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Relationship between urine pH and abnormal glucose tolerance in a community-based study

Sakiko Yoshida[1], Teruki Miyake[1]*, Shin Yamamoto[1], Shinya Furukawa[2,3], Tetsuji Niiya[4], Hidenori Senba[1], Sayaka Kanzaki[1], Osamu Yoshida[1], Toru Ishihara[1], Mitsuhito Koizumi[1], Masashi Hirooka[1], Teru Kumagi[5], Masanori Abe[1], Kohichiro Kitai[6], Bunzo Matsuura[1], Yoichi Hiasa[1]

Departments of [1]Gastroenterology, Metabology, [2]Epidemiology and Preventive Medicine, Ehime University Graduate School of Medicine, [3]Epidemiology and Medical Statistics Unit, Translational Research Center, Ehime University Hospital, Toon, [4]Department of Internal Medicine, Matsuyama Shimin Hospital, Matsuyama, [5]Department of Community Medicine, Ehime University Graduate School of Medicine, Toon, and [6]Ehime General Health Care Association, Matsuyama, Ehime, Japan

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***Correspondence**
Teruki Miyake
Tel.: +81-89-960-5308
Fax: +81-89-960-5310
E-mail address:
teruki-ygc@umin.ac.jp

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ABSTRACT

Aims/Introduction: The association between urine pH and abnormal glucose tolerance in men and women is unclear; therefore, we carried out a community-based, cross-sectional study to investigate sex-specific associations between these values, possible indicators of prediabetes and type 2 diabetes.

Materials and Methods: We enrolled 4,945 Japanese individuals (2,490 men and 2,455 women), who had undergone annual health checkups. To investigate the relationship between low urine pH and abnormal glucose tolerance, participants were divided into three groups based on their fasting plasma glucose levels (<6.11 mmol/L, 6.11–6.99 mmol/L and ≥6.99 mmol/L), and three groups based on their glycated hemoglobin levels (≤44.3 mmol/mol, 44.3–47.5 mmol/mol and ≥47.5 mmol/mol). To examine the effects of urine pH on abnormal glucose tolerance, participants were categorized into five groups based on their urine pH (5.0, 5.5, 6.0, 6.5 and ≥7.0).

Results: Multivariate analysis adjusted for age, body mass index, systolic blood pressure, triglycerides, high-density lipoprotein cholesterol, uric acid, creatinine and antidiabetic agent use showed significant associations between low urine pH and both high fasting plasma glucose and high glycated hemoglobin levels (*P* for trend = 0.0260, 0.0075) in men. Furthermore, after the same adjustments, prevalence rates of abnormal glucose tolerance (≥6.11 mmol/L and ≥6.99 mmol/L), increased significantly as urine pH levels decreased (*P* for trend = 0.0483, 0.0181) in men. In women, a similar trend was observed without a significant difference.

Conclusions: Low urine pH is significantly associated with abnormal glucose tolerance; therefore, measuring urine pH might prove useful for identifying patients at high risk for diabetes.

INTRODUCTION

The prevalence of diabetes continues to increase worldwide, and it has been estimated that the total number of people with diabetes will rise from 171 million in 2000, to 366 million in 2030[1]. Diabetes leads to multiple complications, including cardiovascular disease[2] and diabetic nephropathy[3]. Furthermore, in 2013, an estimated 5.1 million adult deaths were attributable to diabetes[4]. Therefore, early identification of groups at high risk for developing this disease and provision of appropriate interventions is extremely important.

It has recently been reported that urine pH is associated with a variety of diseases; for example, low urine pH causes nephrolithiasis and affects its pathophysiology, therefore, making it a therapeutic target[5,6]. Furthermore, the prevalence of nephrolithiasis has increased among patients with metabolic syndrome and diabetes[7–11]. The relationship between urine pH and metabolic syndrome has been examined[12–14], and not only has low urine pH been associated with metabolic syndrome, but it has also been identified as a risk factor for its onset[14].

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Furthermore, other studies have shown that urine pH has an inverse correlation with body mass index (BMI)[15–17] and insulin resistance[12,18–20], which are associated with the onset of type 2 diabetes mellitus[21,22]. However, these studies involved specific populations, such as outpatients, or small populations, and they did not all differentiate between the sexes[12,18–20]. Thus, it remains unclear whether abnormal glucose tolerance levels, such as those seen in prediabetes and type 2 diabetes, are associated with urine pH.

In response to these facts, we undertook a large community-based, cross-sectional study to investigate associations between urine pH and levels of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), which can be indicators of prediabetes and type 2 diabetes in men and women.

METHODS

Participants and assessments

The present community-based, cross-sectional study began with a review of the medical records of 4,945 Japanese individuals who had undergone at least one annual health checkup at the Ehime General Health Care Association in Ehime, Japan, between April 2013 and March 2014. The group included 2,490 men and 2,455 women whose ages ranged from 23 to 86 years. The annual health checkups involved recording the individuals' medical histories (including all prescription medications), physical examinations, and measurements of anthropometric and routine biochemical variables. The participants' bodyweights and heights were measured while they wore light gowns and no shoes, and these measurements were used to calculate their BMIs. An automated sphygmomanometer was used to measure blood pressure while the participants were seated. Blood samples were drawn during the morning after overnight fasts of >10 h to measure levels of a variety of components, including FPG, HbA1c, total cholesterol, high-density lipoprotein cholesterol, uric acid and creatinine. Similarly, midstream urine samples were collected during the morning after overnight fasting, and these samples underwent dipstick testing.

Approval for this study was obtained from the Ehime University Hospital Research Ethics Board (approval ID #110405) in accordance with the 1995 Declaration of Helsinki. All of the study's procedures were carried out in accordance with the guidelines for good clinical practice, and fulfilled local ethical and legal requirements. To maintain anonymity, we assigned all participants numerical codes, and all data were stored in a secure database.

Statistical analysis

Statistical analyses were carried out using JMP software, version 11 (SAS Institute, Cary, NC, USA). To investigate the relationship between low urine pH and FPG levels, the participants were assigned to one of three groups based on their FPG levels (<6.11 mmol/L, 6.11–6.99 mmol/L or ≥6.99 mmol/L). To examine the association between HbA1c level and urine pH, participants were further assigned to one of three groups based on their HbA1c levels (≤44.3 mmol/mol, 44.3–47.5 mmol/mol or ≥47.5 mmol/mol) or (tertile ≤33.3 mmol/mol, 33.3–37.7 mmol/mol or ≥37.7 mmol/mol). Furthermore, to examine the effects of urine pH on abnormal glucose tolerance, the participants were assigned to one of five groups based on their urine pH values (5.0, 5.5, 6.0, 6.5 or ≥7.0). We defined the low urine pH value as ≤5.5, with reference to previous reports[13,18].

The one-way analysis of variance (ANOVA) was used to determine continuous variables, and the χ^2-test was used to analyze the categorical variables. Logistic regression analysis was carried out to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) of low urine pH in relation to high levels of FPG and HbA1c, and abnormal glucose tolerance in relation to levels of urine pH. Multiple logistic regression analysis was adjusted for the following variables associated with metabolic disease and renal function: age, BMI, systolic blood pressure, triglyceride level, high-density lipoprotein cholesterol level, uric acid level, creatinine level and antidiabetic agent use. The trend of association was assessed by using a logistic regression model that assigned consecutive integers to the categories of the exposure variables. Data are presented as means (standard deviations) or as numbers (percentages). *P*-values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics of the participants categorized according to their FPG levels are shown in Table 1. Among all study participants, those of both sexes who were assigned to one of the high FPG level categories (≥6.11 mmol/L) were older, and had higher BMIs, systolic blood pressures, triglyceride levels and uric acid levels, as well as low high-density lipoprotein cholesterol levels. Furthermore, the male participants who were in the higher FPG level categories had lower creatinine levels than did the male participants in the <6.11 mmol/L group. For both sexes, higher proportions in the abnormal glucose tolerance categories (≥6.11 mmol/L) had been prescribed antidiabetic agents. Higher proportions of the men in the high FPG level categories had lower urine pH values (≤5.5) than did those men in the <6.11 mmol/L category. In the women, although there was no significant difference, a similar trend was observed.

Relationship between low urine pH and FPG levels

A significant association between low urine pH and high FPG levels (≥6.11 mmol/L) was observed in men through a crude analysis (Table 2). Furthermore, after adjustment for age, BMI, systolic blood pressure, triglyceride level, high-density lipoprotein cholesterol level, uric acid level, creatinine level and antidiabetic agent use, the association between low urine pH and the category of 6.11–6.99 mmol/L yielded an OR of 0.98 and a 95% CI of 0.72–1.32. Likewise, low urine pH and its relationship to participants in the category of ≥6.99 mmol/L resulted in an OR of 1.72 and a 95% CI of 1.14–2.62 (*P* for

Table 1 | Baseline characteristics categorized according to fasting plasma glucose levels

	<6.11 mmol/L (*n* = 4,494: 2,136 men and 2,358 women)	6.11–6.99 mmol/L (*n* = 269: 204 men and 65 women)	≥6.99 mmol/L (*n* = 182: 150 men and 32 women)	*P*-value
Age (years)				
Men	46.9 (8.4)	53.0 (7.4)	52.0 (7.7)	<0.0001
Women	46.3 (8.6)	53.8 (8.5)	54.7 (8.6)	<0.0001
Body mass index (kg/m^2)				
Men	23.6 (3.0)	25.7 (4.2)	26.6 (4.2)	<0.0001
Women	21.6 (3.4)	25.5 (4.8)	27.7 (5.4)	<0.0001
Systolic blood pressure (mmHg)				
Men	112.8 (15.3)	120.3 (16.0)	121.1 (15.9)	<0.0001
Women	103.9 (15.4)	117.5 (19.6)	119.9 (19.8)	<0.0001
Triglycerides (mmol/L)				
Men	1.4 (1.2)	1.7 (1.1)	2.2 (2.6)	<0.0001
Women	0.9 (0.5)	1.3 (0.7)	1.5 (0.5)	<0.0001
High-density lipoprotein Cholesterol (mmol/L)				
Men	1.5 (0.4)	1.3 (0.3)	1.3 (0.4)	<0.0001
Women	1.8 (0.4)	1.6 (0.4)	1.5 (0.3)	<0.0001
Uric acid (μmol/L)				
Men	374.9 (71.9)	380.0 (71.7)	356.6 (74.1)	0.0054
Women	263.5 (1.2)	308.2 (7.4)	306.5 (10.5)	<0.0001
Creatinine (μmol/L)				
Men	77.8 (14.9)	76.2 (11.9)	74.0 (14.3)	0.0038
Women	56.6 (0.2)	56.6 (1.0)	53.4 (1.4)	0.0683
Antidiabetic agents, *n* (%)				
Men	9 (0.4)	16 (7.8)	66 (44.0)	<0.0001
Women	5 (0.2)	5 (7.7)	14 (43.8)	<0.0001
Urine pH, ≤5.5, *n* (%)				
Men	1,008 (47.2)	100 (49.0)	91 (60.7)	0.0059
Women	1,053 (44.7)	33 (50.8)	18 (56.3)	0.2695

Values are expressed as mean (standard deviation). For continuous values, differences among groups were assessed using one-way analysis of variance. The χ^2-test was used for comparisons of prevalence. A low urine pH value was defined as urine pH ≤5.5.

trend = 0.0260) in men (Table 2). In women, although the urine pH values did not show a significant association with FPG levels, a similar trend was observed (Table 2).

Relationship between low urine pH and HbA1c levels

The association between low urine pH and HbA1c levels showed a trend similar to the association with FPG. In men, a crude analysis showed that low urine pH is significantly associated with high HbA1c levels (Table S1). After adjustment for the aforementioned factors, multivariate analysis of the association between low urine pH and the category of 44.3–47.5 mmol/mol HbA1c levels yielded an OR of 0.66 and a 95% CI of 0.30–1.37, whereas the association with the ≥47.5 mmol/mol category resulted in an OR of 1.77 and a 95% CI of 1.22–2.57 (*P* for trend = 0.0075) in men (Table S2). In women, a similar trend without statistical significance was observed (Tables S1 and S2). Additionally, when participants were categorized based on their HbA1c levels into tertiles (≤33.3 mmol/mol, 33.3–37.7 mmol/mol or ≥37.7 mmol/mol), the association between low urine pH and HbA1c levels was significant in men (Table S3 and S4). However, urine pH showed no significant association with the HbA1c level tertile among women (Tables S3 and S4).

Relationship between abnormal glucose tolerance and urine pH

Table 3 shows the crude ORs and 95% CIs for the prevalence of abnormal glucose tolerance in relation to urine pH. As urine pH levels decreased, the prevalence rates of abnormal glucose tolerance levels (≥6.11 mmol/L and ≥6.99 mmol/L) increased significantly in men (*P* for trend = 0.0051, 0.0019, respectively). After adjustment for age, BMI, systolic blood pressure, triglyceride level, high-density lipoprotein cholesterol level, uric acid level, creatinine level and antidiabetic agent use, prevalence rates of abnormal glucose tolerance increased significantly as urine pH levels decreased (*P* for trend = 0.0483, 0.0181) in men (Table 3). However, no significant associations were found between urine pH and abnormal glucose tolerance in women. In addition, sex was included as a covariate, and the results of the analysis are shown in Tables S5 and S6. The crude ORs and 95% CIs for the prevalence of abnormal glucose tolerance in relation to urine pH are shown in Table S5. As urine pH

Table 2 | Crude and adjusted odds ratios and 95% confidence intervals for low urine pH in relation to fasting glucose levels

	<6.11 mmol/L (*n* = 4,494: 2,136 men and 2,358 women)	6.11–6.99 mmol/L (*n* = 269: 204 men and 65 women)	≥6.99 mmol/L (*n* = 182: 150 men and 32 women)	*P* for trend
Crude				
Low urine pH				
Men	Reference	1.04 (0.78–1.38)	1.71 (1.23–2.41)	0.0031
Women	Reference	1.27 (0.77–2.09)	1.58 (0.79–3.25)	0.1077
Adjusted				
Low urine pH				
Men	Reference	0.98 (0.72–1.32)	1.72 (1.14–2.62)	0.0260
Women	Reference	1.28 (0.76–2.16)	1.98 (0.85–4.66)	0.0511

The data presented are the odds ratio (95% confidence interval). Adjustments were made for age, body mass index, systolic blood pressure, triglyceride level, high-density lipoprotein cholesterol level, uric acid level, creatinine level and anti diabetic agent use. A low urine pH value was defined as urine pH ≤5.5.

levels decreased, prevalence rates of abnormal glucose tolerance levels increased significantly (*P* for trend = 0.0005, 0.0009). After adjustment for the aforementioned factors, as well as sex, prevalence rates of abnormal glucose tolerance also increased significantly as urine pH levels decreased (*P* for trend = 0.0228, 0.0320; Table S6).

DISCUSSION

The findings from the present community-based, cross-sectional study suggest that, in men, low urine pH is independently associated with a high prevalence of abnormal glucose tolerance. Furthermore, prevalence rates of abnormal glucose tolerance increased significantly as urine pH levels decreased. These significant associations remained after adjustments for potential confounding factors. In women, although the urine pH values did not show a significant association with prevalence rates of abnormal glucose tolerance, a similar trend was observed.

Several recent studies have described associations between low urine pH and impaired glucose tolerance. The findings from a study of 162 male participants with gout, carried out by Takahashi *et al.*[18], showed that the FPG levels were higher in participants with urine pH values of <5.5 as compared with participants with urine pH values of ≥5.5. Maalouf *et al.*[12] carried out a study that involved 148 outpatients who did not have either chronic kidney or kidney stone disease, and their multivariate analysis, which was adjusted for BMI, age, sex, urine sulfate levels and creatinine clearance rates, showed an inverse relationship between 24-h urine pH monitoring and FPG levels. However, the participants in these studies were selected from specific populations, and the patient numbers

Table 3 | Crude and adjusted odds ratios and 95% confidence intervals for abnormal glucose tolerance in relation to urine pH

	pH 5.0 (*n* = 1,289: 662 men and 627 women)	pH 5.5 (*n* = 1,014: 537 men and 477 women)	pH 6.0 (*n* = 1,053: 579 men and 474 women)	pH 6.5 (*n* = 868: 407 men and 461 women)	pH ≥7.0 (*n* = 721: 305 men and 416 women)	*P* for trend
Crude						
≥6.11 mmol/L						
Men	1.44 (1.13–1.83)	0.95 (0.72–1.25)	Reference	0.73 (0.52–1.01)	0.84 (0.58–1.19)	0.0051
Women	1.19 (0.75–1.85)	1.30 (0.79–2.07)	Reference	1.13 (0.67–1.83)	0.89 (0.49–1.52)	0.3978
≥6.99 mmol/L						
Men	1.78 (1.24–2.47)	1.07 (0.71–1.57)	Reference	0.82 (0.50–1.30)	0.67 (0.35–1.15)	0.0019
Women	1.14 (0.50–2.40)	1.63 (0.71–3.44)	Reference	1.21 (0.48–2.68)	1.13 (0.42–2.59)	0.7759
Adjusted						
≥6.11 mmol/L						
Men	1.16 (0.86–1.55)	1.16 (0.83–1.59)	Reference	0.69 (0.46–1.02)	0.78 (0.50–1.17)	0.0483
Women	1.10 (0.63–1.86)	1.69 (0.96–2.88)	Reference	0.87 (0.46–1.54)	0.86 (0.44–1.58)	0.2697
≥6.99 mmol/L						
Men	1.35 (0.87–2.08)	1.48 (0.90–2.38)	Reference	0.76 (0.41–1.33)	0.57 (0.27–1.11)	0.0181
Women	0.88 (0.28–2.40)	3.35 (1.18–9.12)	Reference	0.63 (0.19–1.78)	1.54 (0.49–4.25)	0.7605

The data presented are the odds ratio (95% confidence interval). Adjustments were made for age, body mass index, systolic blood pressure, triglyceride level, high-density lipoprotein cholesterol level, uric acid level, creatinine level and antidiabetic agent use.

were small. Otsuki *et al.*[19] recruited 1,503 male participants who underwent health checkups at the healthcare center in Kinki Central Hospital, and examined the associations between FPG levels and urine pH values. They divided the participants into four groups based on their urine pH values (5, 5.5, 6 and pH ≥6.5), and the study's findings showed that lower urine pH values were associated with an increase in FPG levels[19]. Cho *et al.*[13], in their study of 4,662 individuals who participated in the fifth Korea National Health and Nutrition Examination Survey, showed that low urine pH values (<5.5) were associated with elevated FPG levels in a multivariate analysis that was adjusted for age, sex, blood urea nitrogen, smoking status, drinking status and regular exercise. The findings from a population-based study of 69,094 participants, carried out by Hara *et al.*, in which the participants were divided into four groups based on their urine pH values, (≤5, 5.5, 6.0 and ≥6.5), and according to sex, showed significant inverse correlations between urine pH values and FPG levels when a trend test was used[14]. However, these studies either did not consider sex differences[13,18,19], or the data were not scrutinized using multivariate analyses[14,18,19]. Additionally, the studies did not examine the association between urine pH and levels of FPG and HbA1c, possible indicators of prediabetes and type 2 diabetes, which are the primary findings of the current study.

Mechanisms explaining the relationship between low urine pH and abnormal glucose tolerance might be associated with insulin resistance. Abate *et al.*[20] used a hyperinsulinemic euglycemic clamp and 24-h urine pH monitoring to examine insulin resistance in 55 healthy volunteers and 13 patients with uric acid nephrolithiasis, and reported that insulin resistance was associated with a low urine pH. Additionally, insulin increases renal ammonium production and excretion, and this production/excretion from the renal proximal tubules is reduced in patients with insulin resistance, which lowers urine pH[23]. Conversely, one experimental study showed that insulin increases Na^+/H^+ exchanger activity in a time- and concentration-dependent manner in the proximal tubules; therefore, high insulin levels induced by insulin resistance also lower urine pH[24].

Gluconeogenesis might also affect the relationship between plasma glucose levels and the urine pH, because it increases in the kidney in an environment of chronic acidosis[25]. Furthermore, to counteract acidosis, the extraction of glutamine to the proximal tubule's cells increases not only from the lumen, but also from the blood. Its catabolism induces the transport of HCO_3^- ions to the blood by the $Na^+/3HCO_3^-$ cotransporter, and increases expression of the Na^+/H^+ exchanger that contributes to the transport of ammonium ions to the lumen, thus lowering urine pH. In addition, the catabolism of glutamine simultaneously induces gluconeogenesis in the proximal tubule cells; therefore, individuals with lower urine pH values have higher plasma glucose levels.

The differences between men and women might be associated with the number of individuals with abnormal glucose tolerance. The number of female participants with abnormal glucose tolerance was small, which might explain why the association between low urine pH and abnormal glucose tolerance was not significant in women. However, the differences between men and women might be associated with the differences in the distribution of adipose tissue and estrogen levels[26]. Men have higher amounts of visceral and hepatic adipose tissue, whereas women have more peripheral and subcutaneous adipose tissue. Increases in the levels of visceral and hepatic adipose tissue reduce the level of adiponectin, which lowers glucose production in the liver and improves insulin sensitivity in both muscles and the liver[27]. Furthermore, the level of adiponectin is lower in men than in women[28]. Estrogen has favorable effects on insulin, glucose homeostasis and adipose tissue distribution, and is reported to protect against hyperglycemia by reducing hepatic glucose production and enhancing glucose transport in the muscles[29]. Therefore, being male might stimulate more insulin resistance, and, thus, men might be more apt subjects to show associations between low urine pH and abnormal glucose tolerance than women.

Tables S1 and S2 show a U-shaped association between low urine pH and HbA1c level. However, the present analysis also showed a significant trend for the association between urine pH and HbA1c level. Additionally, after categorizing the participants according to tertiles of HbA1c level, the U-shaped association could not be detected. Therefore, we believe the deflection of the number of participants generated the U-shape.

One of the strengths of the present study was the fact that the participants were selected from a general population. Furthermore, we examined the relationship between urine pH and levels of both FPG and HbA1c, possible indicators of prediabetes, and type 2 diabetes. Nevertheless, there were some limitations to the present study. First, we used spot urine tests to measure urine pH rather than 24-h urine monitoring, although it has been reported that urine pH values measured by both methods are comparable[30]. Second, we measured urine pH using simple dipstick testing; however, this method has been reported to yield data as reliable as those generated by electrochemical pH meters[31]. Furthermore, because measuring urine pH using dipstick testing is simple, non-invasive and inexpensive, it might be useful in screening for abnormal glucose tolerance in high-risk male patients. Third, we used only one blood test to categorize the participants, which might have led to the misclassification of the participants. Fourth, we could not examine other covariates, such as renal tubular acidosis, urinary tract infections, medications and diet. Furthermore, we did not evaluate the effects menopause has on several metabolic disorders. Finally, the present study was cross-sectional, and we were unable to prove causality, and the results obtained in this study might therefore be due to reverse causality. Future studies using a prospective validation design are, therefore, necessary to further evaluate this relationship.

Despite these limitations, the findings of our large, community-based study show a significant association between low urine pH and abnormal glucose tolerance in men, and a similar

trend in women. Thus, measuring urine pH might be an important tool in screening for abnormal glucose tolerance levels in patients at high risk for diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Wild S, Roglic G, Green A, *et al*. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27: 1047–1053.
2. Leon B, Maddox T. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015; 6: 1246–1258.
3. Partanen J, Niskanen L, Lehtinen J, *et al*. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333: 89–94.
4. IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: estimates for the year 2013. *Diabetes Res Clin Pract* 2015; 109: 461–465.
5. Pak CY, Sakhaee K, Peterson RD, *et al*. Biochemical profile of idiopathic uric acid nephrolithiasis. *Kidney Int* 2001; 60: 757–761.
6. Sakhaee K, Nicar M, Hill K, *et al*. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney Int* 1983; 24: 348–352.
7. Meydan N, Barutca S, Caliskan S, *et al*. Urinary stone disease in diabetes mellitus. *Scand J Urol Nephrol* 2003; 37: 64–70.
8. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 2005; 68: 1230–1235.
9. Lieske JC, de la Vega LS, Gettman MT, *et al*. Diabetes mellitus and the risk of urinary tract stones: a population-based case-control study. *Am J Kidney Dis* 2006; 48: 897–904.
10. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA* 2005; 293: 455–462.
11. West B, Luke A, Durazo-Arvizu RA, *et al*. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988–1994. *Am J Kidney Dis* 2008; 51: 741–747.
12. 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.
13. 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.
14. 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.
15. Maalouf NM, Sakhaee K, Parks JH, *et al*. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 2004; 65: 1422–1425.
16. Taylor EN, Curhan GC. Body size and 24-hour urine composition. *Am J Kidney Dis* 2006; 48: 905–915.
17. 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.
18. Takahashi S, Inokuchi T, Kobayashi T, *et al*. Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPARalpha agonists on urine pH. *Horm Metab Res* 2007; 39: 511–514.
19. 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.
20. Abate N, Chandalia M, Cabo-Chan AV, *et al*. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int* 2004; 65: 386–392.
21. Wilson PW, D'Agostino RB, Parise H, *et al*. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005; 112: 3066–3072.
22. Lorenzo C, Okoloise M, Williams K, *et al*. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care* 2003; 26: 3153–3159.
23. Sakhaee K, Adams-Huet B, Moe OW, *et al*. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. *Kidney Int* 2002; 62: 971–979.
24. Klisic J, Hu MC, Nief V, *et al*. Insulin activates Na(+)/H(+) exchanger 3: biphasic response and glucocorticoid dependence. *Am J Physiol Renal Physiol* 2002; 283: F532–F539.
25. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. *Clin J Am Soc Nephrol* 2014; 9: 1627–1638.
26. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. *Gend Med* 2009; 6 (Suppl 1): 60–75.
27. Yamauchi T, Kamon J, Waki H, *et al*. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; 7: 941–946.
28. Cnop M, Havel PJ, Utzschneider KM, *et al*. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 2003; 46: 459–469.

29. Louet JF, LeMay C, Mauvais-Jarvis F. Antidiabetic actions of estrogen: insight from human and genetic mouse models. *Curr Atheroscler Rep* 2004; 6: 180–185.
30. Welch AA, Mulligan A, Bingham SA, *et al*. Urine pH is an indicator of dietary acid-base load, fruit and vegetables and meat intakes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk population study. *Br J Nutr* 2008; 99: 1335–1343.
31. Desai RA, Assimos DG. Accuracy of urinary dipstick testing for pH manipulation therapy. *J Endourol* 2008; 22: 1367–1370.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Crude odds ratios and 95% CIs for low urine pH in relation to glycated hemoglobin levels.
Table S2 | Adjusted odds ratios and 95% confidence intervals for low urine pH in relation to glycated hemoglobin levels.
Table S3 | Crude odds ratios and 95% confidence intervals for low urine pH in relation to glycated hemoglobin levels.
Table S4 | Adjusted odds ratios and 95% confidence intervals for low urine pH in relation to glycated hemoglobin levels.
Table S5 | Crude odds ratios and 95% confidence intervals for abnormal glucose tolerance in relation to urine pH.
Table S6 | Adjusted odds ratios and 95% confidence intervals for abnormal glucose tolerance in relation to urine pH.