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High serum uric acid level and low urine pH as predictors of metabolic syndrome: a retrospective cohort study in a Japanese urban population

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ABSTRACT

The objective of this study was to evaluate whether hyperuricemia, acidic urine, or their combination predicts metabolic syndrome (MetS). In study 1, 69 094 subjects who received a general health checkup between 1985 and 2005 were included in a cross-sectional study of serum uric acid (SUA) and urine pH in relation to MetS. In study 2, the association of SUA and urine pH with MetS development over a 5-year period was evaluated in 5617 subjects with body mass index less than 25 kg/m^2 at the first examination. In study 1, higher SUA and lower urine pH were both positively correlated to MetS status ($P < .001$). The combination of high SUA and low urine pH was significantly associated with higher MetS prevalence compared with the combination of low SUA and high urine pH (odds ratio, 3.383; 95% confidence interval [CI], 3.034-3.784 in men; odds ratio, 4.000; 95% CI, 2.992-5.452 in women). In study 2, the top quartile of SUA levels was associated with higher MetS development compared with the bottom quartile during the 5-year period in men (hazard ratio [HR], 1.793; 95% CI, 1.084-2.966; $P = .023$). In women, the HR was 3.732 (95% CI, 0.391-35.62; $P = .252$) for the upper vs the lower half of SUA levels. For urine pH, the HR was 1.955 (95% CI, 1.089-3.509; $P = .025$) for the bottom vs the top quartile in men. A likelihood ratio test confirmed that high SUA and low urine pH act synergistically in the development of MetS. High SUA, low urine pH, and their combination are predictive risk factors for MetS development.

1. Introduction

Although serum uric acid (SUA) is not included in the diagnostic criteria for metabolic syndrome (MetS), a number of studies have reported a relationship between SUA and MetS [1-7]. Recently, it was reported that SUA was an independent risk factor of nonalcoholic fatty liver disease, which is considered a feature of MetS [8]. Moreover, an inverse relationship between urine pH and insulin resistance, which is a feature of MetS [9], has been reported [10,11]. Obesity, another feature of MetS, is also associated with low urine pH [12,13]; consequently, low urine pH might also be associated with MetS. Although a high SUA level and a low urine pH appear to be related to either MetS or insulin resistance, it

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remains unclear whether high SUA levels and low urine pH play etiological roles in the development of MetS.

In this study, we analyzed clinical data from a study population that underwent general health checkups at our hospital between January 1985 and December 2005 to evaluate whether hyperuricemia, acidic urine, or their combination is associated with MetS development.

2. Methods

2.1. Subjects

2.1.1. Study 1

The first study examined clinical data from 69 094 subjects (48 744 men and 20 350 women) 20 years or older (range, 20-92 years; mean, 46.5 years) who received general health checkups at the Center of Health Management, Toranomon Hospital, in Tokyo between January 1985 and December 2005. All subjects' records included complete measurements of MetS-related factors. The subjects were divided into sex-specific quartiles according to their SUA level (in men, Q1: ≤5.1 mg/dL, Q2: 5.2-5.8 mg/dL, Q3: 5.9-6.6 mg/dL, Q4: ≥6.7 mg/dL; in women, Q1 ≤3.6 mg/dL, Q2: 3.7-4.1 mg/dL, Q3: 4.2-4.7 mg/dL, and Q4: ≥4.8 mg/dL) and urine pH (in men, Q1: ≤5, Q2: 5.5, Q3: 6.0, and Q4: ≥6.5; in women, Q1: ≤5, Q2: 5.5, Q3: 6.0, and Q4: ≥6.5). The corresponding relationships with age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), fasting blood glucose (FBG), and MetS prevalence were analyzed. In addition, the subjects were cross-classified into 4 groups according to their combination of SUA level and urine pH (ie, low SUA [<5.9 mg/dL for men, <4.3 mg/dL for women] with either low urine pH [<6.0] or high urine pH [≥6.0] and high SUA [≥5.9 mg/dL for men, ≥4.3 mg/dL for women] with either low or high urine pH); and the MetS prevalence was compared across the 4 groups.

2.1.2. Study 2

A total of 5617 subjects (4114 men and 1503 women) who received a health checkup at least 5 times over a 5-year period and who had a BMI lower than 25 kg/m^2 at their first checkup were selected from the study 1 population for the analysis of MetS risk factors. The subjects were divided into quartiles according to their SUA level and according to their urine pH at the first checkup, and the 5-year cumulative incidence of MetS was estimated for each group. The analysis was also conducted to verify high SUA level and low urine pH as risk factors for the development of MetS.

In this study, MetS was defined as a BMI of 25 kg/m^2 or higher (the cutoff point in the Japanese diagnostic criteria for obesity) [14] in addition to 2 or more of the following criteria: (1) SBP of at least 130 mm Hg and/or DBP of at least 85 mm Hg; (2) TG of at least 150 mg/dL and/or HDLC less than 40 mg/dL; and (3) FBG of at least 110 mg/dL.

There were fewer women in this study population (woman to man ratio, 2:5) because our hospital is situated in the middle of a government office area in Tokyo, and our subjects were mostly male office workers.

2.2. Measurement of variables

Blood was sampled in the morning after overnight fasting. Serum uric acid was measured by the uricase peroxidase method. Fasting blood glucose was measured by the hexokinase-glucose-6-phosphate dehydrogenase method. Triglycerides were determined by a standardized enzymatic procedure using the glycerol phosphate oxidase assay. High-density lipoprotein cholesterol was measured using the enzymatic method. A urine sample from midstream of the first voiding of the morning after overnight fasting was put into a polystyrene bottle with a screw cap. Urine pH was measured with dipsticks that covered the pH range 4.5 to 8.5.

Blood pressure was measured in the sitting position using a sphygmomanometer. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2).

2.3. Statistical analysis

2.3.1. Study 1

Means and standard deviations of age, BMI, SBP, DBP, TG, HDLC, and FBG were calculated for each quartile of SUA or urine pH for men and women. The MetS prevalence was calculated for each quartile of SUA or urine pH for men and women. Trend tests were performed to analyze the relationships between stratified SUA or urine pH and other laboratory data using an analysis of variance with linear contrast. The relationships between MetS prevalence and stratified SUA or urine pH were analyzed using the Cochran-Armitage trend test. All P values were 2-sided. A $P < .05$ was considered significant.

To examine the association of the combination of SUA and urine pH with MetS prevalence, the subjects were cross-classified into 4 groups according to the combination of SUA level and urine pH as above; and MetS prevalence was calculated for each group. Multiple comparisons based on the Tukey method [15] were performed for pairwise comparisons. Logistic regression analysis was also performed to assess the relationships between these groups and MetS status.

2.3.2. Study 2

The subjects were stratified into quartiles according to SUA level or urine pH, and the cumulative MetS incidence for each group was then estimated using the Kaplan-Meier method.

The Cox proportional hazard model was used to analyze the risk of developing MetS without and with adjustment for age, BMI, SBP, DBP, TG, HDLC, FBG, and the year of the first checkup. The proportional hazard assumption between Q1 and Q4 was confirmed using a log-log plot. The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

To elucidate the influence of high SUA and low urine pH on the development of MetS, Cox proportional hazard analysis and the likelihood ratio test were performed on the 4 models as follows: model 0: age, BMI, SBP, HDLC, TG, FBG, and the year of the first checkup were included as explanatory variables; model 1: model 0 + SUA; model 2: model 0 + urine pH; model 3: model 0 + SUA + urine pH.

For all statistical tests, separate analyses were performed for men and women. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Table 1 – Clinical characteristics and laboratory data of the study population at the first checkup between January 1985 and December 2005

No. of subjects	Men 48 744		Women 20 350	
	Mean	SD	Mean	SD
Age (y)	45.9	±9.3	47.9	±9.6
Height (cm)	169	±6.0	156	±5.6
Body weight (kg)	66.4	±9.0	52.9	±7.5
BMI (kg/m^2)	23.3	±2.7	21.8	±2.9
SBP (mm Hg)	124	±16.0	119.0	±17.5
DBP (mm Hg)	78.6	±11.5	73.7	±11.4
TG (mg/dL)	130	±92.0	80.6	±46.3
HDLC (mg/dL)	50.6	±13.0	61.8	±14.0
FBG (mg/dL)	96.3	±17.4	90.1	±13.4
SUA (mg/dL)	5.9	±1.2	4.2	±0.9
Urine pH	5.6	±0.6	5.7	±0.8
Prevalence of MetS	9.3%		2.6%	

3. Results

3.1. *Study 1*

The clinical characteristics and laboratory data of the population in study 1 are summarized in Table 1. The MetS prevalence was 9.3% and 2.6% in men and women, respectively. Men had a significantly higher prevalence than women ($P < .001$).

The values of the MetS-related laboratory data by SUA level quartiles are shown in Table 2. Trend tests identified significant relationships between SUA level and all laboratory data except for FBG in men ($P < .001$ for trend). Positive correlations with SUA level were observed for BMI, SBP, DBP, and TG, whereas an inverse correlation was observed for urine

Table 2 – Clinical characteristics and laboratory data according to the quartile of SUA level at the first checkup

Men No. of subjects	Q1 (≤5.1 mg/dL) 11 835		Q2 (5.2-5.8 mg/dL) 11 493		Q3 (5.9-6.6 mg/dL) 12 793		Q4 (≥6.7 mg/dL) 12 623		Trend test[a]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
Age (y)	47.0	±9.4	45.9	±9.2	45.5	±9.2	45.3	±9.3	<.001
BMI (kg/m^2)	22.5	±2.6	22.9	±2.5	23.5	±2.6	24.4	±2.8	<.001
SBP (mm Hg)	121.0	±15.8	122.0	±15.5	124.0	±15.6	128.0	±16.1	<.001
DBP (mm Hg)	76.8	±11.3	77.5	±11.1	78.8	±11.3	81.1	±11.7	<.001
TG (mg/dL)	109.0	±70.4	117.0	±73.1	130.0	±83.4	163.0	±120.0	<.001
HDLC (mg/dL)	52.4	±13.5	51.2	±13.0	50.3	±12.7	48.7	±12.3	<.001
FBG (mg/dL)	97.4	±23.8	95.4	±16.2	95.6	±14.6	97.0	±13.4	.286
SUA (mg/dL)	4.4	±0.6	5.5	±0.2	6.2	±0.2	7.4	±0.7	<.001
Urine pH	5.7	±0.7	5.7	±0.7	5.6	±0.6	5.5	±0.6	<.001
Prevalence of MetS	5.3%		6.0%		8.8%		16.5%		<.001
Women No. of subjects	Q1 (≤3.6 mg/dL) 5181		Q2 (3.7-4.1 mg/dL) 4547		Q3 (4.2-4.7 mg/dL) 5148		Q4 (≥4.8 mg/dL) 5474		Trend test[a]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
Age (y)	46.0	±8.7	46.6	±9.2	48.1	±9.7	50.6	±10.1	<.001
BMI (kg/m^2)	21.0	±2.5	21.3	±2.6	21.7	±2.8	23.0	±3.4	<.001
SBP (mm Hg)	115.0	±16.2	117.0	±16.6	118.0	±17.2	123.0	±18.8	<.001
DBP (mm Hg)	71.8	±10.7	72.6	±11.1	73.6	±11.2	76.5	±11.9	<.001
TG (mg/dL)	69.9	±34.6	72.5	±36.4	79.8	±41.6	98.4	±60.2	<.001
HDLC (mg/dL)	62.9	±13.7	63.0	±13.6	61.9	±13.7	59.8	±14.7	<.001
FBG (mg/dL)	88.7	±14.5	88.9	±11.3	89.8	±13.2	92.8	±13.7	<.001
SUA (mg/dL)	3.2	±0.4	3.9	±0.1	4.4	±0.2	5.4	±0.6	<.001
Urine pH	5.9	±0.8	5.8	±0.8	5.7	±0.8	5.6	±0.7	<.001
Prevalence of MetS	0.7%		1.2%		1.8%		6.1%		<.001

[a] Analysis of variance with linear contrast was performed for laboratory tests. The Cochran-Armitage test was performed for the prevalence of MetS.

pH and HDLC, in both men and women. Fasting blood glucose showed a positive correlation with SUA level in women only.

The prevalence of MetS in each SUA level quartile is also shown in Table 2. In both men and women, a significant positive correlation between MetS prevalence and SUA level was found ($P < .001$ for trend).

The values of MetS-related factors by each quartile of urine pH are shown in Table 3. Urine pH was expressed in discrete 0.5 increments; thus, the number of subjects in each of the 4 quartiles was not equal. A significant inverse correlation was observed between the prevalence of MetS and urine pH ($P < .001$ for trend). Significant inverse correlations were also observed between urine pH and SUA level, BMI, TG, and FBG. Significant positive correlations between urine pH and SBP, DBP, and HDLC were observed in men.

The prevalence of MetS increased significantly with increases in SUA in both men and women ($P < .001$ for trend). In addition, the MetS prevalence increased significantly with decreases in urine pH (increased urine acidity) in men; however, this trend was not significant in women ($P = .075$).

Fig. 1 shows the associations between the combinations of SUA and urine pH and the prevalence of MetS. The high-SUA/low–urine pH group, expressed as *HL* in Fig. 1, had a significantly higher MetS prevalence than those with low SUA and high urine pH ($P < .05$). This finding applied to both men and women. As shown in Table 4, in men, the odds ratio was significantly higher for the high-SUA/low–urine pH group than for the low-SUA/high–urine pH group, as determined by logistic regression analysis. In women, whereas the high-SUA group had a higher odds ratio than the low SUA group, the influence of urine pH was not significant.

3.2. *Study 2*

The cumulative MetS incidence for the 4 SUA-level quartiles is shown in Fig. 2A. The results of Cox regression analysis are presented in Table 5A. In women, the Cox regression analysis was performed for the 2 groups defined by the median SUA level (<4.3 and ≥4.3 mg/dL) because the MetS incidence was low and there was no incidence of MetS in Q1. In men, Q2, Q3, and Q4 showed higher risks (with unadjusted HRs of 1.438, 1.894, and 3.711, respectively) relative to Q1. After adjusting for age, BMI, SBP, DBP, TG, HDLC, FBG, and the year of the first checkup, the HR was significantly higher in Q4 (1.793, $P = .023$) than in Q1 by multiple Cox regression analysis.

In women, the high-SUA group had a higher unadjusted risk than did the low-SUA group (HR, 8.716; $P = .043$). However, after adjusting for age, BMI, SBP, DBP, TG, HDLC, FBG, and the year of the first checkup, the risk was not statistically significant (HR, 3.732; $P = .252$).

Table 3 – Clinical characteristics and laboratory data according to the quartile of urine pH at the first checkup

Men	Q1 (≤5)		Q2 (5.5)		Q3 (6.0)		Q4 (≥6.5)		Trend test[a]
No. of subjects[b]	14 236		18 966		8983		6559		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P
Age (y)	46.7	±9.1	45.4	±9.1	45.5	±9.5	46.2	±9.8	.004
BMI (kg/m^2)	23.6	±2.9	23.3	±2.7	23.1	±2.6	23.0	±2.5	<.001
SBP (mm Hg)	124.0	±15.7	123.0	±15.9	124.0	±16.1	125.0	±16.5	.019
DBP (mm Hg)	78.2	±11.2	78.5	±11.5	79.1	±11.7	79.3	±11.7	<.001
TG (mg/dL)	145.0	±107.0	130.0	±91.5	118.0	±75.9	114.0	±72.6	<.001
HDLC (mg/dL)	49.8	±12.6	50.2	±12.9	51.2	±13.1	52.5	±13.4	<.001
FBG (mg/dL)	98.8	±20.2	96.2	±17.5	94.6	±14.7	93.9	±12.3	<.001
SUA (mg/dL)	6.2	±1.2	5.9	±1.2	5.8	±1.1	5.6	±1.1	<.001
Urine pH	5.0	±0.1	5.5	±0.0	6.0	±0.0	6.9	±0.5	<.001
Prevalence of MetS	11.9%		9.2%		7.5%		6.4%		<.001
Women	**Q1 (≤5)**		**Q2 (5.5)**		**Q3 (6.0)**		**Q4 (≥6.5)**		**Trend test[a]**
No. of subjects[b]	6368		5936		3613		4433		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P
Age (y)	48.2	±9.6	46.9	±9.8	48.0	±9.6	48.7	±9.4	<.001
BMI (kg/m^2)	21.7	±3.0	21.7	±3.0	21.8	±2.9	21.9	±2.8	<.001
SBP (mm Hg)	117.0	±16.5	118.0	±17.4	120.0	±18.0	121.0	±18.4	<.001
DBP (mm Hg)	72.5	±10.7	73.4	±11.3	74.4	±11.7	75.2	±12.1	<.001
TG (mg/dL)	83.6	±49.3	78.6	±47.3	78.9	±41.7	80.4	±43.7	.002
HDLC (mg/dL)	61.4	±13.6	61.9	±14.2	62.0	±14.4	62.3	±14.0	.001
FBG (mg/dL)	91.4	±15.2	90.0	±14.2	89.6	±12.1	88.9	±10.0	<.001
SUA (mg/dL)	4.4	±0.9	4.3	±0.9	4.2	±0.9	4.1	±0.9	<.001
Urine pH	5.0	±0.1	5.5	±0.0	6.0	±0.0	7.0	±0.5	<.001
Prevalence of MetS	2.8%		2.5%		2.7%		2.2%		.075

[a] Analysis of variance with linear contrast was performed for laboratory tests. The Cochran-Armitage test was performed for the prevalence of MetS.

[b] Because urine pH was measured in discrete 0.5 increments, the number of subject in each quartile was not equal.

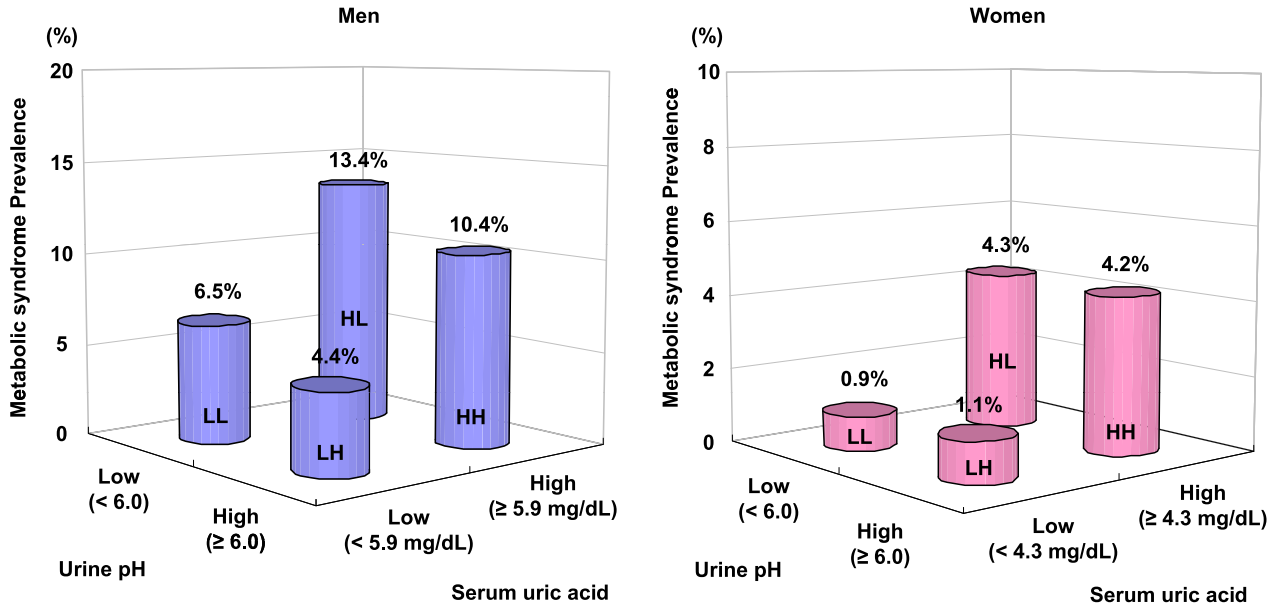

Fig. 1 – Association between combined serum uric acid/ urine pH categories and metabolic syndrome status. LH indicates low SUA/high urine pH; LL, low SUA/low urine pH; HH, high SUA/high urine pH; HL, high SUA/low urine pH. Significant differences (P < .05) were found in the pairwise comparisons in men (LL vs HL, LL vs HH, LL vs LH, LH vs HL, LH vs HH, HL vs HH) and in women (LL vs HL, LL vs HH, LH vs HH, LH vs HL).

The cumulative MetS incidence for the 4 urine pH quartiles is presented in Fig. 2B. The results of univariable and multiple Cox regression analyses for MetS development are shown in Table 5B. In men, Q1, Q2, and Q3 showed higher risk (with HRs of 2.277, 1.261, and 1.264, respectively) than Q4. The risk was significantly higher in Q1 compared with Q4 by both univariable (P = .005) and multiple Cox regression models (HR, 1.955; P = .025). However, in women, no statistical relationship was found with any of the urine pH quartiles by either univariable or multiple Cox regression model (Table 5B).

The results of the model estimation are shown in Table 6. In men, the −2log likelihood decreased in the order of model 0 > model 2 > model 1 > model 3; and the likelihood ratios between model 0 and model 1, model 0 and model 2, model 1 and model 3, and model 2 and model 3 decreased significantly. These results suggest that the addition of SUA level (as "model 0 → model 1" and "model 2 → model 3" in Table 6) and/or urine pH (as "model 0 → model 2" and "model 1 → model 3" in Table 6) to this multiple regression model would have a statistically significant impact. In women, the −2log likelihood also

Table 4 – Association between combined SUA/urine pH categories and MetS: analysis using logistic regression model

SUA group	Urine pH group	No. of subjects	N:MetS[a]	Odds ratio	95% CI			Likelihood ratio test
Men								
Low	–	23 328	1324	1.000				P < .001
High	–	25 416	3211	2.403	2.249	–	2.570	
–	Low	33 202	3445	1.000				P < .001
–	High	15 542	1090	0.651	0.607	–	0.699	
Low	High	8778	385	1.000				P < .001
Low	Low	14 550	939	1.504	1.333	–	1.700	
High	High	6764	705	2.536	2.232	–	2.887	
High	Low	18 652	2506	3.383	3.034	–	3.784	
Women								
Low	–	10 703	108	1.000				P < .001
High	–	9647	412	4.377	3.549	–	5.444	
–	Low	12 304	326	1.000				P = .290
–	High	8046	194	0.908	0.757	–	1.086	
Low	High	4690	52	1.000				P < .001
Low	Low	6013	56	0.838	0.574	–	1.228	
High	High	3356	142	3.941	2.879	–	5.477	
High	Low	6291	270	4.000	2.992	–	5.452	

[a] Number of subjects with MetS.

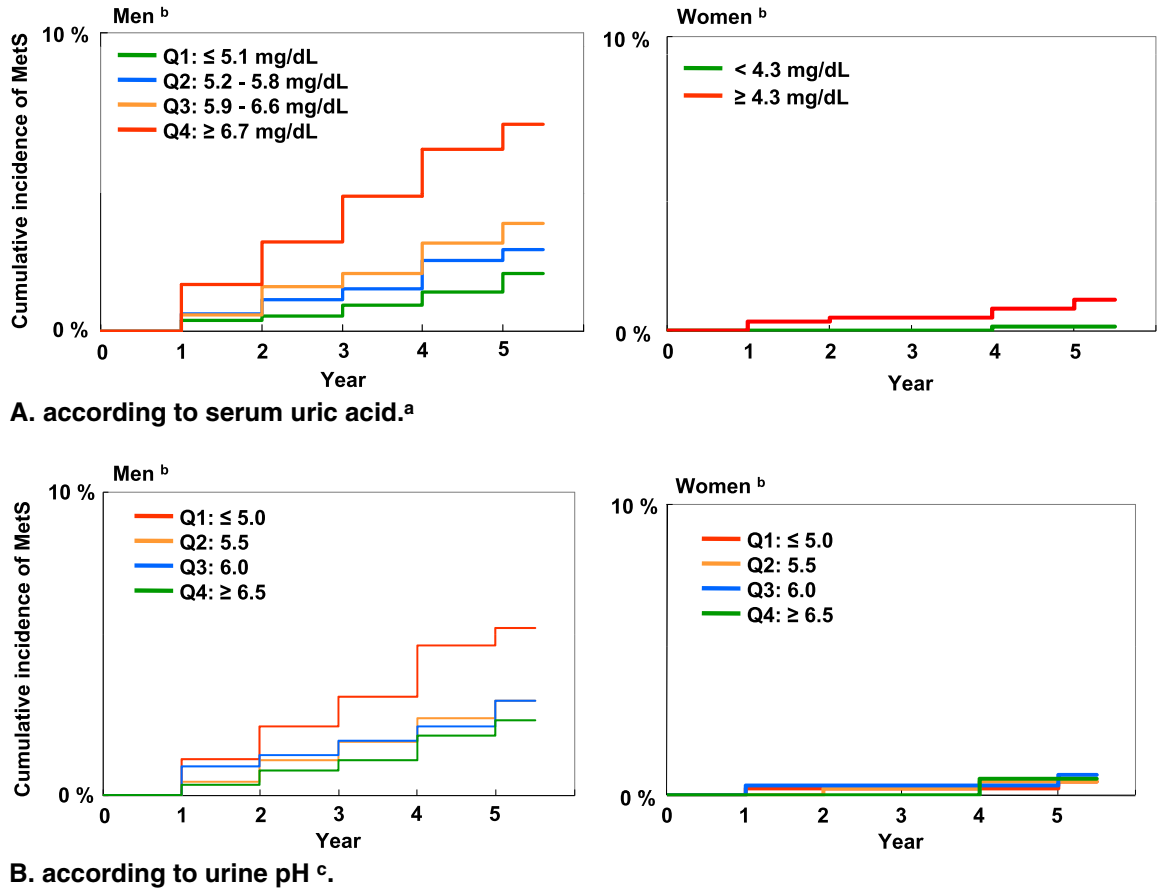

Fig. 2 – Cumulative incidence of metabolic syndrome by quartile of serum uric acid levels and urine pH. The cumulative incidence was calculated based on univariable analysis. a, In women, SUA was divided by the median because MetS was not observed in Q1 of the quartiles. b, With BMI less than 25 kg/m^2 at the first checkup. c, Because urine pH was measured in discrete 0.5 increments, the number of subjects in each quartile was not equal.

decreased in models including SUA (model 1 and model 3 in Table 6), although this result was not significant.

4. Discussion

The major findings of the present study are as follows: (1) A positive relationship between SUA level and the prevalence of MetS and an inverse relationship between urine pH and MetS prevalence were observed. (2) The risk for developing MetS was elevated with higher SUA level and with lower urine pH; and additionally, the risk for developing MetS was significantly higher in men who had high SUA level and low urine pH. (3) It was indicated that SUA level and urine pH act synergistically in the development of MetS in men by multiple Cox regression model analysis.

A number of studies have found a relationship between SUA level and MetS [1-7]. The potential mechanisms that relate hyperuricemia to MetS or its components have been suggested but not clarified [16].

In this retrospective cohort study, we demonstrated that the subjects with an SUA level in the highest quartile had increased risk of developing MetS compared with those with the lowest quartile of SUA level. Moreover, our multiple Cox regression analysis revealed that high SUA level is an independent risk factor for MetS in men. A recent study [17] suggested that uric acid induced in vitro an increase in the production of an adipokine playing an essential role in inducing the proinflammatory state in adipocytes in obesity. Our results may reflect such an essential role for uric acid in MetS development.

Our cohort study also demonstrates an association between acidic urine and MetS. Maalouf et al [10] reported that acidic urine is a feature of MetS and is associated with the degree of insulin resistance, which indicates that insulin resistance may reduce ammonium excretion by the proximal tubule [18]. In addition, even the slightest degree of metabolic acidosis produces insulin resistance in healthy humans [19]. Our cohort study provides evidence of such a causal role of acidic urine in MetS development. Accordingly, we propose that acidic urine is a new predictor of MetS.

We also demonstrate that high SUA and low urine pH act synergistically in MetS development in men. Multiple pathogenic processes may be implicated in MetS development. Insulin resistance leading to elevated SUA and high SUA may in turn aggravate insulin resistance and metabolic diseases [16]. Acidic urine may also exacerbate insulin resistance; and consequently, enhanced insulin resistance further reduces urine pH [18].

Table 5 – Cox regression analysis: MetS HRs and 95% CIs

A. According to SUA level

	No. of subjects [c]	N:MetS [a]	Univariable			Multiple adjusted [b]		
			HR	95% CI	P	HR	95% CI	P
Men								
Q1 (≤5.1 mg/dL)	1,143	22	1.000			1.000		
Q2 (5.2-5.8 mg/dL)	1,054	29	1.438	0.826-2.502	.199	1.227	0.704-2.141	.470
Q3 (5.9-6.6 mg/dL)	1,080	39	1.894	1.123-3.195	.017	1.304	0.771-2.208	.322
Q4 (≥6.7 mg/dL)	837	58	3.711	2.272-6.062	<.001	1.793	1.084-2.966	.023
Women								
SUA <4.3 mg/dL	832	1	1.000			1.000		
SUA ≥4.3 mg/dL	671	7	8.716	1.072-70.84	.043	3.732	0.391-35.62	.252

B. According to urine pH

Men								
Q4 (≥6.5)	609	15	1.000			1.000		
Q3 (6.0)	839	26	1.264	0.670-2.387	.470	1.112	0.587-2.104	.745
Q2 (5.5)	1,649	51	1.261	0.709-2.242	.430	1.290	0.722-2.307	.390
Q1 (≤5.0)	1,017	56	2.277	1.288-4.025	.005	1.955	1.089-3.509	.025
Women								
Q4 (≥6.5)	358	2	1.000			1.000		
Q3 (6.0)	289	2	1.240	0.175-8.803	.830	1.357	0.164-11.21	.777
Q2 (5.5)	441	2	0.812	0.114-5.764	.835	0.890	0.106-7.461	.914
Q1 (≤5.0)	415	2	0.863	0.122-6.124	.882	1.275	0.136-11.99	.831

[a] Number of subjects who developed MetS in 5 years.
[b] Adjusted for age, BMI, SBP, DBP, HDLC, TG, FBG, and the year of the first checkup.
[c] Because urine pH was measured in discrete 0.5 increments, the number of subject in each quartile was not equal.

In women, SUA was not a significant independent predictor of MetS development, a result that was probably due to the low statistical power afforded by the small population of women and the lower incidence of MetS compared with that in men. Nevertheless, when women were stratified by median SUA level, those with higher SUA (≥4.3 mg/dL) tended toward a higher risk of MetS than those with lower levels. The HR was quite high even after adjustment. High SUA level (≥4.6 mg/dL) has been associated with a higher risk for MetS development in women than in men [20,21]. A recent review [22] highlighted the fact that epidemiologic studies have shown a trend for worse prognoses of cardiovascular disease and chronic kidney disease in hyperuricemic women. In view of these observations, including our results, women appear to be sensitive to increases in SUA, showing a lower cutoff value than that for men. The prevalence of MetS is lower in women, but it is still necessary to monitor the development of MetS in women with elevated SUA.

This study has a few limitations. A malfunction of the adipose tissue, especially accumulation of intraabdominal visceral fat, is thought to be upstream of MetS [23]. Thus, waist circumference is a key determinant for diagnosing MetS. However, in this study, BMI was used instead of waist circumference to assess abdominal obesity because waist circumference data were not collected. Some recent studies have reported no difference in results based on whether waist

Table 6 – Metabolic syndrome HRs for SUA level and urine pH by multiple Cox regression models

Model	HR (95% CI) for SUA	HR (95% CI) for urine pH	−2Log likelihood	Likelihood ratio test	P
Men					
Model 0	–	–	1364.9	Model 0 → model 1	.004
Model 1	1.247 (1.073-1.448)	–	1356.5	Model 0 → model 2	.011
Model 2	–	0.689 (0.510-0.931)	1358.5	Model 0 → model 3	.002
Model 3	1.214 (1.044-1.413)	0.733 (0.542-0.991)	1352.2	Model 1 → model 3	.037
				Model 2 → model 3	.011
Women					
Model 0	–	–	68.5	Model 0 → model 1	.333
Model 1	1.592 (0.616-4.113)	–	67.5	Model 0 → model 2	.819
Model 2	–	1.112 (0.454-2.721)	68.4	Model 0 → model 3	.603
Model 3	1.603 (0.619-4.154)	1.141 (0.452-2.882)	67.5	Model 1 → model 3	.783
				Model 2 → model 3	.327

Model 0: age, BMI, SBP, HDLC, TG, FBG, and the year of the first checkup. Model 1: model 0 + SUA. Model 2: model 0 + urine pH. Model 3: model 0 + SUA + urine pH.

circumference or BMI was the criterion for establishing MetS as a predictor of cardiovascular disease and/or diabetes-related events [24,25]. In addition, the use of BMI in place of waist circumference may have posed fewer problems in assessing the relationship between the laboratory data and MetS because it was diagnosed by consistent criteria throughout this study.

Second, the smaller number of women in our study may have resulted in low statistical power and difficulty in making a definitive conclusion on the impact of high SUA on the development of MetS in women. Third, some important confounding variables related to the prevalence of MetS, such as smoking habits, alcohol intake, and dietary habits, were not investigated because these data were not available. Fourth, urolithiasis is also an important factor involved in MetS, hyperuricemia, and acidic urine. However, we had no data regarding renal stones; and we were unable to address any relationship with this factor.

Despite these limitations, our study is the first longitudinal cohort study on the relationships between SUA, urine pH, and the development of MetS. This is the first study to show that hyperuricemia and acidic urine act synergistically in the development of MetS. In terms of clinical implications, our results suggest that urine pH should be recognized as a potentially important screening parameter for MetS.

In conclusion, both high SUA and low urine pH are predictors of MetS. Hyperuricemia with acidic urine contributes to the development of MetS, highlighting the importance of screening and managing both of these factors. A long-term intervention study controlling hyperuricemia and acidic urine may define new strategies to prevent MetS.

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Conflict of Interest

All authors have nothing to declare.

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