Metabolic Basis for Low Urine pH in Type 2 Diabetes

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Background and objectives: Type 2 diabetes is associated with excessively low urine pH, which increases the risk for uric acid nephrolithiasis. This study was conducted to assess the metabolic basis responsible for the excessive urinary acidity of individuals with type 2 diabetes.

Design, setting, participants, & measurements: Nine non–stone-forming patients who had type 2 diabetes and low urine pH and 16 age- and body mass index–matched non–stone-forming volunteers without type 2 diabetes were maintained on a constant metabolic diet for 7 days, and 24-hour urine was collected on the last 2 days of the diet.

Results: Urine dietary markers (potassium, sulfate, phosphorus, and urea nitrogen) were not different between the two groups. Patients with type 2 diabetes exhibited a significantly lower 24-hour urine pH (5.45 ± 0.27 *versus* 5.90 ± 0.42; $P < 0.01$) and higher net acid excretion (NAE; 57 ± 12 *versus* 38 ± 18 mEq/d; $P < 0.01$) compared with control subjects. The proportion of NAE excreted as ammonium (NH_4^+/NAE) was significantly lower in patients with type 2 diabetes than in control subjects (0.70 ± 0.12 *versus* 0.94 ± 0.36; $P < 0.01$); however, the greater NAE in patients with type 2 diabetes was not accounted for by the differences in unmeasured urinary anions.

Conclusions: The overly acidic urine in patients with type 2 diabetes persists after controlling for dietary factors, body size, and age. The lower pH is due to a combination of greater NAE and lower use of ammonia buffers in patients with diabetes, which predisposes them to uric acid urolithiasis.

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Type 2 diabetes is associated with an increased risk for nephrolithiasis (1,2), particularly uric acid (UA) stones (3–5). Urine pH is a key determinant of UA solubility in urine, and an excessively acidic urine is recognized as a major risk factor for UA precipitation and stone formation (5,6). Unduly acidic urine (pH <5.5) is frequently encountered in patients who have type 2 diabetes both with (3,4) and without UA stones (7).

A number of features of type 2 diabetes may explain its association with enhanced urinary acidity. Cross-sectional and metabolic studies have demonstrated a link between insulin resistance, a hallmark of type 2 diabetes, and low urine pH (8,9). Obesity, a common finding in patients with type 2 diabetes, is also associated with lower urine pH (10,11). To date, the role of other confounding factors, such as impaired renal function (12), age (13), ethnicity (14), and dietary factors, that also known to influence urine pH have not been investigated in this population (3,4,7). To understand better the metabolic factors that lead to an unduly acidic urine and thus increase the risk for UA stones in individuals with type 2 diabetes, we conducted a metabolic study under a controlled dietary environment while controlling other variables that are known to influence urinary pH.

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Materials and Methods

Participants

Volunteers with and without type 2 diabetes were recruited for this study *via* local advertisements. The diagnosis of type 2 diabetes was made by the participants' personal physicians before enrollment on the basis of elevated fasting serum glucose (≥126 mg/dl) on two separate occasions. Control subjects without diabetes were recruited as overweight or obese (body mass index [BMI] ≥25 kg/m^2) participants without a history of type 2 diabetes. Inclusion criteria were age >30 years and ability to provide informed consent. Excluded were pregnant women, individuals with a known history of kidney stone disease, chronic diarrhea, creatinine clearance <70 ml/min, and those who were treated with diuretics or alkali therapy. In the type 2 diabetes group, treatment with insulin and/or thiazolidinediones was an additional exclusion criterion. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center (Dallas, TX), and all participants provided informed consent. Patients with type 2 diabetes used either metformin only (six patients) or a combination of metformin and a sulfonylurea (three patients) for glycemic control.

Study Procedures

Participant were provided a fixed metabolic diet for 7 days (30% fat, 55% carbohydrate, 15% protein, and 300 mg of cholesterol per day, providing 400 mg of calcium, 800 mg of phosphorus, 100 mEq of sodium, fixed acid ash content, and a total of 3000 ml of distilled water). They consumed the diet on an outpatient basis during the first 5 days and returned to the inpatient General Clinical Research Center at University of Texas Southwestern on the evening of the fifth day. During the last 2 days on the diet, participants collected two 24-hour urine collections while in the General Clinical Research Center, and two fasting blood samples were obtained at the end of each collection. Urine was collected under mineral oil and kept refrigerated until analysis.

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Measurements

Serum measurements included electrolytes, creatinine, glucose, and UA using a multichannel analyzer. Twenty-four-hour urine was analyzed for total volume, pH, creatinine, sodium, potassium, calcium, magnesium, ammonium (NH_4^+), chloride, phosphorus, UA, oxalate, and citrate as described previously (6). Urine titratable acidity (TA) was measured as the milliequivalents of OH^- required to bring the original pH to 7.4. Urine bicarbonate was calculated from urine pH and Pco_2. Net acid excretion (NAE) was calculated as (NH_4^+ + TA) − (citrate + bicarbonate), all expressed in milliequivalents. The fraction of NAE excreted as ammonium (NH_4^+/NAE) was also determined. Unmeasured urine anions (UUA) was computed as the difference between measured cations (sodium, potassium, calcium, magnesium, and NH_4^+) and measured anions (chloride, phosphorus, urate, oxalate, creatinate [the proportion of urinary creatinine in anionic form at prevalent urinary pH], bicarbonate, and citrate), all expressed in milliequivalents, similar to the calculation described by Kamel *et al.* (15). Net gastrointestinal (GI) alkali absorption was calculated as described previously (16).

Statistical Analysis

Results are presented as means ± SD. Between-group comparisons were conducted using the *t* test. Fisher exact test was used in the comparison of gender and race distribution between the two groups. Statistical analysis was performed using SAS 9.1.3 (SAS Institute, Cary, NC).

Results

Demographics

The demographic characteristics of study participants are shown in Table 1. The two groups were well matched with respect to age, gender, ethnicity, and BMI, with a mean age of approximately 53 years and mean BMI of 31 kg/m^2.

Serum Parameters

Serum electrolytes did not differ significantly between the two groups (Table 2), except for a tendency for higher serum potassium in the type 2 diabetes group (4.1 ± 0.2 *versus* 4.4 ± 0.4 mmol/L; $P = 0.06$). Patients with type 2 diabetes had a higher hemoglobin A_{1c} concentration than control subjects (6.0 ± 0.6 *versus* 5.3 ± 0.3%; $P < 0.01$), although none of the patients with type 2 diabetes had uncontrolled diabetes (maximum hemoglobin A_{1c} 7.7%).

Urine Parameters

Urinary biochemical findings are shown in Table 3. Urine sulfate, a marker of dietary acid intake, was not different between the two groups (38 ± 7 *versus* 37 ± 7 mEq/d; $P = 0.67$).

Table 1. Demographic characteristics of study participants

Characteristic	Control Subjects ($n = 16$)	Patients with Type 2 Diabetes ($n = 9$)	*P*
Age (years; mean ± SD)	52 ± 10	54 ± 11	0.52
BMI (kg/m^2; mean ± SD)	30 ± 3	31 ± 4	0.25
Female gender (%)	50	44	1.00
White race (%)	63	78	0.66

Table 2. Serum biochemistry

Parameter	Control Subjects ($n = 16$)	Patients with Type 2 Diabetes ($n = 9$)	*P*
Sodium (mmol/L)	138 ± 3	138 ± 3	0.76
Potassium (mmol/L)	4.1 ± 0.2	4.4 ± 0.4	0.06
Chloride (mmol/L)	106 ± 2	106 ± 2	0.81
Bicarbonate (mmol/L)	27 ± 2	27 ± 2	0.72
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	0.84
UA (mg/dl)	6.1 ± 1.2	7.1 ± 1.6	0.09
Glucose (mg/dl)	94 ± 9	100 ± 17	0.23
Hemoglobin A_{1c} (%)	5.3 ± 0.3	6.0 ± 0.6	<0.01
Creatinine clearance (ml/min)	120 ± 27	111 ± 20	0.33

Data are means ± SD.

Table 3. Urine biochemistry

Parameter	Control Subjects ($n = 16$)	Patients with Type 2 Diabetes ($n = 9$)	*P*
Volume (L/d)	2.7 ± 0.4	2.5 ± 0.6	0.26
pH	5.90 ± 0.42	5.45 ± 0.27	<0.01
Creatinine (mg/d)	1503 ± 410	1540 ± 550	0.81
Sodium (mEq/d)	97 ± 38	75 ± 30	0.03
Potassium (mEq/d)	36 ± 12	32 ± 10	0.20
Calcium (mg/d)	157 ± 60	160 ± 87	0.92
Magnesium (mg/d)	95 ± 20	71 ± 23	<0.01
Sulfate (mEq/d)	38 ± 7	37 ± 7	0.67
Urea nitrogen (g/d)	8.2 ± 1.6	8.1 ± 1.8	0.80
Phosphorus (mg/d)	518 ± 159	520 ± 189	0.98
Oxalate (mg/d)	23 ± 4	25 ± 5	0.05
Chloride (mEq/d)	93 ± 29	78 ± 18	0.04
UA (mg/d)	518 ± 136	535 ± 147	0.70
Citrate (mg/d)	762 ± 236	499 ± 316	<0.01
Citrate (mEq/d)	11 ± 3	6 ± 4	<0.01
Ammonium (mEq/d)	32 ± 10	39 ± 5	<0.01
TA (mEq/d)	20 ± 8	25 ± 6	<0.01
Bicarbonate (mEq/d)	4 ± 4	1 ± 2	<0.01
NAE (mEq/d)	38 ± 18	57 ± 12	<0.01
NH_4^+/NAE	0.94 ± 0.36	0.70 ± 0.12	<0.01
NAE/sulfate	0.99 ± 0.34	1.57 ± 0.38	<0.01
UUA (mEq/d)	1 ± 5	2 ± 7	0.43
NGIA (mEq/d)	26 ± 18	12 ± 22	0.03

Data are means ± SD and represent the mean of two 24-hour urine collections for each participant. NGIA, net GI alkali absorption.

Urine urea nitrogen, phosphorus, and potassium, additional dietary markers, were also not different. Urine pH was significantly lower in the type 2 diabetes group (5.45 ± 0.27 *versus* 5.90 ± 0.42; $P < 0.01$; Figure 1). Compared with control subjects, the type 2 diabetes group also exhibited higher TA (25 ±

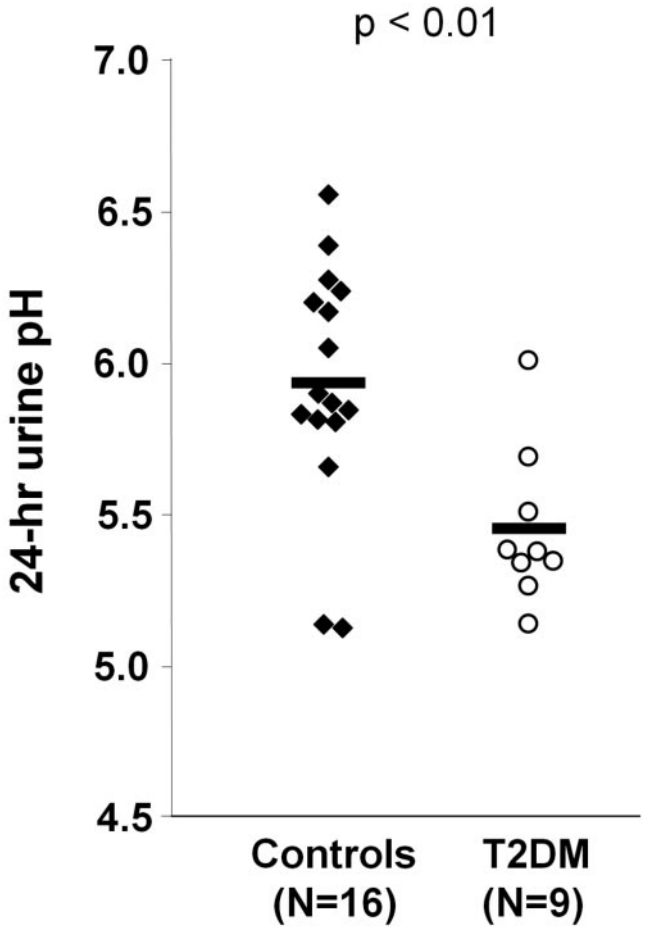

Figure 1. Comparison of 24-hour urine pH between nine volunteers with type 2 diabetes (T2DM; ○) and 16 age- and BMI-matched volunteers without type 2 diabetes (Controls; ♦) evaluated while consuming a fixed metabolic diet. Horizontal bars indicate means for each group. Patients with type 2 diabetes exhibited a significantly lower 24-h urine pH (5.45 ± 0.27 *versus* 5.90 ± 0.42; $P < 0.01$) compared with control subjects. Results represent the mean of two 24-hour urine collections for each participant.

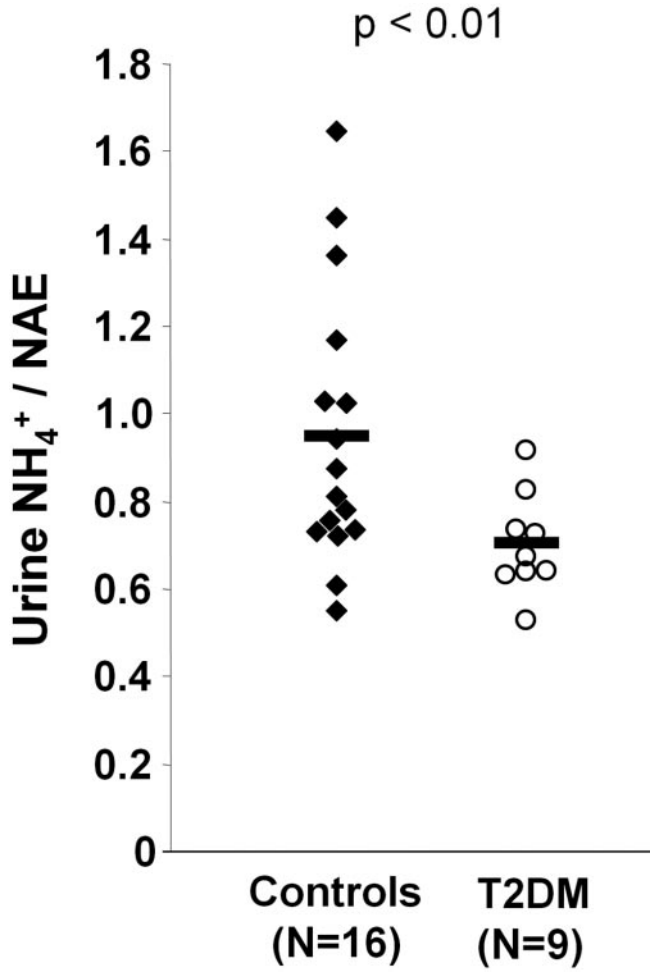

Figure 2. Proportion of NAE excreted as ammonium (NH_4^+/NAE) in nine volunteers with type 2 diabetes (T2DM; ○) and 16 age- and BMI-matched volunteers without type 2 diabetes (Controls; ♦) evaluated while consuming a fixed metabolic diet. Horizontal bars indicate means for each group. NH_4^+/NAE was significantly lower in patients with type 2 diabetes than in control subjects (0.70 ± 0.12 *versus* 0.94 ± 0.36; $P < 0.01$). Results represent the mean of two 24-hour urine collections for each participant.

6 *versus* 20 ± 8 mEq/d; $P < 0.01$) and NAE (57 ± 12 *versus* 38 ± 18 mEq/d; $P < 0.01$). The significantly greater NAE in patients with type 2 diabetes (19 mEq/d greater than control subjects) was due to a combination of higher urine ammonium (7 mEq/d) and TA (5 mEq/d) and lower urine citrate (5 mEq/d) and bicarbonate (3 mEq/d). The ratio of NAE to sulfate was significantly higher in patients with type 2 diabetes (1.57 ± 0.38 *versus* 0.99 ± 0.34; $P < 0.01$). The proportion of NAE excreted as ammonium (NH_4^+/NAE) was markedly lower in patients with type 2 diabetes (0.70 ± 0.12 *versus* 0.94 ± 0.36; $P < 0.01$; Figure 2).

Increased endogenous organic acid production at a steady state normally results in urinary excretion of ammonium accompanied by the organic anion. UUA, the difference between measured cations and anions, should be a surrogate of this entity in the urine. UUA was not significantly different between the two groups (1 ± 5 mEq/d for control subjects *versus* 2 ± 7 mEq/d for patients with type 2 diabetes; $P = 0.43$), although there was a considerable amount of variation. Urine sodium, chloride, magnesium, and citrate and net GI alkali absorption were significantly lower in patients with type 2 diabetes (Table 3) despite identical dietary intake.

Discussion

This is the first study to explore the mechanisms underlying unduly acidic urine in patients with type 2 diabetes and without stones while controlling for dietary and other variables that are known to influence urine pH. The main findings are that patients with type 2 diabetes exhibit greater NAE and excrete a lower proportion of NAE as NH_4^+ than do individuals who do not have diabetes and are of similar age and body weight. Furthermore, the greater NAE in patients with type 2 diabetes is not accounted for by dietary factors or unmeasured anions in urine (Table 3).

The lower urine pH in individuals with type 2 diabetes seen in this study was previously demonstrated by our group (3,7) and others (4); however, those studies did not control for various factors that influence urinary pH, such as consumption of acid-rich foods, age, gender, renal function, and BMI. In contrast, this study overcame these limitations by controlling dietary influences and matching for age, gender, and body size. To remove the dietary confounder, we provided the same metabolic diet to the two groups of participants. Adherence to the metabolic diet was confirmed by similar urine sulfate, urea nitrogen, phosphorus, and potassium between the two groups.

Besides dietary factors, unduly acidic urine could be due to increased acid production, increased GI alkali loss, and/or defective urinary buffers such as NH_4^+ excretion (17). Given that net acid production matches NAE at a steady state, our findings of markedly higher NAE in patients with type 2 diabetes *versus* control subjects (57 ± 12 *versus* 38 ± 18; $P < 0.01$) suggests that net acid production is significantly higher in patients with type 2 diabetes. The source and nature of the putative acid anions remain unknown. We used unmeasured urinary anion, calculated as the difference between all measured urinary cations and anions, as a surrogate measure of possible overproduction of organic acid, which should leave an anion as a footprint; however, this parameter was not significantly different between the two groups in our study (2 ± 7 *versus* 1 ± 5 mEq/d; $P = 0.43$). The discrepancy between NAE and UUA suggests that increased NAE in patients with type 2 diabetes may potentially be due to net GI alkali loss. Although GI alkali absorption was not directly measured, the findings of lower urinary sodium, magnesium, and chloride and calculated net GI alkali absorption may suggest subtle GI alkali loss in patients with type 2 diabetes (Table 3). The mechanism of such GI alkali loss and its association with type 2 diabetes has not yet been investigated. One potential mechanism is pancreatic fat accumulation described in individuals with type 2 diabetes (18,19), which could influence pancreatic exocrine function and bicarbonate secretion, resulting in GI alkali loss. Alternatively, differences in gut microbiota (20) or longer colonic transit time in patients with type 2 diabetes (21) could lead to more bacterial fermentation of colonic content and secondarily to greater organic anion generation and absorption.

Increased endogenous acid production and/or GI alkali loss are not sufficient to cause low urine pH if the appropriate buffers are present in sufficient quantities. The unduly acidic urine in our participants mandates a second defect. Because of its open nature (as opposed to closed buffers such as phosphate) and large capacity for upregulation, NH_3 is a major urinary buffer (22). Defective NH_4^+ excretion has been shown under a fixed metabolic diet in patients with idiopathic UA stone forming (6). In this study, impaired NH_4^+ excretion was shown under metabolic conditions in patients with type 2 diabetes as low NH_4^+/NAE ratio. These results are consistent with biochemical abnormalities previously demonstrated in Zucker diabetic fatty (ZDF) rats, an established animal model of obesity that develops type 2 diabetes (23,24). In this animal model, urinary pH and NH_4^+ excretion were significantly lower and urinary TA was significantly higher than in lean control animals; therefore, impaired ammonium excretion is not a defect specific to UA stone formers but also seen in patients with type 2 diabetes. A potential mechanism for the acidic urine in these two conditions is increased fatty acid provision to the renal proximal tubule, which leads to accumulation of fatty acid and triglycerides that may impair ammonium production and secretion (23,25). Although such a mechanism has been shown in animal and cell models, to our knowledge, it has not been tested in humans. Because serum potassium was slightly higher in patients with type 2 diabetes in our study and hyperkalemia suppresses both ammoniagenesis (26) and NH_4^+ transport in the thick ascending loop (27), we examined the relationship between urine NH_4^+ and serum potassium in the two groups. No decline in urine NH_4^+ was seen with increasing serum potassium in either group (data not shown), suggesting that the small differences in serum potassium do not explain the impaired ammoniagenesis seen in the type 2 diabetes group.

The consequences of an unduly acidic urine in patients with type 2 diabetes may have a significant clinical impact. Protonated UA, the predominant form of UA in urine at 37°C when ambient pH is <5.35 (28), is substantially less soluble than urate salts, favoring its precipitation and potential stone formation. Because urine pH exhibits diurnal fluctuations, 24-hour urine collections may not accurately reflect the duration that urine pH is <5.35 in a given day (29). Furthermore, our 24-hour urine and fasting blood collections may have missed potential postprandial differences in GI acid loads that can transiently alter urine pH.

Our results support the findings of several cross-sectional studies that found greater propensity to and prevalence of UA stones among patients with type 2 diabetes (2–4,7). For the first time, this study explored the metabolic basis and provided that data linking type 2 diabetes and UA stone formation, thereby improving our understanding of the pathophysiologic relationship between these two conditions and providing a foundation for future therapeutic strategies.

Conclusions

The overly acidic urine, which predisposes patients with type 2 diabetes to UA stone formation, persists after controlling for dietary factors, body size, and age. The greater NAE is not accompanied by increased buffering by ammonia in patients with diabetes. The mechanisms of both of these defects need to be further explored.

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Disclosures

None.

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