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Urinary Citrate Levels Do Not Correlate with Urinary pH in Patients with Urinary Stone Formation

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OBJECTIVES Urinary excretion of citrate is dependent on glomerular filtration, tubular reabsorption, and excretion. Acid base status is thought to play a significant role in urinary citrate excretion. It has been assumed that increased urinary citrate will increase urinary pH. The aim of this study was to confirm the association of increased urinary citrate levels with increased urinary pH.

METHODS The 24-hour urine collections of all patients with stones referred to our clinic in the past 4 years were reviewed. The samples were collected and analyzed for routine stone risk profiles by a commercial laboratory (Litholink, Chicago, Ill). The Student *t* test and analysis of variance were used to compare the mean values as applicable. Pearson's correlations were also calculated for each variable.

RESULTS A total of 572 patients had at least one 24-hour urine sample from the past 4 years. The mean urinary citrate was 305 mg/day. The mean urinary pH of all patients was 6.14. Statistical evaluation of all patients showed no correlation between urinary citrate and pH ($r = -0.04$, $P = 0.36$). In a subset of patients with urinary potassium greater than 100 mEq/day (n = 100), urinary citrate and urinary pH were both increased; however, there was still no correlation between the two ($r = 0.011$, $P = 0.806$).

CONCLUSIONS Despite the current dogma that increasing urinary citrate increases urinary pH, in a cohort of patients with urinary stone formation who provided 24-hour urine specimens, no correlation was found between urinary citrate and urinary pH levels. UROLOGY 70: 634–637, 2007.

Citrate supplementation is widely recommended to decrease the risk of recurrent kidney stone formation for many specific 24-hour urinary abnormalities. Three long-term, randomized controlled trials of this intervention have shown a reduction in stone formation in patients with recurrent stones taking a variety of citrate formulations.[1–3] In contrast, in another study, when two groups of patients were treated with specific drug therapy, including alkalinization, versus general stone prevention guidelines, no difference was found in stone recurrence.[4] Similar studies have provided additional conflicting data.[5,6]

The mechanism by which citrate is believed to act as an inhibitor of stone formation is threefold. Citrate complexes with calcium ions in the urine, forming a stable compound.[7] Several investigators have proposed that this mechanism decreases available urinary calcium, thus preventing calcium and oxalate precipitation.[8] Citrate also lowers the spontaneous and heterogeneous nucleation of calcium oxalate.[9] Citrate reduces the crystal growth rates of calcium oxalate in in vitro systems and urine from patients with stone formation.[7] Finally, for patients with stones dependent on an acidic pH, oral citrate supplementation is thought to alkalinize urine in the short and long term.

Total urinary citrate is dependent on glomerular filtration, tubular reabsorption, and excretion.[10] Which of these mechanisms is dominant is unclear, and understanding the relationship between urinary citrate and urinary pH has evolved since it was first investigated more than 70 years ago.[11] It was initially assumed that increased urinary citrate would increase urinary pH. However, researchers later proposed that urinary citrate excretion is actually determined by the systemic acid base balance.[12] Additionally, most oral citrate has been found to be metabolized by the liver, rather than excreted unchanged in the urine.

Citrate is a widely used medication in the treatment of patients with urinary stone disease. Because both urinary citrate and pH typically increase with oral citrate therapy, many have assumed a causative relationship between the two. Additionally, citrate supplementation is sometimes titrated on the basis of the urinary pH. The goal of this study

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Table 1. Relationship of urinary citrate levels to medication use to reduce stone risk

Medication	n (%)	Mean Citrate Level	*P* Value
Allopurinol			
Yes	33 (95.8)	622	0.93
No	539 (94.2)	616	
Alkalinization			
Yes	94 (16.4)	595	0.54
No	478 (83.6)	620	
Hydrochlorothiazide			
Yes	63 (11.0)	618	0.97
No	509 (89.0)	616	

Table 2. Correlation coefficients (*r*) between pH and other urinary constituents

Ion	*r* vs. pH	*P* Value
Ammonium	0.04	0.36
Calcium	−0.08	0.07
Chloride	−0.03	0.46
Citrate	0.06	0.13
Creatinine	−0.15	<0.01
Magnesium	0.04	0.32
Oxalate	0.07	0.10
Phosphorus	−0.25	<0.01
Potassium	0.21	<0.01
Sodium	0.05	0.26
Sulfate	−0.20	<0.01
Urea nitrogen	−0.22	<0.01
Uric acid	0.00	0.99
Volume	0.23	<0.01
Supersaturation (SS) uric acid	−0.78	<0.01
SS calcium oxalate	−0.17	<0.01

was to evaluate the relationship of urinary citrate and urinary pH in a broad cohort of patients with stones.

MATERIAL AND METHODS

An institutional review board-approved retrospective study of 24-hour urine collections was undertaken. Patients included in the study had been referred to a urinary stone practice at a tertiary medical center for management of urolithiasis. Sample data were obtained for all initial 24-hour urine collections from 2001 to 2005. Patients submitted an outpatient 24-hour urine collection and stone history questionnaire. No specific inclusion or exclusion criteria were used. The samples were collected and analyzed for routine stone risk profiles by a commercial laboratory (Litholink, Chicago, Ill). Because many of the patients were referred by an outside urologist, they might or might not have undergone previous 24-hour urine collections, made general or specific dietary modifications, or been prescribed medications according to the stone analysis and/or urine chemistry findings in the hope of reducing recurrent stone disease.

The information was collected centrally by the commercial laboratory and recorded in an electronic database. The urinary stone risk factors assessed included urine volume, pH, calcium, oxalate, citrate, magnesium, sulfate, uric acid, sodium, potassium, and phosphate. Supersaturations were calculated for calcium oxalate, calcium phosphate, and uric acid. In addition, the patient questionnaire contained information on 19 clinical parameters, including family history, personal stone history, and the use of stone risk-modifying medications. Student's *t* test and analysis of variance were used to compare the mean values. Pearson's correlations were calculated for each variable. Statistical analysis was performed using commercially available software (SPSS, Chicago, Ill).

Table 3. Urinary citrate and pH by age, sex, and urine volume

Variable	Citrate	*P* Value	pH	*P* Value
Age (yr)				
<50	580	0.72	6.2	0.03
>50	570		6.1	
<60	580	0.52	6.2	0.19
>60	560		6.0	
<70	590	0.01	6.1	0.68
>70	480		6.1	
Sex				
Male	600	<0.01	6.1	0.81
Female	520		6.1	
Volume (L)				
<2	556	0.378	6.0	<0.01
>2	583		6.2	

RESULTS

A total of 572 patients had at least one 24-hour urine collection. The mean age was 53.4 years. Of the 572 patients, 60% were men. The mean and median self-reported number of calculi was 10 and 3, respectively. Patients had had an average of 2.4 emergency room visits. The average number of shock wave lithotripsies was one, and the mean number of ureteroscopy or open stone procedures was 0.2.

Many patients had been prescribed medications to reduce the stone risk factors. The citrate levels, segregated by individual medication use, were evaluated (Table 1). No significant differences were found in citrate levels with the use of allopurinol, alkalinizing agents, or hydrochlorothiazide.

A comparison of urinary pH with urinary citrate, as well as other urinary parameters, was performed using Pearson's correlations. The results are summarized in Table 2. Urinary pH did not correlate with the absolute citrate levels ($r = 0.06$, $P = 0.13$). The analysis was repeated with the urinary citrate concentration rather than the absolute level. Similarly, the urinary citrate concentration showed no correlation with urinary pH ($r = -0.063$, $P = 0.129$).

Citrate levels and pH can be influenced by age, sex, body weight, urinary volume, and bacteriuria. The patients' body weight and urine culture results were unavailable through the database. The citrate levels and pH were compared for different age cutpoints, a volume cutpoint, and by sex (Table 3). Urinary citrate was significantly greater in older patients and in men compared with women. Urinary pH was significantly greater in

Table 4. Comparison of mean urinary pH and citrate levels among patients with high urinary potassium and those taking alkalinizing therapy

Variable	pH	*P* Value	Citrate	*P* Value
Alkali supplementation				
Yes (n = 94)	6.3	0.014	595	0.543
No (n = 478)	6.15		620	
Urinary potassium (mEq)				
>100 (n = 90)	6.4	<0.001	790	<0.001
<100 (n = 482)	6.12		580	

younger patients and in patients with greater urinary volumes. However, no correlation between citrate and pH was found when stratified by age, sex, or urinary volume.

To isolate those patients taking potassium citrate supplementation and to control for potential variability in compliance with medication dosing, the patients were segregated according to their self-reported use of alkali therapy and by urinary potassium levels of less than versus greater than 100 mEq/day. The mean urinary pH and mean total urinary citrate levels were compared between the high and low urinary potassium groups and between those patients who reported alkali use and those who did not (Table 4). Again, when urinary pH and urinary citrate were specifically compared in those patients with urinary potassium greater than 100 mEq, no correlation was found ($r = 0.009$, $P = 0.925$).

COMMENT

Our study goal was to reexamine the physiologic relationship of urinary citrate and urinary pH in a large cohort of patients with urinary stone formation seen at a referral stone clinic. Many patients had previously undergone 24-hour urine collections and had been prescribed stone risk-modifying agents, including approximately one sixth of the patients who self-reported use of alkalinization therapy.

In this study, we found no correlation between urinary citrate and urinary pH, including among patients taking or not taking alkalinizing medications. Other known markers of urinary acid load, however, such as urine sulfate and urea nitrogen, did correlate with urinary pH, serving as a positive control for the pH data in our cohort. These findings contradict data from previous experimental models that found a direct correlation between urinary citrate excretion and urinary pH.[13] Furthermore, dietary modification in the form of greater fluid intake, lower protein, and lower salt in patients with idiopathic stone formation has been shown, in the short term, to increase both urinary citrate and urinary pH.[14] In a complementary fashion, the elimination of fruits and vegetables from the diets of patients with stone formation was shown to decrease urinary citrate excretion, urinary pH, urinary potassium and to increase supersaturation of calcium phosphate and calcium oxalate.[15]

In contrast, a longitudinal study demonstrated that although in the short term (3 months), both urinary citrate and urinary pH increased in patients prescribed potassium citrate, in the long term (12 months), the urinary citrate and pH values did not correlate.[16] Patients maintained an elevated urine citrate if compliant with therapy; however, urinary pH returned to baseline values. Other data have suggested that patients taking citrate supplementation regress toward baseline stone risk as the interval from treatment initiation increases.[17] It is unclear whether this latter observation resulted from homeostatic conservation of body acid base status or poor long-term compliance. In any case, the relationship between urinary citrate and pH evidently is far from clear.

To further investigate this particular phenomenon of apparent oral citrate "tolerance," we examined a subset of patients who likely were taking potassium citrate supplementation and were compliant with therapy. These patients were identified by 24-hour urine potassium levels greater than 100 mEq/day. Typically, for every 1 mEq of oral potassium ingested, an equivalent increase occurs in urinary potassium excretion. Thus, compliance with supplementation can be verified. The subgroup presumed compliant with potassium citrate supplementation as determined by urinary potassium levels had significantly greater urinary pH and urinary citrate levels compared with patients who were likely not taking potassium citrate therapy. The absolute difference in pH, 0.28, was not as great as that (0.55 to 0.85) observed by Pak and Peterson[18] when treating patients with hyperuricosuric calcium stone formation. Pak *et al.*[19] also observed a much greater increase in pH (0.9) with citrate therapy when treating patients with uric acid stone formation.

When we evaluated our select patients with urinary potassium levels greater than 100 mEq/day, however, despite confirming increases in urinary citrate and pH, we continued to observe no correlation between the two. Therefore, although the results of this study have confirmed that oral alkalinization therapy with potassium citrate leads to increased urinary pH and urinary citrate, these two parameters did not correlate. Additionally, citrate and pH are influenced by age, sex, body weight, urinary volume, and thiazide use. We did not find a correlation between urinary citrate and pH when we controlled for differences in these factors. Our hypothesis is that the global acid base balance drives urinary pH, which could also explain the attenuation in the citrauric response in patients taking long-term citrate supplementation.

The limitations of this study included its retrospective nature, reliance on patient recall rather than medical charts for historical data and medication use, and an inability to assess the types of stones formed. Also, many patients had previously undergone 24-hour urine collection and could potentially have made lifestyle adjust-

ments, such as increasing fluid intake, decreasing sodium intake, and eating less animal protein, which initially contributed to their stone disease. However, no reason is evident to suppose that these dietary or lifestyle modifications would have confounded the intrinsic relationship between urinary citrate and urinary pH.

We also were unable to differentiate the particular kind of alkalinization therapy taken (ie, potassium citrate, calcium citrate, sodium bicarbonate). However, we were able to identify patients likely to be taking potassium citrate on the basis of the total urinary potassium values (although this could have been confounded by potassium chloride use). We did not have detailed information on medications such as angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs, both of which could affect the relationship between urinary citrate and pH. Finally, information on the presence of urinary tract infection at the 24-hour urine collection was not available. However, all collections were performed once the patient had been rendered stone free and not in the presence of known struvite stone or symptomatic urinary tract infection, likely negating the potential consumption of urinary citrate by bacteria.

We did show that the difference in urinary citrate levels was not statistically significant between patients who were taking hydrochlorothiazide and those who were not. The serum chemistry findings were not routinely checked at the 24-hour urine collection, and unrecognized hypokalemia or acidosis due to thiazide diuretic use could have been present, even if patients had been taking potassium citrate supplementation. Thiazide diuretics lead to intracellular acidosis within the proximal tubule, which could alter citrate excretion and the subsequent ratio of urinary citrate and urinary pH. Similarly, information on patients with urinary acidification defects and subsequent baseline severe hypocitraturia was not available in the data set. These patients could have achieved "normal" urinary citrate levels with supplementation, but their urinary pH response to increasing citrate might differ significantly from that of patients with hypocitraturia of other origins.

This retrospective, database-driven study should be considered hypothesis generating. We are currently planning a prospective study of urine collections obtained from patients with nephrolithiasis both before the first initiation of citrate therapy and at defined intervals during therapy, which will allow us to characterize in more detail the relationship between urinary citrate and urinary pH.

CONCLUSIONS

Urinary citrate is an important determinant of stone risk, and citrate supplementation is widely used to increase both urinary citrate levels and urinary pH. Our data have demonstrated that although both citrate and pH increase with citrate supplementation, the two parameters do not correlate and urinary citrate is not a primary determinant of urinary pH, regardless of supplementation status. This finding stands in contrast to traditional teaching and requires additional evaluation in prospective studies.

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