Fasting Single-Spot Urine pH Is Associated with Metabolic Syndrome in the Japanese Population

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Significance of the Study

- In this study, a significant, inverse relationship between urine pH and metabolic syndrome and the number of its components were identified after controlling for confounding factors, including serum uric acid levels. The examination of urine pH could be a practical screening tool for metabolic syndrome.

Keywords

Diabetes · Dyslipidemia · Hypertension · Metabolic syndrome · Obesity · Urine pH

Abstract

Objective: To investigate the relationship between urine pH and metabolic syndrome (MetS) and its components, while controlling for covariates. **Subjects and Methods:** This cross-sectional study was conducted on 5,430 Japanese subjects (4,691 without MetS; 739 with MetS) undergoing health assessments. Partial correlation analysis and analysis of covariance were used for controlling confounding parameters (age, gender, levels of serum uric acid and high-sensitivity C-reactive protein, estimated glomerular filtration rate, and smoking and drinking status). Using multiple logistic regression analyses, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for MetS incidence were calculated

across urine pH categories. Path analysis was used to determine the relationship between MetS and urine pH. **Results:** Subjects with MetS had significantly lower urine pH (5.9 ± 0.7) than those without MetS (6.0 ± 0.7) ($p < 0.001$). Partial correlation analysis showed that systolic and diastolic blood pressure, and triglyceride and fasting plasma glucose levels were negatively correlated with urine pH, while high-density lipoprotein cholesterol was positively correlated with urine pH. Analysis of covariance indicated that urine pH decreased with an increasing number of metabolic abnormalities. Adjusted ORs (95% CI) for the presence of MetS in subjects with urine pH 5.5–6.0 and pH <5.5 were 1.34 (1.04–1.73) and 1.52 (1.09–2.13), respectively (reference: subjects with a urine pH >6.0). **Conclusion:** The MetS and its components were independently associated with lower urine pH.

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Introduction

Metabolic syndrome (MetS) is associated with a variety of physiological and metabolic alterations, and is clinically recognized by numerous constitutive traits, including abdominal obesity, hypertension, dyslipidemia, and hyperglycemia [1]. This cluster of features is strongly associated with type 2 diabetes, cardiovascular disease, and increased cardiovascular and all-cause mortality [1].

Recently, a relationship between low urine pH (pH <5.5) and diabetes [2] and insulin resistance [3] had been reported. Obesity, another feature of MetS, is also associated with a low urine pH [4]. In addition, non-high-density lipoprotein cholesterol (HDL-C) could have a significant association with a lower urinary pH [3]. In a recent cohort study, it was proposed that low urine pH is a causative and predictive factor for the development of MetS [5]. However, the relationship between urine pH and blood pressure has been investigated in only a few studies [5, 6], and only a limited number of studies has considered confounding variables such as smoking habits and alcohol intake [7, 8]. Epidemiological studies have revealed a close relationship between serum uric acid (UA) levels and the presence of MetS [9, 10]. Nevertheless, while patients with high serum UA levels were reported to have a low urine pH [5, 6, 11], it is unclear whether or not low urine pH relates to MetS in a manner independent of serum UA levels. Therefore, to ascertain whether or not urine pH is related to MetS and its components, a cross-sectional study was conducted in a Japanese population.

Subjects and Methods

Study Subjects

This study included 5,721 individuals who underwent routine health check-ups in Iida Municipal Hospital, Iida City, Japan, from January 2013 to December 2015. When data were available for individuals from multiple visits, only data acquired at the first visit were included. Exclusion criteria were: the potential for advanced renal dysfunction such as in those with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², evidence of albuminuria as indicated by urine dipstick albumin >2+, and advanced age (>80 years). Consequently, of the 5,721 individuals, 5,430 subjects were included in the final analysis (4,691 patients without MetS and 739 patients with MetS). This study was approved by the Institutional Ethics Review Board of Iida Municipal Hospital and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Definitions of Variables

According to the classification described by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria [12], MetS is defined by the presence of ≥3 components

of the following 5 abnormalities: (a) waist circumference (WC) ≥90 cm and ≥80 cm in Japanese men and women, respectively; (b) systolic blood pressure (SBP) ≥130 mm Hg and/or diastolic blood pressure (DBP) ≥85 mm Hg, or treatment for previously diagnosed hypertension; (c) triglyceride (TG) levels ≥150 mg/dL or receiving specific treatment for hypertriglyceridemia; (d) HDL-C levels <40 mg/dL in males and <50 mg/dL in females, or receiving specific treatment for low HDL-C; (e) fasting plasma glucose (FPG) levels ≥100 mg/dL or previously diagnosed diabetes. Individuals with <3 criteria for the diagnosis of MetS served as controls.

Clinical and Anthropometric Measurements

WC was measured between the lower rib margin and iliac crest after a normal expiratory breath. SBP and DBP were measured using an automated measuring device (HEM-7080IT, Omron Co., Tokyo, Japan). Two separate measurements were taken after 15 min of resting, with an interval of at least 30 s between the 2, and the mean of these was considered.

Information regarding various comorbidities, including hypertension, dyslipidemia, and diabetes, were collected by in-person interviews. The smoking status and alcohol consumption of study participants were assessed using a standardized questionnaire. The smoking status was considered as current smoking (daily and occasional smoking) and nonsmoking (never and former smoking). Alcohol consumption was classified as current drinkers (at least once per week) and noncurrent drinkers.

Laboratory Measurements

Blood samples were obtained after an overnight fast. To obtain a serum sample, the blood sample was centrifuged in a plain vacutainer within 20–30 min of blood clotting. Total serum cholesterol, TG, HDL-C, low-density lipoprotein cholesterol, UA, FPG, high-sensitivity C-reactive protein (hs-CRP), and creatinine levels were measured using standard methods (Hitachi 47 automatic analyzer, Hitachi Ltd., Japan). eGFR was calculated using the formula of the Japanese Society of Nephrology according to the equation: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ mL/min/1.73 m², further multiplied by 0.739 for female subjects [13]. An early morning mid-stream urine sample was collected for urine chemistry following an overnight fasting period, and was analyzed immediately using an automated urine dipstick analyzer (Aution Max AX-4030, ARKRAY Inc., Japan). Kraut and Madias [14] indicate that in the absence of impaired renal acidification, acidic urine should be defined as having a pH of ≤5.5, neutral urine a pH of 6.0–7.5, and alkaline urine a pH of ≥8.0.

Statistical Analysis

Statistical analyses were performed using SPSS software v21.0 (SPSS Inc. IL, USA). Characteristics of the subjects with and without MetS were compared using the independent *t* test for continuous variables and the χ^2 test for dichotomous variables. Skewed distribution variables were analyzed after logarithmic transformation. Correlations between urine pH and variables of MetS components were analyzed using the Pearson correlation analysis, and partial correlation analysis was performed to control confounding factors (age, gender, eGFR, serum UA, hs-CRP, and smoking and drinking status). In these correlation analyses, the subjects taking antihypertensive, antihyperglycemic, and antidiabetic agents were excluded to avoid the effects of drugs on the variables associated with MetS components. Analysis of covariance models were

Table 1. Demographic and metabolic characteristics of study participants

	Non-MetS (n = 4,691)	MetS (n = 739)	p value
Mean urine pH	6.0±0.7	5.9±0.7	<0.001
Urine pH >6.0	33.5%	27.2%	
Urine pH 5.5–6.0	53.7%	53.9%	
Urine pH <5.5	12.8%	18.8%	<0.001
Males	54.2%	77.0%	<0.001
Age, years	50.4±12.1	53.9±11.3	<0.001
BMI	22.1±2.8	26.7±3.2	<0.001
WC, cm	78.5±8.5	90.7±7.6	<0.001
eGFR, mL/min/1.73m ²	78.8±14.5	74.5±16.5	<0.001
Serum UA, mg/dL	6.2±1.4	5.3±1.4	<0.001
hs-CRP, mg/dL	0.10±0.44	0.15±0.25	0.019
SBP, mm Hg	120.1±17.2	136.7±15.4	<0.001
DBP, mm Hg	72.3±11.9	82.8±11.4	<0.001
Lipids, mg/dL			
TC	201.8±33.2	209.8±35.3	<0.001
TG	198.1±128.5	97.7±60.7	<0.001
HDL-C	50.0±11.9	64.1±15.5	<0.001
LDL-C	116.4±30.2	123.2±33.0	<0.001
Glucose parameters			
HbA _{1c} , %	5.9±0.6	5.6±0.5	<0.001
FPG, mg/dL	96.2±14.4	114.7±27.3	<0.001
Medication used			
Antihypertensive	22.3%	15.4%	<0.001
Antidiabetic	10.1%	6.2%	<0.001
Antidyslipidemic	17.2%	12.1%	<0.001
Current drinker	24.3%	22.5%	0.285
Current smoking	20.3%	17.9%	0.124

Values are expressed as means ± SD, unless otherwise indicated. MetS, metabolic syndrome; eGFR, estimated glomerular filtration rate; UA, uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose; WC, waist circumference.

used to examine the relationship between urine pH and the number of MetS abnormalities. We used multiple logistic regression analyses to adjust confounding factors to determine the adjusted odds ratios (ORs) for MetS incidence between different urine pH categories (pH <5.5, 5.5–6.0, and >6.0).

Results

Characteristics of Subjects with and without MetS

The incidence of MetS in all subjects, males, and females were 13.6, 18.3, and 7.3%, respectively. The physi-

Table 2. Correlation coefficients between urine pH and MetS components

	Urine pH			
	unadjusted		adjusted ¹	
	r	p	r	p
WC	–0.022	0.111	–0.007	0.404
SBP	–0.065	<0.001	–0.037	0.044
DBP	–0.032	<0.001	–0.010	0.006
TG ²	–0.072	<0.001	–0.033	0.035
HDL-C	0.081	<0.001	0.043	0.019
FPG	–0.092	<0.001	–0.072	<0.001
Gender	–0.060	<0.001	–	–
Age	–0.046	0.001	–	–
eGFR	0.112	<0.001	–	–
UA	–0.137	<0.001	–	–

MetS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; UA, uric acid.

¹ Partial correlation analysis adjusted for age, gender, serum UA, eGFR, high-sensitivity CRP, and smoking and alcohol status.

² log-transformed.

cal and biochemical characteristics of the study subjects are summarized in Table 1. Subjects with MetS had a significantly lower urine pH (5.9 ± 0.7) than those without MetS (6.0 ± 0.7) ($p < 0.001$). Serum UA levels were significantly higher in subjects with MetS than in those without MetS (6.2 ± 1.4 and 5.3 ± 1.4 , respectively) ($p < 0.001$).

Correlations between Urine pH and MetS Components

Some of MetS components (SBP, DBP, TG, and FPG levels) were negatively correlated with urine pH, whereas HDL-C showed a positive correlation, even after adjusting for confounding factors, including serum UA (Table 2). However, WC was not a correlation factor with urine pH.

Urine pH according to the Number of Abnormal Metabolic Components

Mean urine pH adjusted for confounding factors is shown in Figure 1. Urine pH decreased from 6.00, 6.01, 5.97, and 5.89, to 5.81, along with an increasing number of metabolic abnormalities (i.e., with 0, 1, 2, 3, and 4 or 5 abnormalities, respectively). Subjects with ≥ 3 metabolic abnormalities had a significantly lower urine pH than those with ≤ 2 metabolic abnormalities ($p_{\text{for trend}} < 0.001$).

Fig. 1. Mean urine pH adjusted for age, gender, and estimated glomerular filtration rate (eGFR) plotted against the number of metabolic syndrome (MetS) components. Bars indicate means $\pm$ SEM. p for trend < 0.001 .

Table 3. OR and 95% CI of the presence of MetS according to urine pH category

Urine pH	Unadjusted		Adjusted	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
>6.0	1.00 (ref)		1.00 (ref)	
5.5–6.0	1.21 (1.01–1.44)	0.021	1.34 (1.04–1.73)	0.005
<5.5	1.71 (1.35–2.17)	<0.001	1.52 (1.09–2.13)	<0.001

The OR was adjusted for age, gender, serum uric acid, estimated glomerular filtration rate, and smoking and alcohol status. OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome.

ORs of MetS according to Urine pH

Unadjusted and adjusted ORs of the presence of MetS according to different urine pH categories are shown in Table 3. The ORs increased with a decrease in urine pH. Compared with subjects with a urine pH >6.0 , the adjusted ORs (with 95% confidence intervals [CIs]) for the presence of MetS in subjects with a urine pH of 5.5–6.0 and <5.5 were 1.34 (1.04–1.73) and 1.52 (1.09–2.13), respectively.

Discussion

In this study, there was a significant inverse relationship between urine pH and MetS and the number of abnormal metabolic components. In addition, urine pH was

correlated with variables of MetS components. These results did not change even after adjusting for a range of confounding factors such as age, gender, eGFR, hs-CRP, UA, and smoking and drinking status.

Our findings are consistent with those of previous studies [2–5] regarding the relationship between urine pH and metabolic parameters. For example, urine pH has been found to be significantly lower in patients with type 2 diabetes than in normal volunteers [2]. In another study, a low urine pH showed an association with an increase in WC, and FPG and TG levels and a decrease in HDL-C levels [6]. Furthermore, participants with MetS had a significantly lower 24-h urine pH than those without MetS [15], and low urine pH could be a predictive factor for the development of MetS [5]. Our results and these previous studies indicate that urine pH correlates with metabolic parameters and that a low urine pH is associated with the incidence of MetS.

Although the precise reasons for the relationship between MetS and a lower urine pH remain unclear at this time, a low urine pH could result from increased acid excretion, impaired urinary buffering, or both. Ammonium is the primary buffer in the urine [16], and its renal production and excretion are regulated by the ambient acid-base environment. Insulin is known to influence both of these processes [17], and mechanisms of acid-base homeostasis may be altered in a state of insulin resistance [18]. Considering our data along with those from previous studies [2–5], we hypothesize that acidic urine may be a renal manifestation of insulin resistance resulting from MetS.

Although serum UA is not included in the diagnostic criteria for MetS, epidemiological studies have established a close relationship between elevated serum UA levels and the increasing prevalence of MetS [9, 10, 19]. Serum UA, a weak acid, may also affect urine pH. Indeed, previous studies have reported that subjects with higher serum UA levels have lower urine pH [5, 6, 11]. In this study, serum UA levels were negatively correlated with urine pH, which is consistent with the results of previous reports. In addition, the relationship between lower urine pH and MetS persisted, even after adjusting for serum UA, suggesting that high serum UA levels alone cannot account for the more acidic urine. Aging [20] and renal dysfunction [21] are also known to be related with a decrease in urine pH. Our results are consistent with the following previous findings: age had an inverse relationship with urine pH whereas eGFR had a positive relationship. In this study, individuals who exhibited potential signs of advanced renal dysfunction and/or advanced age

were excluded. However, the relationship between MetS and its components with urine pH was unchanged even after adjusting for age and eGFR.

In this study, fasting single-spot urine samples, and not urine collected over 24 h, were used to determine the urine pH. Although the diurnal variation in urine pH has been confirmed, Capolongo et al. [22] demonstrated that fasting urine pH is significantly correlated with 24-h urine pH in a large cohort. Additionally, the measurement of urine pH using the indicator method is known to be less reliable than using electrodes; however, the indicator method might be more appropriate for routine health check-ups because of its convenience and lower cost.

The strength of the study was its relatively large, well-characterized, community-based population. However, it also has some limitations which include its cross-sectional design which did not permit the determination of causality. In addition, nutritional records were not available for the patients, and so we could not include dietary patterns in the analyses. Furthermore, the study population consisted of Japanese patients only; consequently, it is uncertain whether these findings could be generalized to other ethnic groups.

Conclusion

In this study, there was a relationship between MetS and low urine pH, in a manner which is independent of serum UA levels. In addition, a progressive decline in urine pH was noted with an increasing number of MetS features. Hence, the examination of fasting urine pH could be a practical screening tool for MetS, and this practice might be beneficial in recognizing the segment of a Japanese population with lower urine pH, particularly urine pH <5.5. Further studies are needed to elucidate the mechanisms responsible for the lower urine pH in individuals with MetS.

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Disclosure Statement

There were no conflicts of interest.

References

- Hu G, Qiao Q, Tuomilehto J, et al: Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 2004;164:1066–1076.
- Cameron MA, Maalouf NM, Adams-Huet B, et al: Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. *J Am Soc Nephrol* 2006;17:1422–1428.
- Torricelli FC, De SK, Gebreselassie S, et al: Dyslipidemia and kidney stone risk. *J Urol* 2014;191:667–672.
- Maalouf NM, Sakhaee K, Parks JH, et al: Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 2004;65:1422–1425.
- Hara S, Tsuji H, Ohmoto Y, et al: High serum uric acid level and low urine pH as predictors of metabolic syndrome: a retrospective cohort study in a Japanese urban population. *Metabolism* 2012;61:281–288.
- Otsuki M, Kitamura T, Goya K, et al: Association of urine acidification with visceral obesity and the metabolic syndrome. *Endocr J* 2011;58:363–367.
- Cho YH, Lee SY, Jeong DW, et al: The association between a low urine pH and the components of metabolic syndrome in the Korean population: findings based on the 2010 Korea National health and nutrition examination survey. *J Res Med Sci* 2014;19:599–604.
- Park M, Jung SJ, Yoon S, et al: Association between the markers of metabolic acid load and higher all-cause and cardiovascular mortality in a general population with preserved renal function. *Hypertens Res* 2015;38:433–438.
- Choi HK, Ford ES: Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med* 2007;120:442–447.
- Onat A, Uyarel H, Hergenc G, et al: Serum uric acid is a determinant of metabolic syndrome in a population-based study. *Am J Hypertens* 2006;19:1055–1062.
- Nakanishi N, Fukui M, Tanaka M, et al: Low urine pH is a predictor of chronic kidney disease. *Kidney Blood Press Res* 2012;35:77–81.
- Alberti KG, Eckel RH, Grundy SM, et al: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–1645.
- Matsuo S, Imai E, Horio M, et al: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–992.
- Kraut JA, Madias NE: Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol* 2010;6:274–285.
- Maalouf NM, Cameron MA, Moe OW, et al: Low urine pH: a novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol* 2007;2:883–888.
- DuBoise TD Jr, Good DW, Hamm LL, et al: Ammonium transport in the kidney: new physiological concepts and their clinical implications. *J Am Soc Nephrol* 1991;1:1193–1203.
- Fuster DG, Bobulescu IA, Zhang J, et al: Characterization of the regulation of renal Na⁺/H⁺ exchanger NHE3 by insulin. *Am J Physiol Renal Physiol* 2007;292:F577–F585.
- Abate N, Chandalia M, Cabo-Chan AV Jr, et al: The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int* 2004;65:386–392.
- Liu PW, Chang TY, Chen JD: Serum uric acid and metabolic syndrome in Taiwanese adults. *Metabolism* 2010;59:802–807.
- Agarwal BN, Cabebe FG: Renal acidification in elderly subjects. *Nephron* 1980;26:291–295.
- Schwartz WB, Relman AS: Acidosis in renal disease. *N Engl J Med* 1957;256:1184–1186.
- Capolongo G, Sakhaee K, Pak CY, et al: Fasting versus 24-h urine pH in the evaluation of nephrolithiasis. *Urol Res* 2011;39:367–372.