinemia, recent evidence reveals the primary role of uric acid in mediating metabolic syndrome\textsuperscript{6,35-37}. Vuorinen-Markkola, et al indicated that SUA level is inversely correlated with insulin sensitivity and is positively correlated with serum triglycerides\textsuperscript{35}. A prospective followup study revealed that high SUA is associated with increased risk of type 2 diabetes mellitus independent of obesity, dyslipidemia, and hypertension\textsuperscript{36}. Sui, et al reported that high SUA is a strong and independent predictor of incident metabolic syndrome in men and women\textsuperscript{37}. Second, fructose intake has been linked to metabolic syndrome and hyperuricemia. Fructose is known to increase uric acid concentrations in humans\textsuperscript{38}, and uric acid may in turn increase the risk of metabolic syndrome\textsuperscript{25,39}. Rat studies indicate that fructose can quickly cause metabolic syndrome and increased SUA. Lowering uric acid in fructose-fed rats prevents features of the metabolic syndrome\textsuperscript{39-41}. Nakagawa et al\textsuperscript{39} demonstrated that fructose-fed rats treated with allopurinol (a xanthine oxidase inhibitor) and benziodarone (a uricosuric agent) exhibit reduced plasma uric acid and triglycerides and significantly decreased systolic blood pressure. This suggests that uric acid is a causal factor in the pathogenesis of fructose-induced metabolic syndrome and renal damage\textsuperscript{39}. Another experimental study\textsuperscript{40} showed that hyperuricemia induced by a high-fructose diet is associated with hypertension, hyperinsulinemia, and hypertriglyceridemia as well as glomerular hypertension. Normalization of SUA with febuxostat (a nonpurine xanthine oxidase inhibitor) in rats with fructose-induced metabolic syndrome alleviated both metabolic and glomerular hemodynamic alterations\textsuperscript{40}; these animal studies\textsuperscript{39-41} demonstrate the pathogenic role of hyperuricemia in fructose-induced metabolic syndrome and renal damage. Whether uric acid exerts hypertension-promoting and nephrotoxic effects in humans is still unclear and requires further study.

Strengths and limitations of our study require comment. The drawbacks are the cross-sectional design and the lack of information on waist circumference. However, Ryan, et al\textsuperscript{42} reported that cardiovascular disease risk factor status did not substantially vary between subjects classified by waist circumference (central obesity) and those classified by BMI (overall obesity)\textsuperscript{42}. We used BMI as a surrogate for central obesity in the definition of metabolic syndrome\textsuperscript{23} and also analyzed each component of metabolic syndrome risk factors; however, waist circumference data were unavailable. Further studies are required to validate the efficacy of comparing waist circumference and BMI\textsuperscript{43-45} for diagnosing metabolic syndrome in Chinese populations and in other ethnic groups. The BMI cutoff point is ethnicity-specific. Taiwan recently adopted BMI cutoff values of 24 and 27 for overweight and obese status, respectively\textsuperscript{43,44}. The cutoff
values are determined for Asian populations by using the same cutoff points for body fat percentage that are used to define overweight and obese status in Caucasians: BMI of 25 and 30 kg/m², respectively. Our study was limited to subjects aged 20–49 years; associations and effects in older subjects were not addressed. Moreover, the possibility of a significant misclassification of CKD by estimated GFR could not be excluded. For example, individuals with stage 2 CKD (eGFR 60 to 89 ml/min/1.73 m²) require evidence of structural damage to meet the CKD definition. We regret, however, this cross-sectional study did not provide these data. The strengths of our study are that it analyzed data from a large sample of community-dwelling adults, which enabled generalizing the findings, and compared results with the most widely used clinical renal function assessments. Plasma creatinine may not reflect glomerular filtration rate, especially in the early stages of CKD. The Modification of Diet in Renal Disease equations provide reasonably accurate GFR estimation and are recommended by the Kidney Disease Outcome Quality Initiatives clinical practice guidelines. To our knowledge, this is the first report of associations of uric acid with metabolic disturbances in patients with and without CKD (eGFR-MDRDc < 60 ml/min/1.73 m²) or renal function impairment (eGFR-MDRDc < 90 ml/min/1.73 m²). Another limitation is that data for subjects’ fructose intake, which might have affected SUA levels, were unavailable. However, this limitation is common to other studies. Our study contributes to the rather limited knowledge of the role of uric acid in CKD and metabolic syndrome.

In summary, uric acid is a nontraditional risk factor independently associated with chronic kidney disease and metabolic syndrome. Our results indicate that hyperuricemia is strongly associated with metabolic syndrome in subjects with or without impaired renal function (defined as eGFR-MDRDc < 90 ml/min/1.73 m²). The increasing incidence of hyperuricemia and the growing awareness of the relationship between hyperuricemia and cardiovascular risk as well as metabolic syndrome and CKD highlight the importance of hyperuricemia. Although it remains uncertain whether hyperuricemia is an independent risk factor for cardiovascular disease, a diagnosis of hyperuricemia should prompt a search for metabolic syndrome, cardiovascular risk factors, and chronic kidney disease. Further studies in other populations are needed to confirm these results.

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