

Low Urine pH: A Novel Feature of the Metabolic Syndrome

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Background and Objectives: The metabolic syndrome is associated with alterations in renal function. An overly acidic urine has been described as a renal manifestation of the metabolic syndrome in patients with kidney stone disease. This study examined the association between the metabolic syndrome and urine pH in individuals without a history of nephrolithiasis.

Design, Setting, Participants, & Measurements: A total of 148 adults who were free of kidney stones were evaluated in this outpatient cross-sectional study. Height, weight, BP, fasting blood, and 24-h urine chemistries were obtained. Urine pH was measured by pH electrode. The following features of the metabolic syndrome were evaluated: BP; body mass index; and serum triglyceride, glucose, and HDL cholesterol concentrations. The degree of insulin resistance was assessed by the homeostasis model assessment of insulin resistance.

Results: Participants with the metabolic syndrome had a significantly lower 24-h urine pH compared with participants without the metabolic syndrome. Mean 24-h urine pH, adjusted for age, gender, creatinine clearance, and 24-h urine sulfate, decreased from 6.15, 6.10, 5.99, 5.85, to 5.69 with increasing number of metabolic syndrome abnormalities. An association was observed between 24-h urine pH and each metabolic feature. After adjustment for age, gender, creatinine clearance, urine sulfate, and body mass index, a significant inverse relationship was noted between 24-h urine pH and the degree of insulin resistance.

Conclusions: An unduly acidic urine is a feature of the metabolic syndrome and is associated with the degree of insulin resistance.

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The metabolic syndrome (MS) is characterized by a constellation of metabolic features including dyslipidemia, hyperglycemia, hypertension, obesity, and insulin resistance (1,2). This cluster of features is strongly associated with type 2 diabetes, atherosclerotic cardiovascular disease, and increased cardiovascular and all-cause mortality (3,4). Alterations in renal homeostatic mechanisms have also been associated with the MS and its features (5–7). Sodium and uric acid retention are linked to insulin resistance (7–9), whereas a renal hyperhemodynamic state has been ascribed to obesity (10). Moreover, an association between MS and chronic kidney disease (CKD) was recently described; patients with increasing features of the MS had a greater incidence and prevalence of CKD (11,12).

Another novel renal manifestation of the MS may be an overly acidic urine. This finding was first described in uric acid kidney stone formers, the majority of whom were afflicted with the MS (13). Furthermore, an unduly acidic urine was recently demonstrated in non-stone-forming patients with type 2 diabetes (14). This cross-sectional study extends these findings and

examines the relationship between urinary acidity and multiple features of the MS across a wide range of non-stone-forming individuals.

Materials and Methods

Study Participants

We used local advertisements to recruit volunteers who were willing to participate in the study. Inclusion criteria were age >21 yr and ability to provide informed consent. We wished to evaluate individuals with a wide range of body weight; therefore, body weight and/or body mass index (BMI) was not used for the inclusion/exclusion criteria. Excluded from the study were individuals with conditions that are known to alter urine pH, such as CKD (defined by creatinine clearance <70 ml/min [<1.17 ml/s]), renal tubular acidosis, chronic diarrheal illness, kidney stone disease (by history), primary hyperparathyroidism, or urinary tract infections. Participants were instructed to hold any medications that are known to influence urine pH (e.g., alkali therapy, diuretics) for 1 wk before the study. Individuals with type 2 diabetes were allowed to participate if they were not taking insulin or thiazolidinediones. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center (Dallas, TX).

Data Collection and Measurements

All participants collected a 24-h urine sample under mineral oil, and the urine container was kept refrigerated or maintained in an ice chest during collection. At the end of the urine collection, the participants had fasting blood drawn, and height, weight, and BP were measured. The American Heart Association/National Heart, Lung, and Blood

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Institute updated the definition of the metabolic syndrome in 2005 (15) to the presence of three or more of the following: (1) An elevated fasting blood glucose (≥ 100 mg/dl, ≥ 6 mmol/L) or drug treatment for elevated glucose; (2) an elevated BP defined as systolic BP (SBP) >135 mmHg, diastolic BP >85 mmHg, or drug treatment for hypertension; (3) elevated fasting serum triglycerides defined as >150 mg/dl (>1.70 mmol/L) or drug treatment for hypertriglyceridemia; (4) low fasting serum HDL cholesterol <50 mg/dl (<1.30 mmol/L) in women and <40 mg/dl (<1.04 mmol/L) in men or drug treatment for low HDL; and (5) abdominal obesity defined as waist circumference >88 cm in women and >102 cm in men. Because waist circumference was not available for many individuals, a BMI of ≥ 30 kg/m² was used as an index of obesity. BMI is considered a satisfactory substitute for waist circumference because the two parameters are highly correlated (16). BMI has been used instead of waist circumference in modified criteria for the definition of the MS in several previous studies (17,18). Insulin resistance was calculated from fasting glucose and insulin measurements using the homeostasis model assessment for insulin resistance (HOMA-IR) (19,20).

Analytical Procedures

Serum electrolytes, glucose, triglycerides, total and HDL cholesterol, creatinine, and uric acid concentrations were measured using an automated system (Beckman CX9ALX, Fullerton, CA). Urine pH was measured by pH electrode. Urine creatinine was determined using the picric acid method, and endogenous creatinine clearance was calculated from values of creatinine in the serum and urine. Urine sulfate was evaluated by ion chromatography. Urine bicarbonate (HCO_3^-) was calculated from urine pH and Pco_2 . Urine ammonium (NH_4^+) was determined by the glutamate dehydrogenase method, and urine titratable acidity was measured directly using the automated burette end point titration system (Radiometer, Copenhagen, Denmark). Urine citrate was evaluated enzymatically using reagents from Boehringer-Mannheim Biochemicals (Indianapolis, IN), and milliequivalents of citrate were calculated from urine pH and a pKa of citrate²⁻/citrate³⁻ of 5.6. Urine net acid excretion (NAE) was calculated as urine (NH_4^+ + titratable acidity) - (citrate + HCO_3^-), all in milliequivalents. The proportion of net acid excreted as ammonium is described by the ratio of NH_4^+ to NAE (NH_4^+/NAE). Serum insulin was assessed by ELISA (Mercodia, Metuchen, NJ).

Statistical Analyses

Categorical comparisons were performed using the χ^2 test. Serum triglycerides and HOMA-IR were log-transformed before statistical analyses. For normally distributed continuous variables, comparisons of participants with and without MS were made with two-sample *t* test. For urine NH_4^+/NAE , the Wilcoxon rank sum test was used. Tests of linear trend were conducted by one-way ANOVA with polynomial contrasts. The urine NH_4^+/NAE trend was analyzed with the Jonckheere-Terpstra test. Analysis of covariance models were used to examine the relationship between urinary pH with the number of MS abnormalities and for assessing each MS feature while adjusting for the potential confounding effects of covariates. BMI, age, gender, urine sulfate, and creatinine clearance were included as covariates. Statistical analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC).

Results

Demographic Characteristics

A total of 148 individuals participated in the study. The demographic characteristics of the entire cohort are shown in Table 1. The average age (\pm SD) was 44 ± 14 yr, and the mean

Table 1. Characteristics of study participants^a

Characteristic	Value
No. of participants	148
Gender (male/female; <i>n</i> [%])	66/82 (45/55)
Race (white/black/Asian/Hispanic)	89/34/13/12
Age (yr; mean \pm SD)	44 ± 14
Height (cm; mean \pm SD)	168 ± 10
Weight (kg; mean \pm SD)	80 ± 21
BMI (kg/m ² ; mean \pm SD)	28.4 ± 6.7
Elevated BMI (<i>n</i> [%]) ^b	50 (33.8)
Elevated fasting blood glucose (<i>n</i> [%])	53 (35.8)
Elevated triglycerides (<i>n</i> [%])	37 (25.0)
Low HDL (<i>n</i> [%])	70 (47.3)
Elevated BP (<i>n</i> [%])	50 (33.8)
No. of MS features (median [IQR])	1 (1 to 3)
MS (<i>n</i> [%])	44 (29.7)

^aBMI, body mass index; IQR, interquartile range; MS, metabolic syndrome.

^bDefined as BMI ≥ 30 kg/m².

BMI was 28.4 ± 6.7 kg/m². The average number of MS features was 1.76 ± 1.51 , and 29.7% of the cohort met the definition of the MS.

Urine pH and the MS

The demographic and metabolic characteristics of participants with (MS+) and without (MS-) the MS are shown in Table 2. There was no significant difference in the racial distribution between MS+ and MS- participants. MS+ participants were significantly older and had significantly greater BMI, SBP and diastolic BP, and serum glucose and triglycerides. Participants with the MS had a significantly lower 24-h urine pH compared with participants without the MS (5.71 ± 0.47 versus 6.11 ± 0.42 ; $P < 0.001$). This significant difference in urine pH between MS+ and MS- participants was noted in both genders. The 24-h urine potassium was not different between the two groups. MS+ participants had significantly greater NH_4^+ and NAE, although NH_4^+/NAE was significantly lower than in MS- participants.

Urine pH and Features of the MS

Participants were further classified according to the number of metabolic abnormalities (Table 3). Mean urine pH according to the number of characteristics of the MS is shown in Table 3. Mean 24-h urine pH values decreased with increasing number of MS features (from 6.19, 6.14, 5.96, 5.83 to 5.60; $P < 0.0001$ for trend). Age, creatinine clearance, and 24-h urine sulfate (a surrogate for dietary acid ingestion) were also significantly correlated with urine pH in univariate analysis ($P < 0.05$). These variables were included in a multivariate model to examine the relationship between urine pH and the MS. Mean 24-h urine pH adjusted for age, gender, creatinine clearance, and urine sulfate decreased from 6.15, 6.10, 5.99, 5.85, to 5.69 with increasing number of metabolic abnormalities ($P < 0.005$ for trend; Figure 1).

Table 2. Biochemical features in participants with and without the MS^a

Parameter	MS-	MS+	P (MS+ versus MS-)
No. of participants	104	44	
Gender (female/male; %)	59/41	47/53	0.22
Race (white/black/Asian/Hispanic; %)	61/22/11/6	57/25/5/13	0.28
Age (yr; mean \pm SD)	41 \pm 13	51 \pm 13	<0.001
BMI (kg/m ² ; mean \pm SD)	25.6 \pm 5.6	34.2 \pm 5.4	<0.001
Glucose (mg/dl; mean \pm SD) ^b	92 \pm 13	118 \pm 37	<0.001
Triglycerides (mg/dl; median [IQR]) ^c	76 (51 to 109)	175 (91 to 221)	<0.001
HDL cholesterol (mg/dl; mean \pm SD) ^d	52 \pm 13	40 \pm 8	<0.001
Systolic BP (mmHg; mean \pm SD)	118 \pm 15	135 \pm 21	<0.001
Diastolic BP (mmHg; mean \pm SD)	74 \pm 10	83 \pm 11	<0.001
HOMA-IR (median [IQR])	0.90 (0.61 to 1.20)	1.81 (1.36 to 2.53)	<0.001
Creatinine clearance (ml/min; mean \pm SD) ^e	113 \pm 33	129 \pm 43	0.03
24-h urine sulfate (mmol/d; mean \pm SD)	18 \pm 7	21 \pm 8	0.02
24-h urine potassium (mmol/d; mean \pm SD)	57 \pm 23	56 \pm 17	0.82
24-h urine ammonium (mEq/d; mean \pm SD)	29 \pm 15	37 \pm 20	0.02
24-h urine NAE (mEq/d; mean \pm SD)	36 \pm 24	59 \pm 34	<0.001
Urine NH ₄ ⁺ /NAE (median [IQR])	0.73 (0.60 to 0.93)	0.58 (0.51 to 0.68)	<0.001
24-h urine pH (mean \pm SD)	6.11 \pm 0.41	5.71 \pm 0.47	<0.001

^aHOMA-IR, homeostasis model assessment of insulin resistance; MS+, participants with MS; MS-, participants without MS; NAE, net acid excretion.

^bTo convert values to millimoles per liter, multiply by 0.05549.

^cTo convert values to millimoles per liter, multiply by 0.01129.

^dTo convert values to millimoles per liter, multiply by 0.0259.

^eTo convert values to milliliters per second, multiply by 0.01667.

Twenty-four-hour urine pH was significantly correlated with serum HDL cholesterol and inversely and significantly associated with BMI, SBP, serum glucose, and serum triglycerides (Table 4). After adjustment for age, gender, creatinine clearance, and urine sulfate, 24-h urine pH was still significantly associated with BMI, SBP, serum glucose, and serum HDL cholesterol, although the magnitude of the association decreased (Table 4).

Urine pH and Insulin Resistance

Twenty-four-hour urine pH was inversely correlated with the degree of insulin resistance estimated by the HOMA-IR ($P < 0.0001$; Table 4). After adjustment for age, gender, BMI, creatinine clearance, and urine sulfate, the inverse relationship between 24-h urine pH and HOMA-IR remained statistically significant (Table 4).

Discussion

The MS is associated with a variety of physiologic and metabolic alterations. This cross-sectional study evaluated the relationship between the MS and urine pH. In a diverse outpatient population, patients with the MS were found to have a more acidic urine than individuals without the MS. In addition, we found a strong, significant, inverse relationship between 24-h urine pH and the number of features of the MS. This correlation was independent of factors that are known to influ-

ence urinary pH, including age, gender, creatinine clearance, and urine sulfate.

Our study is the first to demonstrate an inverse relationship between 24-h urine pH and the number of MS features. Previous reports have shown an inverse correlation between body weight and urine pH in kidney stone-forming (21) and non-stone-forming individuals (14). Similarly, a recent report found an inverse relation between BMI and urine pH among stone formers and non-stone formers (22). Our study confirms these findings because a higher BMI, a surrogate of abdominal obesity, was associated with more acidic urine. However, 24-h urine pH also correlated with each of the other MS components after adjustment for BMI, suggesting that the relationship is not driven by body mass alone. The association of urine pH with SBP, serum glucose, triglycerides, and HDL cholesterol has not been previously reported.

The major deleterious consequence of an overly acidic urine is the development of uric acid kidney stones. Uric acid is poorly soluble and has a pKa of 5.51 at 37°C (23). As urine pH exceeds this value, an increasing proportion of uric acid exists in the form of its base, urate, which is relatively soluble. Therefore, urine pH is the principal determinant of uric acid precipitation, and, in fact, an overly acidic urine is the primary pathogenic finding in uric acid stone formers (24). Our findings suggest that the presence of increasing number of MS features augments the propensity for uric acid stone formation. This

Table 3. Distribution of biochemical features according to the number of features of the MS

Parameter	No. of Features of the MS					P for Trend
	0	1	2	3	≥4	
No. of participants	36	41	27	20	24	
Gender (female/male; %)	61/39	61/39	56/44	55/45	42/58	
Age (yr; mean ± SD)	39 ± 12	39 ± 13	47 ± 13	49 ± 15	52 ± 12	<0.001
BMI (kg/m ² ; mean ± SD)	23.0 ± 3.4	26.1 ± 5.6	29.6 ± 5.9	33.4 ± 5.1	34.9 ± 5.6	<0.001
Glucose (mg/dl; mean ± SD) ^a	88 ± 7	90 ± 9	101 ± 19	112 ± 34	124 ± 40	<0.001
Triglycerides (mg/dl; mean ± SD) ^b	65 ± 29	87 ± 49	155 ± 122	100 ± 45	255 ± 120	<0.001
HDL cholesterol (mg/dl; mean ± SD) ^c	58 ± 12	48 ± 12	48 ± 14	43 ± 9	38 ± 6	<0.001
Systolic BP (mmHg; mean ± SD)	113 ± 9	116 ± 17	126 ± 15	137 ± 26	133 ± 14	<0.001
Diastolic BP (mmHg; mean ± SD)	72 ± 8	73 ± 11	79 ± 9	84 ± 13	82 ± 8	<0.001
HOMA-IR (mean ± SD)	0.76 ± 0.38	0.95 ± 0.56	1.39 ± 0.64	1.68 ± 0.85	2.37 ± 1.26	<0.001
Creatinine clearance (ml/min; mean ± SD) ^d	103 ± 23	114 ± 35	124 ± 40	127 ± 44	131 ± 43	0.001
24-h urine sulfate (mmol/d; mean ± SD)	17 ± 7	17 ± 8	20 ± 7	18 ± 6	24 ± 9	0.004
24-h urine potassium (mmol/d; mean ± SD)	57 ± 26	54 ± 20	62 ± 23	54 ± 23	58 ± 19	0.82
Urine NH ₄ ⁺ /NAE (median [IQR])	0.82 (0.64 to 1.00)	0.74 (0.57 to 0.94)	0.64 (0.52 to 0.68)	0.56 (0.52 to 0.68)	0.61 (0.49 to 0.68)	<0.001
24-h urine pH (mean ± SD)	6.19 ± 0.27	6.14 ± 0.26	5.96 ± 0.29	5.83 ± 0.31	5.60 ± 0.30	<0.001

^aTo convert values to millimoles per liter, multiply by 0.05549.
^bTo convert values to millimoles per liter, multiply by 0.01129.
^cTo convert values to millimoles per liter, multiply by 0.0259.
^dTo convert values to milliliters per second, multiply by 0.01667.

Table 4. Relationship between urine pH and individual features of the MS^a

Variable	Unadjusted (Standardized Regression Coefficient [95% CI])	Adjusted for BMI (Standardized Regression Coefficient [95% CI])	Multivariate Adjusted (Standardized Regression Coefficient [95% CI]) ^b	Multivariate Adjusted (Standardized Regression Coefficient [95% CI]) ^c
BMI	-0.314 (-0.471 to -0.157)			
Fasting glucose	-0.319 (-0.476 to -0.162)	-0.252 (-0.410 to -0.094)	-0.205 (-0.380 to -0.028)	-0.175 (-0.339 to -0.011)
Triglycerides ^d	-0.251 (-0.411 to -0.091)	-0.166 (-0.330 to -0.002)	-0.145 (-0.307 to 0.017)	-0.100 (-0.267 to 0.067)
Systolic BP	-0.326 (-0.483 to -0.169)	-0.263 (-0.420 to -0.106)	-0.206 (-0.390 to -0.022)	-0.186 (-0.369 to -0.003)
HDL cholesterol	0.274 (0.115 to 0.433)	0.204 (0.044 to 0.364)	0.226 (0.052 to 0.400)	0.185 (0.006 to 0.364)
HOMA-IR ^d	-0.317 (-0.489 to -0.156)	-0.219 (-0.428 to -0.010)	-0.253 (-0.415 to -0.091)	-0.221 (-0.421 to -0.021)

^aThe standardized regression coefficient (β) represents the change in urine pH for 1 SD change in each variable. CI, confidence interval.
^bAdjusted for age, gender, urine sulfate, and creatinine clearance.
^cAdjusted for BMI, age, gender, urine sulfate, and creatinine clearance.
^dVariable was log-transformed in the analysis.

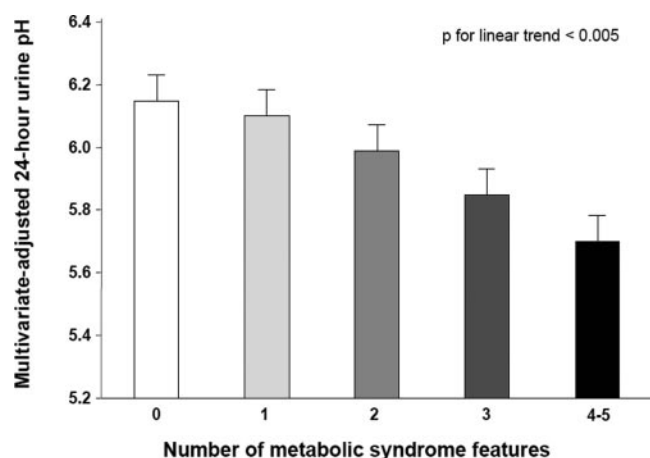


Figure 1. Mean 24-h urine pH adjusted for age, gender, creatinine clearance, and 24-h urine sulfate plotted against number of features of the metabolic syndrome (MS). Bars indicate means \pm SEM. $P < 0.005$ for linear trend. Test of linear trend was conducted by analysis of covariance model comparing urine pH with the number of MS abnormalities while adjusting for age, gender, creatinine clearance, and 24-h urine sulfate.

notion is supported by cross-sectional studies that show a significantly greater prevalence of uric acid nephrolithiasis among obese stone-forming individuals and in nephrolithiasis patients with type 2 diabetes (25–28). Insulin resistance is a common feature in obesity (29), type 2 diabetes (30), and the MS (2) and is thought to cause the overly acidic urine in patients with these conditions (14,21). This concept is supported by our finding of a significant relationship between 24-h urine pH and HOMA-IR, a measure of insulin resistance.

The exact pathophysiologic mechanism underlying the overly acidic urine in insulin resistance has not been fully elucidated. A low urine pH may result from increased acid excretion, impaired urinary buffering, or both. Higher NAE may occur because of lower intake of dietary alkali, greater ingestion of dietary acid, or higher endogenous acid production. In our study, urinary potassium, an indirect measure of dietary alkali intake, was not different in participants with and without the MS, suggesting that differences in alkali consumption are not likely to explain the differences in urine pH. Furthermore, the lower urine pH with the MS persisted after adjustment for urine sulfate, suggesting that dietary factors alone cannot account for the more acidic urine. Alternatively, these patients may have greater endogenous acid production, although we did not specifically investigate this possibility. A low urine pH may also result from impaired urine buffering. Ammonium is an important urinary buffer (31). Renal ammonium production and excretion are regulated by the ambient acid-base environment. Insulin influences these two processes (32,33), and mechanisms of acid-base homeostasis may be altered in a state of insulin resistance (13). Consistent with this possibility, participants with the MS in our cohort exhibited lower ammonium excretion per NAE (NH_4^+/NAE).

One of the limitations of this study is the evaluation of individuals while on random outpatient diets, because dietary

factors may influence urine pH. Although there was a tendency for urine sulfate to increase with increasing number of MS components, the relationship between urine pH and MS features persisted after controlling for urine sulfate.

Conclusions

This study is the first to demonstrate a relationship between the MS and low urine pH that is independent of age and renal function. In addition, a progressive decline in urine pH was noted with increasing number of MS features. The more acidic urine places patients with the MS at greater propensity for uric acid nephrolithiasis. Further studies are needed to elucidate the mechanism(s) responsible for the lower urine pH in individuals with the MS.

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Disclosures

None.

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See the related editorial, "Metabolic Syndrome: An Emerging Threat to Renal Function," on pages 869-871.