Uric Acid is Positively Associated with Metabolic Syndrome but Negatively Associated with Diabetes in Japanese Men

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Abstract

Background The relationships between uric acid and metabolic syndrome (MetS) and diabetes, as well as the gender differences in these relationships are controversial.

Methods Medical check-up data from 2,449 Japanese men and 1,448 Japanese women were examined. The prevalence of MetS and diabetes was calculated by the quartiles of serum levels of uric acid. Correlation coefficients between uric acid and MetS-related risk factors were calculated and compared between men and women.

Results The prevalence of MetS in the 3rd quartile (Q3) of uric acid was significantly higher than that in the 1st (lowest) quartile (Q1) and the prevalence of MetS in the 4th quartile (Q4) was significantly higher than that in Q1, the 2nd quartile (Q2), and Q3 in men. The prevalence of MetS in Q4 was significantly higher than that in Q1, Q2, and Q3 in women. The prevalence of diabetes in Q3 was significantly lower than that in Q1 and the prevalence of diabetes in Q4 was significantly lower than that in Q1 and Q2 in men. The prevalence of diabetes was not significantly different among the quartiles of uric acid in women. The age-adjusted correlation coefficient between uric acid and fasting glucose was not significant in men.

Conclusion Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men.

Key words: uric acid, metabolic syndrome, diabetes, gender difference

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Introduction

Uric acid is the final oxidation product of purine catabolism and increased serum concentrations of uric acid have been implicated in cardiovascular disease. Facchini et al demonstrated that urinary uric acid clearance decreases in proportion to the increase in insulin resistance leading to an increase in serum uric acid concentration (1). Thus, uric acid may be a component of insulin resistance syndrome or metabolic syndrome (MetS) (2-5). Various mechanisms have been suggested through which uric acid may be implicated in the atherosclerotic process and its clinical complications. However, the contribution of uric acid to atherosclerotic vascular disease is still controversial. Uric acid can act as a prooxidant, particularly at increased concentrations, and may

thus be a marker of oxidative stress, but it may also have a therapeutic role as an antioxidant (6). Patterson et al, using a normal human serum ultrafiltrate, demonstrated that uric acid protects native low-density lipoprotein (LDL) against oxidation by transition metal ions, but it accelerates the oxidation of mildly oxidized LDL (7). Thus, although there are plausible mechanisms to suggest uric acid as a potential direct mediator of MetS, diabetes, and cardiovascular disease, the relationships between uric acid and diabetes and cardiovascular disease are controversial and there may be gender and ethnic differences in these relationships (8-14).

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Methods

Subjects

Between April 1, 2008 and March 31, 2009, 2,541 men and 1,502 women visited our medical check-up center for “Ningen Dock”, a program for general health screening recommended by Japan Society of “Ningen Dock” (general health screening). Visitors were all required to fill out a questionnaire prepared by the Ministry of Health, Labor, and Welfare for the purpose of “Special Health Examination and Instruction” including questions about history of stroke and ischemic heart disease, smoking and drinking status, and antihypertensive, hypoglycemic, and antihyperlipidemic medications. Among these persons 25 men and 20 women without signed consent, 12 men and 15 women lacking respiratory function data, 5 men and a woman lacking body fat percentage data, a man and a woman lacking renal function data, and 33 men and 12 women with high-sensitivity C-reactive protein (hs-CRP) levels of higher than 10 mg/L were excluded from the subjects of the present study resulting in a total of 2,449 men and 1,448 women. The protocol for the present study was approved by the Ethics Committee at Tachikawa Medical Center and signed informed consent was obtained from each subject.

Measurements

After an overnight fast, blood samples were obtained to measure blood levels of routine medical check-up tests: glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, hemoglobin A1c, uric acid, blood cell counts, electrolytes, liver and kidney function tests, and hs-CRP. Simple qualitative urinalyses were performed with test papers. Chemical measurements were performed at BML Nagaoka (Nagaoka, Japan) with routine laboratory methods except for hs-CRP which was measured at BML General Laboratory (Tokyo, Japan) with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). The measurement limit of hs-CRP was 0.02 mg/L and the value of hs-CRP less than the measurement limit was considered as 0.01 mg/L. Respiratory function tests were performed with Autspirometer System 7 (Minato Medical Science, Osaka, Japan). Estimated glomerular filtration rate (eGFR) was calculated as $eGFR (mL/min/1.73 m^2) = 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ in men, and $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ in women according to the recommendation from the Japanese Society of Nephrology. Body fat percentage was measured with bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). An average systolic blood pressure (SBP) and diastolic blood pressure (DBP) was calculated from two measurements with the subjects in a sitting position after 5 minutes rest. Heart rate was automatically recorded with electrocardiography. Body weight was measured with the subjects wearing light clothes provided by our center and the weight of the clothes was sub-

tracted from the measured body weight. Waist circumference was measured at the level of the umbilicus. Body mass index (BMI) was calculated as weight in kilograms divided by height squared in meters.

Definitions

We adopted the revised National Cholesterol Education Program (NCEP) definition (3) for MetS criteria because the Japanese definition of MetS (JMetS) (15) which includes obesity as an inevitable component was already revealed to be inappropriate by recent large longitudinal epidemiological studies (16-19). MetS was defined by NCEP criteria (3) as three or more of five components where the cut-off point of waist circumference was modified for Japanese as ≥ 90 cm in men and ≥ 80 cm in women according to the recommendation by International Diabetes Federation (4). The cut-off points of other components were SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg for blood pressure, ≥ 150 mg/dL for triglycerides, < 40 mg/dL in men and < 50 mg/dL in women for HDL cholesterol, and ≥ 100 mg/dL for fasting glucose. Subjects receiving antihypertensive or hypoglycemic medication were considered to have the respective component. JMetS defined by the Examination Committee for Criteria of Metabolic Syndrome (15) was also examined. The criteria of JMetS is waist circumference ≥ 85 in men and ≥ 90 in women plus 2 or more of the following 3 components; SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, triglycerides ≥ 150 mg/dL and/or HDL cholesterol < 40 mg/dL, and fasting glucose ≥ 110 mg/dL. Diabetes was defined as fasting glucose ≥ 126 mg/dL and/or hypoglycemic medication. Impaired fasting glucose (IFG) was defined as $100 \text{ mg/dL} \leq \text{fasting glucose} < 126 \text{ mg/dL}$. Chronic kidney disease (CKD) was defined as $eGFR < 60 \text{ mL/min/1.73 m}^2$ and/or proteinuria.

Statistical analysis

The prevalence of MetS, JMetS, IFG, and diabetes was compared among the quartiles of serum uric acid level by gender. Spearman's correlation coefficients and age-adjusted correlation coefficients between uric acid and other MetS-related risk factors were calculated by gender. Spearman's correlation coefficients were recalculated excluding diabetic patients. Statistical analyses were performed using Dr SPSS-2. Means were compared with 2-sided t-tests, ratios were compared with chi-square tests. P values of < 0.05 were considered to be statistically significant except for ratios among the quartiles for which p values of < 0.008 were considered to be statistically significant according to a Bonferroni's test.

Results

Basal data are shown in Table 1. The subjects were 2,449 Japanese men aged 51.9 ± 9.6 (mean $\pm$ SD) years and 1,448 Japanese women aged 51.5 ± 9.8 years. BMI, waist circumference, SBP, DBP, fasting glucose, triglycerides, hs-CRP, gamma glutamyltransferase (GGT), alanine aminotransferase

Table 1. Basal Data

	men n = 2449	women n = 1448	p
age (year)	51.9 ± 9.6	51.5 ± 9.8	ns
body mass index (kg/m ²)	23.2 ± 3.0	21.7 ± 3.1	<0.0001
body fat percentage (%)	22.2 ± 5.1	26.8 ± 5.9	<0.0001
waist circumference (cm)	84.3 ± 8.1	78.9 ± 8.6	<0.0001
systolic blood pressure (mmHg)	122.0 ± 17.4	112.6 ± 17.2	<0.0001
diastolic blood pressure (mmHg)	77.4 ± 10.8	70.4 ± 10.4	<0.0001
fasting glucose (mg/dL)	96.2 ± 15.4	89.7 ± 11.2	<0.0001
triglycerides (mg/dL)	122.6 ± 81.3	72 (56, 99)	<0.0001
HDL cholesterol (mg/dL)	57.7 ± 14.5	67.1 ± 14.7	<0.0001
high-sensitivity CRP (mg/L)	0.31 (0.17, 0.64)	0.22 (0.11, 0.47)	<0.0001
gamma glutamyltransferase (IU/L)	36 (24, 58)	18 (14, 25)	<0.0001
alanine aminotransferase (IU/L)	26.9 ± 18.6	18.3 ± 13.9	<0.0001
LDL cholesterol (mg/dL)	121.0 ± 29.7	120.8 ± 29.6	ns
uric acid (mg/dL)	6.1 ± 1.3	4.5 ± 1.0	<0.0001
hemoglobin A1c (%)	5.1 ± 0.5	5.0 ± 0.4	0.0004
white blood cell count (/L ⁻⁶)	5574 ± 1489	4881 ± 1295	<0.0001
eGFR (mL/min/1.73m ²)	78.2 ± 12.8	79.9 ± 13.2	<0.0001
metabolic syndrome	14.5	9.0	<0.0001
Japanese metabolic syndrome	13.4	3.0	<0.0001
diabetes	5.8	1.9	<0.0001
chronic kidney disease	8.8	7.6	ns
coronary heart disease	4.2	1.6	<0.0001
stroke	1.7	1.1	ns
antihypertensive medication	18.9	10.2	<0.0001
hypoglycemic medication	3.7	1.2	<0.0001
antihyperlipidemic medication	9.4	10.4	ns
current smoker	34.0	7.9	<0.0001
everyday drinker	51.0	15.7	<0.0001

Data are presented as mean ± SD, median (the 1st quartile, the 3rd quartile), or %.

(ALT), uric acid, hemoglobin A1c, and white blood cell count were significantly higher in men than in women and body fat percentage, HDL cholesterol, and eGFR were significantly lower in men than in women. LDL cholesterol was not significantly different between men and women. The prevalence of MetS, diabetes, and coronary heart disease was significantly higher in men but the prevalence of CKD and stroke was not significantly different between men and women. The prevalence of JMetS in women was very low. Table 2 shows the prevalence of MetS, JMetS, IFG, and diabetes by the quartiles of serum uric acid level and Fig. 1 illustrates the prevalence of MetS and diabetes by the quartiles of serum uric acid level. The prevalence of MetS in the 3rd quartile (Q3) was significantly higher than that in the 1st (lowest) quartile (Q1) ($p<0.008$) and the prevalence of MetS in the 4th quartile (Q4) was significantly higher than those in Q1 ($p<0.0001$), the 2nd quartile (Q2) ($p<0.0001$), and Q3 ($p<0.001$) in men. The prevalence of MetS in the 4th quartile (Q4) was significantly higher than those in Q1 ($p<0.0001$), Q2 ($p<0.0001$), and Q3 ($p<0.0001$) in women. The differences in the prevalence of JMetS by the quartiles of uric acid were nearly similar to those of MetS.

The prevalence of IFG was higher in Q4 than in Q1 in men ($p<0.008$). The prevalence of IFG was higher in Q3 ($p<0.008$) and in Q4 ($p<0.0001$) than in Q1 in women. The prevalence of diabetes in Q3 was significantly lower than that in Q1 ($p<0.008$) and the prevalence of diabetes in Q4 was significantly lower than those in Q1 ($p<0.0001$) and Q2 ($p<0.008$) in men. The prevalence of diabetes was not significantly different among the quartiles of uric acid in women. Spearman's correlation coefficients between uric acid and MetS-related risk factors are shown in Table 3. The correlation coefficient between uric and fasting glucose and that between uric acid and hemoglobin A1c were not significant in men. Then, age-adjusted correlation coefficients between uric acid and MetS-related risk factors were calculated as shown in Table 4 because the correlation coefficient between uric acid and age was negative in men. The age-adjusted correlation coefficient between uric acid and body fat percentage and that between uric acid and fasting glucose were not significant in men and the age-adjusted correlation coefficient between uric acid and waist circumference was not significant in women. Table 5 presents Spearman's correlation coefficients between uric acid and MetS-related

Table 2. Prevalence of MetS, JMetS, IFG, and Diabetes by the Quartiles of Uric Acid

quartiles		Q1	Q2	Q3	Q4
range of uric acid (mg/dL)		1.0-5.2	5.3-6.0	6.1-6.8	6.9-12.1
n		614	568	632	635
men	MetS (%)	9.3	10.4	15.2*	22.5**
	JMetS (%)	9.9	9.7	12.0	21.3 [#]
	IFG (%)	18.2	19.7	21.4	25.6*
	diabetes (%)	9.1	6.5	5.2*	2.7 [†]
	range of uric acid (mg/dL)	1.8-3.8	3.9-4.4	4.5-5.0	5.1-9.5
n		370	359	350	369
women	MetS (%)	3.2	3.6	7.1	20.0 [#]
	JMetS (%)	0.8	1.4	2.0	7.6**
	IFG (%)	4.6	8.6	9.4	18.7**
	diabetes (%)	0.5	1.4	3.1	2.7
	range of uric acid (mg/dL)	1.8-3.8	3.9-4.4	4.5-5.0	5.1-9.5

MetS: metabolic syndrome, JMetS: Japanese metabolic syndrome, IFG: impaired fasting glucose. * $p < 0.008$ compared with Q1, ** $p < 0.0001$ compared with Q1 or Q2, $p < 0.001$ compared with Q3, [#] $p < 0.0001$ compared with Q1, Q2, or Q3, [†] $p < 0.0001$ compared with Q1, $p < 0.008$ compared with Q2.

Figure 1. Prevalence of metabolic syndrome (MetS) and diabetes by quartiles of uric acid.

risk factors excluding diabetic patients. The correlation coefficient between uric acid and fasting glucose was 0.083 ($p < 0.0001$) in men excluding diabetic individuals.

Discussion

The concept of insulin resistance syndrome (syndrome X) (2) or MetS (3, 4) was considered as the clustering of risk factors for diabetes and cardiovascular disease in the same individual. However, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes jointly stated that no existing definition of MetS meets criteria as a syndrome (5) and there have been endless debates on the pros and cons of diagnosing this syndrome for individuals (20-23). Criteria that regard obesity as an inevitable component of MetS have a serious pit hole because there are a substantial number of metabolically obese nor-

mal weight individuals (24) and only about one-third of most insulin-resistant individuals are actually obese (22). An essential drawback of JMetS (visceral fat syndrome) (15) is that it regards subcutaneous adipose tissue as a protective factor against the morbid effect of visceral adipose tissue and ignores the risk contribution of abdominal subcutaneous adipose tissue (25-27). A detailed criticism was discussed in a recent review by Oda (28). JMetS or IDF MetS where obesity is an inevitable component is already revealed to be inferior to the revised NCEP MetS as a predictor of cardiovascular disease in Japanese (18, 19). Therefore, in the present study, NCEP criteria where obesity is not an inevitable component was adopted as the definition of MetS.

In the present cross-sectional study in Japanese, we found that 1) the prevalence of MetS increased linearly through the quartiles of serum uric acid level in both men and women, although the prevalence of diabetes was decreased linearly through the quartiles of uric acid in men, 2) the correlation between uric acid and age was negative in men, and 3) the correlation between uric acid and fasting glucose was not significant even after the adjustment for age in men. However, the correlation between uric acid and fasting glucose was weakly positive in men excluding diabetic patients.

Prospective studies of uric acid as an independent risk factor of diabetes are limited and controversial. Taniguchi et al investigated the association between serum uric acid level and incident diabetes in a prospective cohort study of 6,365 Japanese male employees aged 35-61 years and reported that uric acid was not significantly associated with incident diabetes (11). Nakanishi et al studied the association of serum uric acid with development of IFG or diabetes over a 6-year follow-up among 2,310 Japanese male office workers aged 35-59 years and reported that the adjusted relative risk (95% confidence interval) of quintile 2, 3, 4, and 5 of serum uric acid for IFG or diabetes was 1.55 (0.95-2.63), 1.62 (0.98-2.67), 1.61 (1.01-2.58), and 1.78 (1.11-2.85), respectively compared with quintile 1 of serum uric acid (12).

Table 3. Spearman's Correlation Coefficients between Uric Acid and Other Related Risk Factors

	men n = 2449		women n = 1448	
	r	p	r	p
age	-0.132	<0.0001	0.167	<0.0001
body mass index	0.242	<0.0001	0.243	<0.0001
body fat percentage	0.181	<0.0001	0.277	<0.0001
waist circumference	0.250	<0.0001	0.146	<0.0001
systolic blood pressure	0.182	<0.0001	0.200	<0.0001
diastolic blood pressure	0.192	<0.0001	0.209	<0.0001
fasting glucose	0.038	ns	0.143	<0.0001
triglycerides	0.255	<0.0001	0.236	<0.0001
HDL cholesterol	-0.165	<0.0001	-0.124	<0.0001
high-sensitivity CRP	0.199	<0.0001	0.273	<0.0001
gamma glutamyltransferase	0.264	<0.0001	0.322	<0.0001
alanine aminotransferase	0.239	<0.0001	0.282	<0.0001
LDL cholesterol	0.120	<0.0001	0.137	<0.0001
hemoglobin A1c	-0.009	ns	0.206	<0.0001
white blood cell count	0.115	<0.0001	0.164	<0.0001
eGFR*	-0.241	<0.0001	-0.333	<0.0001

* estimated glomerular filtration rate

Table 4. Age-adjusted Correlation Coefficients between Uric Acid and Other Related Risk Factors

	men n = 2446		women n = 1445	
	r	p	r	p
body mass index	0.230	<0.0001	0.256	<0.0001
body fat percentage	0.014	ns	0.240	<0.0001
waist circumference	0.179	<0.0001	-0.002	ns
systolic blood pressure	0.183	<0.0001	0.170	<0.0001
diastolic blood pressure	0.205	<0.0001	0.195	<0.0001
fasting glucose	-0.023	ns	0.133	<0.0001
triglycerides	0.212	<0.0001	0.261	<0.0001
HDL cholesterol	-0.161	<0.0001	-0.115	<0.0001
high-sensitivity CRP	0.091	<0.0001	0.172	<0.0001
gamma glutamyltransferase	0.185	<0.0001	0.193	<0.0001
alanine aminotransferase	0.174	<0.0001	0.224	<0.0001
LDL cholesterol	0.119	<0.0001	0.104	<0.0001
hemoglobin A1c	-0.046	<0.05	0.154	<0.0001
white blood cell count	0.089	<0.0001	0.197	<0.0001
eGFR*	-0.289	<0.0001	-0.318	<0.0001

* estimated glomerular filtration rate

However, the latter study combined IFG and diabetes together. This study design made it impossible to detect the direct association of uric acid with diabetes. Chien et al conducted a community-based prospective cohort study of a median 9-year follow-up among 2,690 Chinese subjects aged 35-97 years and reported that the adjusted relative risk (95% confidence interval) for diabetes in the fifth quintile of serum uric acid was 1.63 (1.20-2.23) compared with the first quintile and, after additional adjustment for MetS, it was

1.40 (1.02-1.92) (13). However, after further adjustment for HOMA insulin resistance index, the association between uric acid and diabetes became non-significant (the relative risk of the fifth quintile compared with the first quintile became 1.22 [0.85-1.74]) (13). Chien et al combined men and women together. This method made it impossible to determine gender differences in the association between uric acid and diabetes. Nonetheless, these studies demonstrate that the association, if any, between uric acid and diabetes is medi-

Table 5. Spearman's Correlation Coefficients between Uric Acid and Other Related Risk Factors Excluding Diabetic Patients

	men n = 2306		women n = 1420	
	r	p	r	p
age	-0.124	<0.0001	0.160	<0.0001
body mass index	0.257	<0.0001	0.239	<0.0001
body fat percentage	0.188	<0.0001	0.270	<0.0001
waist circumference	0.273	<0.0001	0.153	<0.0001
systolic blood pressure	0.190	<0.0001	0.193	<0.0001
diastolic blood pressure	0.196	<0.0001	0.202	<0.0001
fasting glucose	0.083	<0.0001	0.136	<0.0001
triglycerides	0.263	<0.0001	0.237	<0.0001
HDL cholesterol	-0.176	<0.0001	-0.121	<0.0001
high-sensitivity CRP	0.212	<0.0001	0.271	<0.0001
gamma glutamyltransferase	0.274	<0.0001	0.320	<0.0001
alanine aminotransferase	0.250	<0.0001	0.275	<0.0001
LDL cholesterol	0.122	<0.0001	0.144	<0.0001
hemoglobin A1c	0.037	ns	0.198	<0.0001
white blood cell count	0.129	<0.0001	0.157	<0.0001
eGFR*	-0.227	<0.0001	-0.327	<0.0001

* estimated glomerular filtration rate

ated by insulin resistance. Chou et al reported in a study among 3,218 Chinese men and 4,265 Chinese women aged 30-89 years that the serum uric acid level was associated with insulin resistance and plasma glucose levels more strongly in women than in men (14). The correlation between serum uric acid and fasting glucose was negative in Austrian men (10) and was not significant in Japanese men in the present study. Serum uric acid has been described as being increased in the prediabetic stage of diabetes and as being decreased in overt diabetes (29). Conflicting data exist about uric acid levels in type 2 diabetes, as low levels were found in overt diabetes, while elevated serum uric acid is a feature of insulin resistance and impaired glucose tolerance (30). Bo et al reported that hyperuricemia in type 2 diabetes seems to be associated with MetS and the early onset or increased progression to overt nephropathy, while hypouricemia is associated with hyperfiltration and a late onset or decreased progression to overt nephropathy (30). In the present study, the prevalence of IFG was higher in Q4 than Q1 and the correlation between uric acid and fasting glucose was weakly positive in men, excluding diabetic patients. Thus, the negative association between serum uric acid levels and the prevalence of diabetes in Japanese men may be a result

of hyperuricosuria in overt diabetes. However, this negative association between uric acid and diabetes was not seen in women.

Limitations

The present study is a cross-sectional study and the subjects were not a general population but rather visitors to a medical check-up center which is in a central city of a rural region in Japan and information about antihyperuricemic medication was not available. Studies with more detailed information among more general populations and other ethnic populations and prospective studies are required to confirm our conclusions.

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