Kidney International, Vol. 65 (2004), pp. 1422–1425

Association of urinary pH with body weight in nephrolithiasis

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Background. The prevalence of kidney stone disease in the United States is progressively increasing, paralleling the growing rate of obesity. Uric acid nephrolithiasis, a condition associated with a low urinary pH, has been linked to obesity and insulin resistance. Based on these observations, we hypothesized that urinary pH may be inversely associated to body weight in nephrolithiasis.

Methods. Data were retrieved from 4883 patients with nephrolithiasis who underwent ambulatory evaluation at two established stone clinics in Dallas and Chicago. The patients collected 24-hour urine samples on an outpatient basis, while avoiding any drug that could alter urinary pH. Patients were divided in increasing sextiles of body weight, and urinary pH was adjusted for urinary creatinine and for age.

Results. Urinary pH had a strong, graded inverse association with body weight. Urinary creatinine and age were both found to be significant covariates of urinary pH, while gender was not a significant independent variable after adjustment for urinary creatinine. Mean 24-hour urinary pH, adjusted for age and urinary creatinine, were 6.09, 6.04, 6.01, 5.99, 5.97, and 5.91 for sextiles of body weight in increasing order from Dallas (P for linear trend <0.0001), and 6.18, 6.10, 6.04, 6.02, 5.97, and 5.88 for the sextiles from Chicago (P for linear trend <0.0001).

Conclusion. We conclude that urinary pH is inversely related to body weight among patients with stones. The results confirm the previously proposed scheme that obesity may sometimes cause uric acid nephrolithiasis by producing excessively acid urine due to insulin resistance.

The prevalence of kidney stone disease is increasing in the United States as well as in other countries [1–3], paralleling the escalating rate of obesity in many nations [4–6]. This finding has led some authors to speculate whether obesity has a role in the development of nephrolithiasis [7–9]. The prevalence and incidence of stone disease have been reported to be associated with body weight and body mass index (BMI) [9]. However, these epidemiologic studies did not distinguish between the different types of kidney stones, evaluate the biochemical data, or consider underlying biochemical mechanisms.

Recent studies have shown that patients with recurrent uric acid nephrolithiasis display metabolic and clinical features characteristic of the metabolic syndrome [10, 11]. Moreover, a recent retrospective analysis showed that patients with kidney stones who suffer from type 2 diabetes mellitus have a higher prevalence of uric acid nephrolithiasis than in a general population of patients with renal stones [12].

A persistently low urinary pH (<5.5, the pK_a for uric acid) is a distinctive feature of idiopathic uric acid nephrolithiasis previously termed as "gouty diathesis" [13, 14]. In such an unduly acidic urinary environment, the concentration of sparingly soluble undissociated uric acid increases, resulting in the formation of uric acid stones by direct precipitation [15]. Calcium oxalate stones may also develop by heterogeneous nucleation of calcium oxalate by uric acid [16–18].

Based on the above observations, it has been proposed that resistance to insulin action in the kidney ("renal insulin resistance") may lead to excessive urinary acidification and formation of uric acid stones [10, 11, 19]. The purpose of the current study was to test this hypothesis by examining the relationship between urinary pH (a surrogate of renal insulin resistance) and body weight (a surrogate of peripheral insulin resistance) in a large population of kidney stone formers from two well-established kidney stone centers in the United States.

METHODS

Patient data

Data were derived from patients who underwent ambulatory evaluation for nephrolithiasis in two established stone clinics, the University of Texas Southwestern Medical Center (Dallas group) and at the University of Chicago (Chicago group). To avoid selection bias, all adult patients (age $\geq$ 18 years old) who were evaluated between the years 1975 and 2002 in Dallas and

Key words: nephrolithiasis, urinary pH, body weight, obesity, uric acid stones.

Received for publication July 21, 2003
and in revised form September 15, 2003
Accepted for publication November 12, 2003

between 1969 and March 2003 in Chicago were included. A 24-hour urinary pH was routinely measured in both groups. In the Dallas group, both body weight and height were measured, but not in all patients. In the Chicago group, body weight was routinely obtained but height was not obtained. This retrospective data analysis was based on a total of 4883 patients, 3168 from Chicago and 1715 from Dallas, in whom 24-hour urinary pH and body weight were available.

Study protocol

In the Dallas group, two 24-hour urine samples were collected while the patients consumed their usual diet, and one 24-hour urine sample was obtained while subjects were maintained on a diet restricted in calcium, sodium, and oxalate. In Chicago, three 24-hour urine samples on a random diet were collected. At the time of collection, the subjects were not receiving any medications that could alter their urinary pH, such as alkali therapy with potassium citrate, nor taking any treatment for kidney stone disease, such as thiazide diuretics or allopurinol. Urine samples were collected under refrigeration or utilizing an ice chest. Urinary pH was obtained using a pH electrode. Urinary creatinine was measured by the picric acid method. The weight of the patient was determined at the time of delivery of the urinary samples.

Statistical methods

The mean urinary pH used in the analysis was calculated for each patient from one restricted and two random urine samples from the Dallas group and three 24-hour urine samples from the Chicago group. Patients from each group were separated into six categories by increasing sextiles of body weight. Data from the two groups were analyzed separately. Analysis of covariance models were used to compare urinary pH between the weight sextiles while adjusting for the potential confounding effects of covariates. Age, gender, and urinary creatinine were assessed as covariates. Tests of linear trend were conducted by one-way analysis of variance.

For the data from the Dallas group, a subgroup analysis was also performed using the same statistical methods, after excluding 219 patients with conditions known to affect urinary pH (inflammatory bowel disease, renal tubular acidosis, infection stones, and primary hyperparathyroidism). In addition, data from the random diet and restricted diet were analyzed separately, and the association of urinary pH with BMI was assessed. Moreover, in order to ascertain whether a high acid ash diet might have contributed to low urinary pH, data for the restricted diet was further analyzed after adjusting for urinary sulfate and phosphorus, markers of dietary acid ash content.

Table 1. Demographic information

	Dallas	Chicago
Patients *number*	1715	3168
Gender *men/women*	1130/585	2121/1047
Age *years*	43 ± 13	44 ± 13
Range	(18–78)	(20–87)
Weight *kg*	79 ± 19	80 ± 18
Range	(36–204)	(30–210)

Data are presented as mean ± standard deviation.

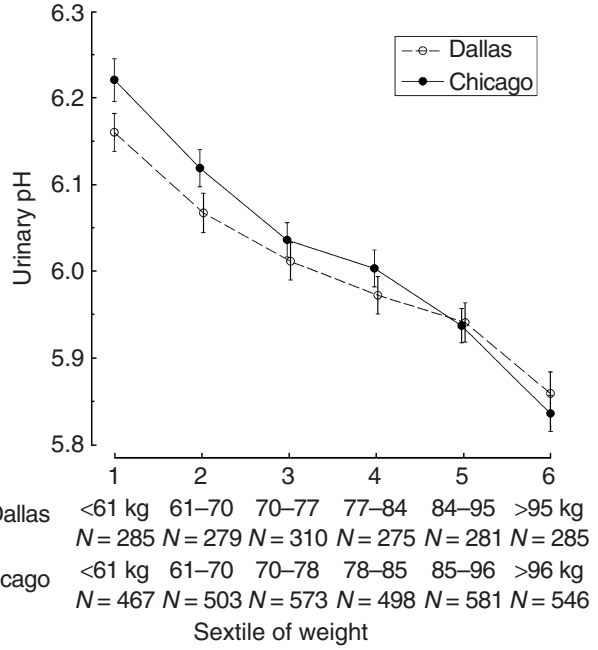

Fig. 1. Urinary pH by sextile of body weight. Vertical bars indicate mean ± SE.

Statistical analysis was performed with SAS version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

The demographic information of the group at each site is summarized in Table 1. The patients from Dallas comprised 1130 men and 585 women, while those from Chicago included 2121 men and 1047 women. The mean age was 43 years for the Dallas group and 44 years for the Chicago group, and the mean weight was 79 kg for the Dallas group and 80 kg for the Chicago group. The sextiles of body weight were similar between the two groups.

In both Dallas and Chicago, unadjusted urinary pH displayed a stepwise decrease with increasing sextiles of body weight (Fig. 1). The mean 24-hour urinary pH values for the respective sextiles were 6.16, 6.07, 6.01, 5.97, 5.94, and 5.86 for the Dallas group (P for linear trend <0.0001), and 6.22, 6.12, 6.04, 6.00, 5.94, and 5.84 for the Chicago group (P for linear trend <0.0001).

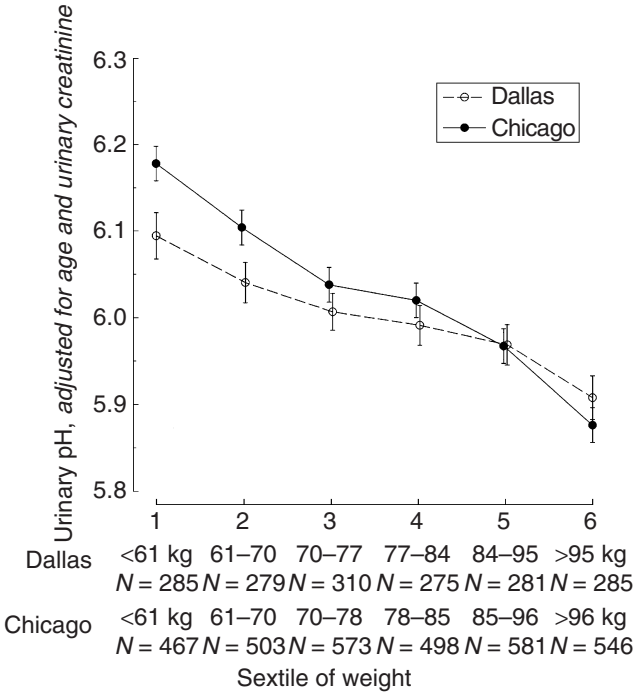

Fig. 2. Urinary pH adjusted for age and urinary creatinine by sextile of body weight. Vertical bars indicate mean ± SE.

In the analysis of covariance models, urinary creatinine and age were found to be significant covariates of urinary pH at both sites. After adjustment for urinary creatinine, gender was not a significant independent variable. In order to control for the effects of age and urinary creatinine on urinary pH, data analysis was repeated after adjusting for these two variables, and the inverse relationship between urinary pH and body weight persisted. The adjusted mean 24-hour urinary pHs were 6.09, 6.04, 6.01, 5.99, 5.97, and 5.91, for the sextiles of body weight in increasing order from the Dallas group (P for linear trend <0.0001), and 6.18, 6.10, 6.04, 6.02, 5.97, and 5.88, from the Chicago group (P for linear trend <0.0001) (Fig. 2).

After excluding data from 219 patients with conditions that could affect urinary pH, the same association was found between adjusted urinary pH and body weight (P for linear trend <0.0001). Moreover, the same stepwise reduction in urinary pH was displayed with increasing body weight, when only the data from the restricted urine samples were employed: For the data on the restricted diet, values for urinary pH, adjusted for age and urinary creatinine, were 6.11, 6.03, 5.96, 5.97, 5.89, and 5.84 for sextiles of body weight in increasing order (P for linear trend <0.0001). Values for urinary pH adjusted for age, urinary creatinine, sulfate, and phosphorus were 6.13, 6.02, 5.95, 5.96, 5.89, and 5.83 for sextiles of body weight in increasing order (P for linear trend <0.0001). Urinary pH displayed a similar but less steep stepwise decrease with increasing BMI. For all three urine samples from Dallas, mean values for urinary pH, adjusted for age and urinary creatinine, were 6.05, 6.04, 6.01, 6.01, 5.96, and 5.94 for sextiles of BMI in increasing order (P for linear trend = 0.003).

DISCUSSION

The purpose of our study was to examine the association between urinary pH and body weight in a large number of patients with nephrolithiasis evaluated at two established stone centers. We found that 24-hour urinary pH significantly decreases with increasing body weight. This inverse relationship between urinary pH and body weight was independent of gender, but was partly influenced by age and urinary creatinine.

We would like to suggest that a possible explanation for the progressive decline in urinary pH with increasing body weight is insulin resistance, which decreases renal ammonia excretion and impairs hydrogen ion buffering. Experimental studies in vitro and in vivo have previously demonstrated that insulin plays a critical role in renal ammonia synthesis [20, 21] and excretion by the activation of the sodium hydrogen exchanger 3 (NHE3) [22, 23]. Moreover, in human subjects with and without kidney stones, we have also recently shown that insulin influences renal ammonium excretion [11]. Thus, low insulin bioactivity (due to insulin resistance from obesity) in the renal proximal tubule can theoretically lead to defective ammonium production and/or excretion, and thus affect urinary pH.

The above scheme is substantiated by our finding of a strong inverse correlation between decreased disposal rate of glucose (a measure of insulin resistance) and 24-hour urinary pH in normal subjects as well as in patients with uric acid stones [11]. It is also compatible with the report that uric acid is much more commonly encountered as a stone constituent among diabetic patients with stones than in a general population of patients with stones [12]. Overall, the results suggest that insulin resistance may be one of the important causes of gouty diathesis or idiopathic uric acid nephrolithiasis.

Ingestion of a diet high in acid ash content (high animal protein intake) is known to reduce urinary pH [24], due to the generation of protons during the oxidation of sulfur in animal proteins to sulfate [25]. In our study, the inverse relationship between urinary pH and body weight persisted after adjusting for urinary sulfate, a finding that supports operation of a diet-independent mechanism. This conclusion is in line with previous studies in idiopathic uric acid nephrolithiasis, in which persistently low urinary pH was found despite the use of a neutral ash diet [10, 11].

The pathophysiologic mechanism underlying the decline in urinary pH with age may be the defective ammonium excretion by the aging kidney [26, 27]. This association was previously shown in a study of 300 healthy

volunteers, in whom 24-hour urinary pH declined with advancing age [28].

An unexpected finding in our study was the inverse correlation between urinary creatinine and urinary pH. Although at steady-state urinary creatinine excretion is a good estimate of lean body mass [29, 30], it is also in part affected by the dietary intake of animal protein [31]. In this study, the inverse relationship between body weight and urinary pH was maintained after adjustment for urinary creatinine. This finding suggests that both lean body mass and another mechanism, possibly body fat content, might be involved in producing low urinary pH. This interesting observation deserves further exploration in future studies.

CONCLUSION

Body weight (a marker of peripheral insulin sensitivity) was shown to be inversely related to urinary pH (a marker of renal insulin sensitivity) in a large population of kidney stone formers. This relationship was found to persist after adjustment for age and markers of dietary indiscretion. The results support the previously postulated scheme that obesity may sometimes cause uric acid stones by producing renal insulin resistance that in turn reduces urinary pH.

ACKNOWLEDGMENTS

This work was supported by USPHS grants P01-DK20543, P01-DK56788, T32-DK07307, and M01-RR00633 from the National Institutes of Health. This work was conceived while Dr. Coe was visiting Dallas on the occasion of the creation of the "Frederic L. Coe Professorship in Urolithiasis Research." The authors from both institutions are delighted over the opportunity of working together on this project.

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