Kidney International, Vol. 65 (2004), pp. 386–392

HORMONES – CYTOKINES – SIGNALING

The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance

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The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance.

Background. Uric acid nephrolithiasis primarily results from low urinary pH, which increases the concentration of the insoluble undissociated uric acid, causing formation of both uric acid and mixed uric acid/calcium oxalate stones. These patients have recently been described as exhibiting features of insulin resistance. This study was designed to evaluate if insulin resistance is associated with excessively low urinary pH in overtly healthy volunteers (non-stone formers) and if insulin resistance may explain the excessively low urinary pH in patients with uric acid nephrolithiasis.

Methods. Fifty-five healthy volunteers (non stone-formers) with a large range of body mass index and 13 patients with recurrent uric acid nephrolithiasis underwent hyperinsulinemic euglycemic clamp, 24-hour urinary studies, and anthropometric measurements of adiposity. A subgroup of 35 non-stone formers had 2-hour timed urinary collection before and during the hyperinsulinemic phase of the clamp studies.

Results. For the non-stone former population, low insulin sensitivity measured as glucose disposal rate significantly correlated with low 24-hour urinary pH ($r = 0.35$; $P = 0.01$). In addition to the previously described acidic urine pH and hypouricosuria, patients with recurrent uric acid nephrolithiasis were found to be severely insulin resistant (glucose disposal rate: uric acid stone-formers vs. normals; 4.1 ± 1.3 vs. 6.9 ± 2.1 mg/min/kg of lean body mass, $P = 0.008$). Acute hyperinsulinemia was associated with higher urinary pH (6.1 ± 0.7 at baseline to 6.8 ± 0.7 during hyperinsulinemia; $P < 0.0001$), urinary ammonia excretion (2.7 ± 1.6 mEq/2 hr at baseline and 4.0 ± 2.6 mEq/2 hr $P = 0.002$) and urinary citrate excretion (48 ± 33 mg/2 hr at baseline and 113 ± 68 mg/2 hr $P < 0.0001$).

Conclusion. We conclude that one renal manifestation of insulin resistance may be low urinary ammonium and pH. This defect can result in increased risk of uric acid precipitation despite normouricosuria.

Key words: insulin resistance, uric acid stones, renal acidification, metabolic syndrome, nephrolithiasis.

Received for publication April 3, 2003
and in revised form July 9, 2003
Accepted for publication August 26, 2003

An increasing percentage of our population is affected by obesity and the metabolic syndrome, a condition metabolically characterized by insulin resistance and clinically defined by the clustering of abdominal obesity, dyslipidemia, elevated blood pressure, and elevated fasting plasma glucose [1–3]. We have recently reported that patients with recurrent uric acid kidney stones manifest clinical and metabolic abnormalities consistent with the metabolic syndrome [4, 5]. Uric acid stone formers typically have urinary pH <5.5. This results in increased concentrations of the sparingly soluble undissociated uric acid (pK_a 5.5), which directly promotes formation of uric acid stones [5–8]. Calcium oxalate stones can also develop from uric acid–induced crystallization of calcium salts [8–10]. The term "gouty diathesis" has been coined to describe this empiric collection of findings [11, 12]. Because of the overlap of clinical features between gouty diathesis and the metabolic syndrome [13], the question arises whether defective biologic activity of insulin also affects urinary acidification, the main pathophysiologic abnormality of gouty diathesis. Little is known about the physiologic role of insulin in the kidney beyond renal gluconeogenesis [14]. However, insulin has been shown to be antinatriuretic [15–18], and stimulate renal Na+ transport in vitro [19–20] and ammonium production from L-glutamine in renal proximal tubules [21, 22]. It is therefore possible that impaired biologic activity of insulin in insulin-resistant individuals extends beyond abnormalities in peripheral glucose utilization to abnormalities in urinary acidification. This study was designed to evaluate whether insulin resistance is associated with excessively low urinary pH in overtly healthy volunteers (non-stone formers) and whether insulin resistance may explain the excessively low urinary pH in patients with uric acid nephrolithiasis.

METHODS

Experimental subjects

A total of 55 non-stone former volunteers (33 males and 22 females) with a wide range of adiposity (body fat between 6% and 47% of body weight) were included in this study. An additional group of 13 patients (11 males and 2 females) with diagnosis of uric acid urolithiasis was enrolled from the stone clinic at the Center of Mineral Metabolism and Clinical Research of the University of Texas Southwestern Medical Center. The ethnic composition was: 47 Caucasians, 17 Asian Indians, 2 Hispanics, and 2 African Americans). Subjects with chronic diarrhea, impaired renal function (creatinine clearance less than 60 mL/min), urinary tract infection, liver disease, and cardiovascular disease, and those on converting enzyme inhibitors, angiotensin receptor blockers, or β-blockers were excluded. Subjects who were receiving lipid-altering drugs, who had abnormal thyroid function tests or proteinuria, or were participating in strenuous physical exercise programs were also excluded from the study. The stone-formers were instructed to discontinue all medications or treatment for renal stones (thiazide, alkali therapy) 1 month prior to entering the study. No one received drugs that could affect urate metabolism (such as allopurinol or a high dose acetyl-salicylate). None were receiving oral hypoglycemic agents and/or insulin. The stone-forming patients were identified by records of stone analysis. The University of Texas Southwestern Institutional Review Board Committee approved the study and informed consent was obtained from each of the participating subjects.

Study protocol

The study comprised an outpatient evaluation and a stabilization phase, during which each participating subject was maintained on an isocaloric diet (30% fat, 55% carbohydrate, 15% protein, and 300 mg cholesterol, 400 mg calcium, 800 mg phosphorus, 100 mEq sodium, 40 mEq potassium) with a fixed acid ash content and sufficient fluid (distilled water) to ensure 2 liters of urine per day. After 2 days of stabilization, subjects were admitted in the General Clinical Research Center (GCRC) for 3 days (study days 3, 4, and 5) and maintained on a constant metabolic diet of the above composition. During study days 3 and 4, 24-hour urine was collected under mineral oil and refrigerated. Urine samples were later analyzed for total volume, pH, creatinine, sodium, potassium, chloride, uric acid, citrate, sulfate, ammonium, titratable acidity, and bicarbonate/CO_2. On the morning of study day 5, breakfast was withheld, and euglycemic hyperinsulinemic clamp procedure was performed after an overnight fast. Two polyethylene catheters were placed under local anesthesia. One catheter was placed in a dorsal hand vein for blood sampling and the hand was kept in a heat box at 70°C for arterialization of venous blood. An arterialized venous blood sample was obtained for determination of pH, blood gases, and lipid profile at 0800, 1000, and 1200 hours. At 0800, a primed-continuous infusion of regular insulin (Humulin, Squibb-Novo, Princeton, NJ, USA) was started at a rate of 80 mU/m^2 (body surface area)/min, and was continued for 2 hours (until 1000 hours). The insulin infusion rate of 80 mU/m^2/min was expected to assure complete suppression of the hepatic glucose output during the hyperinsulinemic phase of study. A 20% glucose infusion was started after 4 minutes of insulin infusion at the rate calculated to maintain plasma glucose concentration at the fasting levels throughout the clamp procedure, according to the method of DeFronzo et al [23]. Blood for plasma glucose concentration measurements was drawn every 5 minutes for the entire duration of the study. The rate of glucose infusion was calculated based on glucose concentration obtained at various times during the clamp study. Mean plasma glucose concentrations were 88 ± 9 and 96 ± 13 mg/dL in the non-stone formers group and in the uric acid nephrolithiasis group, respectively, during the last 40 minutes of the study. Blood for the determination of insulin levels was drawn every 10 minutes from −30 to 0 minutes (baseline phase) and from 80 to 120 minutes (hyperinsulinemic phase, following 80 minutes of equilibration time). Mean plasma insulin concentrations were 180 ± 46 and 172 ± 29 μU/mL in the non-stone formers and in the uric acid nephrolithiasis patients, respectively, during the last 40 minutes of the study. In a subgroup of 35 non-stone formers (22 males and 13 females) we also obtained 2-hour urine from 0600 to 0800 before initiation of insulin infusion. Urine was collected under mineral oil for evaluation of total volume, pH, creatinine, citrate, and ammonium. At the end of the hyperinsulinemic clamp (2 hours' duration) we again collected 2-hour urine for analysis.

All participants had anthropometric measurements during hospitalization at the GCRC. Height and weight were measured by standard procedures. Waist circumference was measured using a flexible measuring tape with a tension caliper at the extremity (Gulick-Creative Health Product, Inc., Plymouth, MI, USA), midway between xyphoid and umbilicus during the mid-expiratory phase. Body composition was determined using underwater weighing, as previously reported [24].

Analytic procedures and calculations

Serum sodium, potassium, chloride, and total carbon dioxide, calcium, phosphorus, uric acid, BUN, creatinine, cholesterol, and triglyceride concentrations were obtained as a part of chem-24 (GCRC Core Laboratory

using Beckman CX9ALX; Beckman Coulter, Inc., Fullerton, CA, USA). Serum very low-density lipoprotein-cholesterol (VLDL-C), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) concentrations were measured at the Center for Human Nutrition at the Investigator's Laboratory. Plasma glucose was determined by the glucose oxidase method using a Beckman glucose analyzer (Beckman Coulter, Inc.). Plasma insulin was determined by immunoassay at Linco Research, Inc. (St. Louis, MO, USA). Urinary sodium and potassium were measured by flame photometry. Urinary chloride was measured calorimetrically by silver precipitation. Urinary uric acid was analyzed by the uricase method and creatinine by the picric acid method. Urinary pH was measured with a pH electrode. Urinary citrate was determined enzymatically using reagents from Boehringer-Mannheim Biochemicals (Indianapolis, IN, USA). Urinary ammonium was determined by the glutamate dehydrogenase method. Urinary sulfate was determined by ion chromatography. Urinary titratable acidity was measured directly using automated burette end point titration system (Radiometer, Copenhagen, Denmark). The milliequivalents of OH^- required titrating the urinary pH to 7.4 yielded titratable acidity (TA). Net acid excretion (NAE) was calculated as (NH_4^+ + TA) − (HCO_3^- + ionized citrate), all expressed in milliequivalents. Urinary HCO_3^- was calculated from urinary pH and pCO_2, and milliequivalents of ionized citrate was calculated from urinary pH and a pKa of citrate 2-/citrate 3- of 5.6. Arterialized venous blood and urinary pH and blood and urinary carbon dioxide were determined aerobically at 37°C Radiometer BMS-3 pH electrode (Copenhagen, Denmark) and Servinghaus electrode. The arterialized venous plasma bicarbonate concentration was calculated from blood pH and pCO_2 (Henderson-Hasselbach equation). Glucose disposal rate during the hyperinsulinemic phase was calculated from the infusion rate of glucose during each 10-minute interval from time 80 to 120 minutes. Urinary glucose loss was accounted for in the calculation of glucose disposal rates as an estimate of insulin sensitivity in the study subjects.

Statistical analysis

Student *t* test was used for comparison of study groups. Spearman correlation coefficients were used to assess the association between continuous variables. Paired *t* test was used to compare means of urinary variables at baseline and during hyperinsulinemic phase of the clamps. Results are presented as mean ± standard deviation (SD). Statistical analysis was performed with SAS 8.0 (SAS Institute, Cary, NC, USA).

Table 1. General and metabolic characteristics of non-stone formers and uric acid nephrolithiasis patients

	Non-stone formers	Uric acid nephrolithiasis patients	*P* value
N (male/female)	55 (33/22)	13 (11/2)	–
Age *years*	31 ± 11	53 ± 10	<0.0001
BMI kg/m^2	24 ± 4	31 ± 4	<0.0001
Body fat % *of body weight*	23 ± 10	36 ± 7	<0.0001
Waist circumference *cm*	83 ± 13	105 ± 11	<0.0001
Systolic blood pressure *mm Hg*	116 ± 19	138 ± 11	0.0002
Diastolic blood pressure *mm Hg*	73 ± 10	86 ± 10	0.0002
Total plasma cholesterol *mg/dL*	160 ± 32	201 ± 30	0.0007
Plasma triglycerides *mg/dL*	99 ± 69	200 ± 81	0.002
LDL-cholesterol *mg/dL*	97 ± 27	128 ± 27	0.002
HDL-cholesterol *mg/dL*	45 ± 10	34 ± 10	0.004
Fasting glucose *mg/dL*	87 ± 9	101 ± 15	<0.0001
Fasting insulin *U/mL*	13 ± 9	13 ± 7	0.9
Glucose disposal rate *mg/min/kg of lean body mass*	9.0 ± 2.5	6.3 ± 2.4	0.008

Results are expressed as mean ± SD. *P* values are derived from Student *t* test.

RESULTS

Table 1 is a summary of the general and metabolic characteristics of the study population, which included 55 subjects with no history of kidney stones and 13 subjects with history of uric acid nephrolithiasis. The ethnic composition was 47 Caucasians (originating from Europe), 17 Asian Indians (originating from the Indian Subcontinent), 2 Hispanics (originating from Latin America), and 2 African Americans. None of the subjects with uric acid nephrolithiasis had a history of diabetes. Two patients were found to have elevated fasting glucose, and one patient was diagnosed with diabetes at the time of entry into the study. As expected, the patients with uric acid nephrolithiasis had general features of the metabolic syndrome, including increased body fat content, waist circumference, blood pressure, serum triglycerides, and low serum HDL-cholesterol concentrations. Glucose disposal rate during hyperinsulimemia was also significantly lower in the patients with uric acid nephrolithiasis. The results on serum and urinary chemistries are summarized in Tables 2 and 3, respectively. The main biochemical changes found in serum of uric acid stone-forming patients were slightly higher concentrations of sodium, potassium, and uric acid (Table 2). Uric acid stone-formers had lower urinary pH and citrate, and higher titratable acid and net acid excretion (Table 3). Although urinary ammonium was not significantly lower, the fraction of net acid excretion composed of ammonium was significantly decreased in uric acid stone-formers, indicating that more protons are excreted with non-NH_3 buffers.

To evaluate the relationship between insulin resistance and urinary acidification we first analyzed the correlation between glucose disposal rate during hyperinsulinemic

Table 2. Serum chemistries in non-stone formers and in uric acid nephrolithiasis patients

	Non-stone formers	Uric acid nephrolithiasis patients	*P* value
Na *mEq/L*	138 ± 6	144 ± 11	0.005
K *mEq/L*	4.0 ± 0.3	4.3 ± 0.4	0.008
Cl *mEq/L*	105 ± 2	10.5 ± 3	0.9
CO_2 *mEq/L*	26 ± 2	23 ± 3.0	0.1
BUN *mg/dL*	12 ± 3	13 ± 2.0	0.1
Cr *mg/dL*	0.9 ± 0.2	1.0 ± 0.2	0.3
Ca *mg/dL*	9.0 ± 0.4	8.9 ± 0.60	4
P *mg/dL*	3.0 ± 0.4	3.0 ± 0.4	0.7
Uric acid *mg/dL*	5.8 ± 1.3	7.6 ± 1.4	<0.0001
pH	7.40 ± 0.02	7.42 ± 0.02	0.02
pCO_2 *mm Hg*	42.3 ± 3.8	40.5 ± 2.7	0.1
HCO_3^- *mEq/L*	25.7 ± 1.8	25.7 ± 1.2	0.9

Results are expressed as mean ± SD. *P* values are derived from Student *t* test.

Table 3. Urinary chemistries and acid excretion in non-stone formers and uric acid nephrolithiasis patients

	Non-stone formers	Uric acid nephrolithiasis patients	*P* value
pH	6.2 ± 0.4	5.5 ± 0.2	<0.0001
NH_4^+ *mEq/d*	34 ± 11	33 ± 9	0.9
Citrate *mg/d*	638 ± 285	367 ± 184	0.002
Citrate *mEq/d*	7.5 ± 3.4	4.9 ± 2.4	0.01
Titratable acids *mEq/d*	23 ± 10	32 ± 8	0.002
Bicarbonate *mEq/d*	2.6 ± 4.0	0.34 ± 0.2	0.0001
NAE *mEq/d*	46 ± 20	60 ± 13	0.02
NH_4^+/NAE	0.8 ± 0.3	0.55 ± 0.09	0.002
Total volume *mL/d*	2335 ± 851	2095 ± 500	0.3
Na *mEq/d*	103 ± 48	75 ± 29	0.05
K *mEq/d*	55 ± 21	31 ± 7	<0.0001
Cl *mEq/d*	100 ± 49	78 ± 23	0.1
Cr *mg/d*	1590 ± 420	1623 ± 515	0.8
SO_4 *mEq/d*	11.4 ± 3.6	9.5 ± 2.5	0.07
Cr clearance *mL/min*	121 ± 41	123 ± 29	0.9

Results are expressed as mean ± SD. *P* values are derived from Student *t* test.

clamps and 24-hour urinary pH in the two study groups. As shown in Figure 1, for non-stone formers, the relationship was significant with an *r* value of +0.35 ($P = 0.01$). Lower glucose disposal rate was associated with lower urinary pH. The uric acid stone formers tended to cluster in the area of more severe insulin resistance with relatively lower variability in both glucose disposal rates and urinary pH, as compared to the non-stone formers. Likely as a consequence of the smaller sample size, the smaller range of insulin sensitivity and urinary pH, no significant relationship was found between insulin sensitivity and urinary pH within the group of patients with uric acid nephrolithiasis.

Factors such as age and body composition can confound the evaluation of the role of insulin resistance on the excessive urinary acidity of patients with uric acid nephrolithiasis. To minimize the effect of age and body composition on insulin resistance differences between non-stone formers and nephrolithiasis patients, we

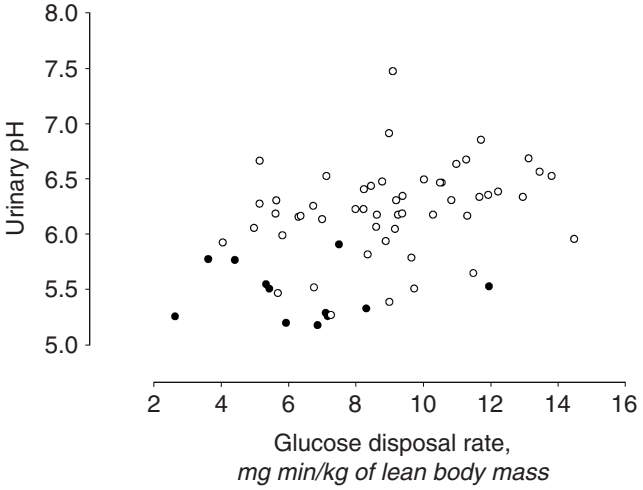

Fig. 1. Relationship between glucose disposal rate during hyperinsulinemic-euglycemic clamp and 24-hour urinary pH. Open dots represent data from non-stone formers and closed dots represent data from patients with uric acid nephrolithiasis. The *r* value for the correlation was 0.35 ($P = 0.01$ Spearman correlation) within the non-stone formers.

Table 4. General characteristics, urinary, and metabolic data in the study subgroup selected for age above 40 years

	Non-stone formers	Patients with uric acid nephrolithiasis	*P* value
N (male/female)	13 (6/7)	13 (11/2)	
Age *years*	50 ± 6	53 ± 10	0.3
Body fat content % *of total body mass*	28 ± 10	36 ± 7	0.06
Waist circumference *cm*	91 ± 19	105 ± 11	0.06
Glucose disposal rate *mg/min/kg of lean body mass*	7.8 ± 2.1	6.3 ± 2.4	0.2
Urinary pH	6.1 ± 0.5	5.5 ± 0.2	0.0003
Urinary NH_4^+ *mEq/d*	37 ± 9	33 ± 9	0.3
Urinary NH_4^+/NAE	0.92 ± 0.38	0.55 ± 0.09	0.002
Urinary citrate *mg/d*	698 ± 252	367 ± 184	0.001
Urinary citrate *mEq/d*	7.5 ± 3.3	4.9 ± 2.4	0.01
Urinary citrate/NAE	0.2 ± 0.2	0.08 ± 0.04	<0.0001

Results are expressed as mean ± SD. *P* values are derived from Student *t* test.

further analyzed selected subjects who were older than 40 years of age from the two study groups. As shown in Table 4, these subgroups were more homogeneous and more comparable in terms of body fat content, waist circumference, and glucose disposal rates. Despite the similarities of metabolic and body composition variables, the patients with uric acid nephrolithiasis still have significantly lower urinary pH when compared to this non-stone formers subgroup. The differences in urinary pH remained significant even after statistical adjustment for age, total body fat content, and waist circumference (P value = 0.046). Similar to what was found in the comparison with the whole non-stone former group, this young subgroup of uric acid nephrolithiasis patients had decreased urinary citrate and decreased ratio of ammonium to net acid excretion.

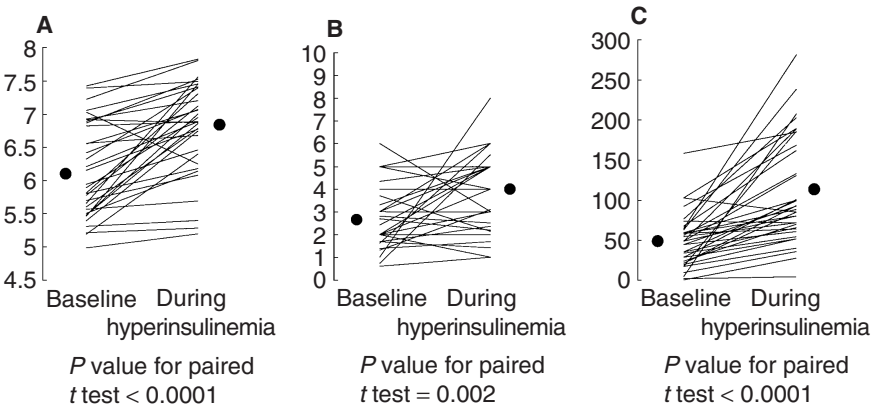

Fig. 2. Urinary pH (*A*), urinary ammonium (*B*), and urinary citrate (*C*) at baseline and during the hyperinsulinemic phase of the clamp studies. These studies were performed in 2-hour timed urinary collection for 22 males and 13 females of the non-stone formers group. Plasma insulin concentrations were 14 ± 10 μU/mL at baseline and 173 ± 26 μU/mL during the last 40 minutes of the clamp studies. Lines represent individual changes. Means (•) are reported for each variable at baseline and during hyperinsulinemia. Mean and SD for urinary pH were 6.1 ± 0.7 and 6.8 ± 0.7. Mean and SD for urinary ammonia were 2.7 ± 1.6 and 4.0 ± 2.6 mEq/2 hr. Mean and SD for urinary citrate were 48 ± 33 and 113 ± 68 mg/2 hr. *P* values are derived from paired *t* test.

If insulin resistance contributes to lower urinary pH, ammonium, and citrate, one would expect an increase in these parameters during hyperinsulinemia. Figure 2 depicts the changes in urinary variables at baseline plasma insulin concentrations and during hyperinsulinemia. Thirty-five non-stone formers (22 males and 13 females) had 2-hour timed urinary collection before and during hyperinsulinemic clamp. The ethnic composition of these subjects was 19 Caucasians, 15 Asian Indians, and 1 Hispanic. In these subjects, urinary pH, ammonium, and citrate all increased during hyperinsulinemia when compared to baseline.

DISCUSSION

There are three salient findings in this study. First, insulin resistance is associated with excessively low urinary pH, which can potentially predispose the subjects to uric acid stone formation. Second, obesity-related insulin resistance significantly contributes to, but does not entirely explain, the undue urinary acidity of uric acid nephrolithiasis patients. Third, insulin acutely affects renal acidification in non-stone formers.

We deliberately chose overtly healthy subjects with a wide degree of adiposity to ensure adequate spread in insulin sensitivity measured using hyperinsulinemic-euglycemic clamps. In this population of non-stone formers, we found that decreased glucose disposal rate correlated (Fig. 1) with reduction in mean 24-hour urinary pH. The patients carrying a diagnosis of uric acid nephrolithiasis were more obese and, likely as a consequence, had more significant insulin resistance. It is noteworthy that these patients were selected solely based on the presence of uric acid kidney stones and not other metabolic parameters, and yet they exhibited the least sensitivity to insulin and the lowest urinary pH (Tables 2 and 3, Fig. 1).

We and others have previously shown that despite normouricosuria, patients with undue low urinary pH are at increased risk for development of either uric acid or mixed calcium oxalate/uric acid kidney stones. These patients typically have persistently low urinary pH (below 5.5), seemingly as a consequence of impaired ammonium excretion when challenged with an acute acid load [4]. As expected, low urinary pH was found in the uric acid stone formers compared to the non-stone formers. Despite the lower percentage of net acid excreted as ammonium, net acid excretion was maintained by higher titratable acidity and lower citrate. An as of yet unexplained finding is the higher net acid excretion in uric acid stone formers despite being on an identical diet as the non stone-formers. Acid intake as indicated by sulfate excretion was similar in the two groups, with a numerically but statistically insignificantly lower value in the uric acid stone-formers. There may be a yet unrecognized increased intestinal base loss in uric acid stone formers.

The mechanistic relationship between insulin resistance and low urinary pH is unclear at the moment but it may be secondary to defective ammonia synthesis both by the proximal tubule cell as well as ammonium transport into the renal tubular lumen. In vitro studies have indicated that insulin stimulates renal ammoniagenesis from the substrate L-glutamine [21, 22] and the proximal renal tubule Na^+/H^+ exchanger [20] that is critical for either direct transport or ionic trapping of NH_4^+ in the urinary lumen [25]. Substrate competition may also play a role. L-glutamine is both a major ammoniagenic and ATP precursor for the renal proximal tubular cells. If an alternative metabolic substrate, such as free fatty acids, is provided to the proximal renal tubular cell, the result is a reduction in glutamine usage and ammoniagenesis [25–30]. It is of interest that insulin resistance is often associated with excessive plasma free fatty acid circulation [31].

Clearly, the uric acid–stone formers had more insulin resistance and lower urinary pH compared to the non-stone formers. In addition, they tended to exhibit excessively low urinary pH even for their degree of insulin

resistance (Fig. 1). When we selected two subgroups of similar age and body fat content (Table 4) we found excessively low urinary pH in the stone formers independent of insulin resistance and obesity. These results suggest that uric acid–stone formers may have yet unidentified mechanisms leading to unduly low urinary pH that are not entirely accounted for by insulin resistance. The mechanism for the hypocitraturia is also unknown but may be related to proximal tubular cell acidification due to defective apical membrane H^+ and NH_4^+ secretion. Alternatively, excessive proximal tubule luminal acidification can increase apical membrane citrate uptake as long as citrate metabolism is maintained high, and hypocitraturia can ensue. The hypocitraturia may predispose uric acid stone formers to have mixed uric acid/calcium stones.

Of interest are the findings on the effects of acute hyperinsulinemia on urinary variables during the hyperinsulinemic-euglycemic clamps. Acute renal effects of insulin have included suppression of renal glucose release and stimulation of glucose uptake [32–34], alterations in filtration rate [35–38], and natriuresis [15–17]. We now show that acute hyperinsulinemia induces elevation in urinary pH in the non-stone formers. This alkalinization was accompanied by elevation of urinary citrate and ammonia excretion. Our findings suggest that insulin directly affects renal ammonium excretion in humans. It is conceivable that reduced biologic activity of insulin in the kidney may prevent elevation of urinary pH during physiologic hyperinsulinemia, such as in post-absorptive conditions. This altered kidney response to insulin may determine a tendency toward a decrease in 24-hour mean urinary pH in insulin resistant subjects.

CONCLUSION

This study shows that a possible renal manifestation of insulin resistance is low urinary ammonium and pH. Acid-base balance is maintained by increased titratable acid and reduced citrate excretion. This defect is particularly prevalent and pronounced in patients with uric acid nephrolithiasis and results in increased risk of uric acid precipitation despite hypouricosuria. In addition to the reduced ammonium excretion associated with insulin resistance, there are additional mechanisms leading to the reduced ammonium excretion in uric acid stone formers. Because a growing percentage of our population has features of insulin resistance, as indicated by recent epidemiologic observations on the prevalence of obesity [1], diabetes [39, 40], and the metabolic syndrome [2], there may be a surge in the population risk and incidence for kidney stones. Our study identifies insulin resistance as a predisposing factor and major potential target of intervention to either reduce risk for kidney stone formation in high-risk patients or improve the clinical outcome of patients who already have kidney stones.

ACKNOWLEDGMENTS

The authors were supported by the National Institutes of Health [K23- RR16075 (NA), PO1-DK20543 (OWM, KS), MOl-RR00633 (NA, KS), RO1-DK48482 (OWM), and RO1-DK54396 (OWM)], and the Department of Veterans Affairs Research Service (OWM). The authors wish to acknowledge the expertise of the nursing staff, specifically Ms. Marsha Roberts, dietitian Linda Brinkley, and statistician Beverley Adams-Huet at the General Clinical Research Center at the University of Texas Southwestern Medical Center. The authors are grateful to Dr. Charles Y.C. Pak for helpful discussions. The authors are thankful for the skilled secretarial assistance of Mrs. Linda A. Jarvis.

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