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Effect of Dietary Control of Urinary Uric Acid Excretion in Calcium Oxalate Stone Formers and Non-Stone-Forming Controls

Vernon M. Pais Jr., M.D.¹, Ross P. Holmes, M.D.¹, and Dean G. Assimos, M.D.²

¹Division of Urology, University of Kentucky Chandler Medical Center, Lexington, Kentucky

²Department of Urology, Wake Forest University School of Medicine, Winston Salem, North Carolina

Abstract

Background and Purpose—Hyperuricosuria is a well-recognized risk factor for calcium oxalate urolithiasis. Some studies have demonstrated elevated urinary uric acid excretion in stone formers compared with non-stone-forming controls; nevertheless, these studies were limited by patient consumption of self-selected diets. With the recognition that dietary differences may induce variations in urinary uric acid excretion, we evaluated excretion of this compound in stone formers and controls consuming a standardized diet.

Subjects and Methods—A standardized formula diet was administered to 65 calcium oxalate stone formers and 61 age-matched non-stone-forming controls. During the 3 days of dietary intervention, 24-hour urine collections were obtained. Mean urinary uric acid excretion indexed to urinary creatinine was calculated for each subject, and the results in the two groups were compared.

Results—Stone-forming subjects did not have an elevation in urinary uric excretion compared with control subjects, with mean indexed urinary uric acid excretions of 337 ± 64 mg/g of creatinine and 379 ± 76 mg/g of creatinine, respectively.

Conclusions—With dietary standardization, there was no observed increase in urinary uric acid excretion in our sampled populations. These findings emphasize the role of dietary factors in urinary uric acid excretion and highlight the potential value of dietary interventions.

INTRODUCTION

The Association between hyperuricosuria and calcium oxalate urolithiasis is well recognized. It is generally agreed that hyperuricosuria plays a role in stone generation in some calcium oxalate stone formers.^{1–3} Several mechanisms have been postulated to account for the role of hyperuricosuria in this process. Epitaxial crystal growth is one potential mechanism. This occurs when there is sufficient geometric homology to allow the lattice of one crystal to serve as the scaffold on which a similarly structured crystal may grow. The crystallographic

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Address reprint requests to: Vernon M. Pais, Jr., M.D., Div. of Urology, University of Kentucky Chandler Medical Center, Lexington, KY 40536, E-mail: E-mail: vmpais2@uky.edu.

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dimensions of calcium oxalate and uric acid are similar enough to allow epitaxial growth.³ Heterogeneous nucleation is another potential driving force. This does not require precise crystalline alignment. Instead, crystal nucleation from the metastable solution occurs on any foreign body or solid-phase particle. Hyperuricosuria promotes the formation of sodium and potassium urate crystals, both of which may serve as a (heterogenous nidus) for the nucleation of other crystals such as calcium oxalate. A third proposed mechanism is that of a uric acid-mediated inactivation of inhibitors of calcium oxalate formation and aggregation.³ Finally, a (salting out) phenomenon has been postulated in which the abundance of urate decreases the capacity of urine to dissolve calcium oxalate.⁴

The significance of hyperuricosuria was demonstrated in a randomized double-blind study in which hyperuricosuric recurrent calcium oxalate stone formers received either allopurinol, an agent that inhibits uric acid production, or placebo.⁵ Stone activity at 2 years of follow-up was significantly less in the allopurinol cohort, and this treatment was associated with a significant reduction in uric acid excretion from baseline levels. The latter reduction did not occur in the placebo group.

There are conflicting reports regarding the prevalence of hyperuricosuria in both calcium oxalate stone formers and non-stone formers. Coe³ reported a 26% prevalence of hyperuricosuria in calcium stone formers, while the figure reported by Fellstrom and associates⁶ was only 13%. In addition, one review of the literature⁷ revealed that the prevalence of hyperuricosuria was similar in stone formers and non-stone formers. Some investigators have reported higher mean 24-hour uric acid excretion in stone formers than in non-stone-forming subjects; others have noted no such difference.^{8–11} However, these studies were based on urine collections obtained while the subjects were consuming self-selected diets, and it is well documented that uric acid excretion can be impacted by dietary factors. For example, the consumption of foods with high purine content such as animal protein promotes urinary uric acid excretion.¹² It therefore is possible that the aforementioned differences in results reflect differences in diet.

We performed a study in which controlled diets were administered to adult calcium oxalate stone formers and non-stone formers in order to limit environmental variability and thus allow better assessment of urinary uric acid excretion in these two groups.

SUBJECTS AND METHODS

This study had the approval of our Institutional Review Board. Sixty-five adult calcium oxalate stone formers and 61 age-matched non-stone-forming controls participated. In the stone-forming group, there were 51 men and 14 women, while the control group consisted of 12 men and 49 women. The mean age for both groups was 43 years. Subjects consumed a standardized formula diet for 3 days (Ensure; Ross Labs) adjusted for caloric needs as determined by the Ohio Weight Loss Planner (Ohio Distinctive Software). Three consecutive 24-hour urine specimens were collected from each of the subjects during the period of dietary intervention. These specimens were acidified with boric acid and kept refrigerated during collection. Uric acid and creatinine (Cr) were assayed using a spectrum analyzer with assay kits provided by the manufacturer (Abbott).

We tested the null hypothesis that urinary uric acid excretion would be equal in the two groups when the diet was controlled. The mean of the three 24-hour urinary uric acid values indexed to urinary Cr was calculated for each subject. These data were then subjected to statistical analysis. An unpaired, two-tailed Student *t*-test was employed, with α set at 0.05. Commercial statistical software (Microsoft Excel Analysis ToolPak) was utilized for data analysis.

RESULTS

The mean urinary uric acid excretions are shown in Table 1. In the stone-forming group, the mean uric acid excretion was 337 ± 64 mg/g of Cr. This was less than the mean urinary uric acid excretion in the control group, 379 ± 76 mg/g of Cr ($P < 0.05$).

We additionally evaluated uric acid excretion by sex, as a gender influence has been identified.⁶ We found no statistically significant differences when comparing male stone formers with male controls or female stone formers with female controls (Table 1). However, among all women, female non-stone formers, and female stone formers, there was a statistically significant elevation in Cr-adjusted uric acid excretion compared with their male counterparts (Table 2).

The normal range of urinary uric acid excretion and, by corollary, the limits defining hyperuricosuria have been assigned many values by different investigators and laboratories.¹³ We utilized a definition of hyperuricosuria as those values exceeding 2 standard deviations from the mean of our control population on the formula diet. The calculated value is 531 mg/g of Cr. Two hyperuricosuric subjects (3%) in the control group and one (2%) in the stone-forming group were identified. Histogram plots of the distribution of adjusted urinary uric acid are seen in Figure 1.

DISCUSSION

The association between hyperuricosuria and calcium oxalate urolithiasis is well recognized. Coe and colleagues have elegantly demonstrated the induction of calcium oxalate crystallization by urate with *in-vitro* models.¹⁴ Several groups have reported a higher prevalence of hyperuricosuria in stone-formers and elevated excretion of uric acid in stone formers compared with controls.^{3,8,9} Medical therapy directed at reducing uric acid production and excretion may reduce the incidence of calcium oxalate stone formation.^{5,15} In general, medical therapy offers significant benefit to those with an otherwise-uncorrectable inborn metabolic defect; however, it may be unnecessary if correction of environmental factors would achieve the same effect. Furthermore, chronic medical management is not without significant expense, and patients require monitoring for adverse effects for the duration of therapy. The majority of studies have evaluated subjects on self-selected diets, which do not control for the potential influences of diet. We thus evaluated urinary uric acid excretion in both a stone-forming and a control population using dietary control.

Higher urinary uric acid excretion in calcium oxalate-stone-forming populations than in non-stone formers has been reported by several groups.^{3,8,9} Although Leonetti and colleagues⁹ noted significantly higher urinary excretion of uric acid in stone formers than in controls, this was positively correlated with urinary urea excretion. This finding indicates that the difference in uric acid excretion is at least partly attributable to a difference in dietary protein intake. In our study, we eliminated this factor by administering a standardized diet. Additionally, we have used urinary Cr as a surrogate for lean body mass to control for the influence of body size. Utilizing these controls, we found that mean urinary uric acid excretion is no higher in calcium oxalate stone formers than it is in controls. In fact, adjusted urinary uric acid excretion was 12% higher in controls than in stone formers. This result is in accordance with the findings of Curhan et al,¹³ who also noted higher urinary uric acid excretion in non-stone formers than in stone formers. However, their subjects were not on controlled diets, and urinary uric acid excretion was not indexed to urinary Cr.

With the control of diet and lean body mass, we additionally noted that the frequency of hyperuricosuria is similar in our cohorts of calcium oxalate stone formers and non-stone-forming controls. Furthermore, the frequency of hyperuricosuria in both groups is less than

has been reported in subjects on self-selected diets.^{3,6,7} These findings suggest that a substantial portion of clinically identified hyperuricosuria is dietary.

We noted a statistically significantly higher adjusted excretion of urinary uric acid in women than in men. This is in contrast to the findings of Fellstrom and colleagues,⁶ who noted higher urinary uric acid excretion in men. Several explanations are possible. In the earlier study, diet was not controlled, and uric acid excretion was not indexed to Cr. Additionally, there may be gender-specific responses to the formula diet and differences in endogenous purine metabolism or renal tubular handling of uric acid.

Our study was not designed to evaluate the genetic contribution to hyperuricosuria. The recent identification of specific urate transporters responsible for maintaining uric acid homeostasis and the identification of polymorphisms with distinct phenotypic differences in uric acid homeostasis suggest that genetic factors influence uric acid excretion in certain stone formers.^{16,17} However, the absence of a bimodal or trimodal distribution of urinary uric acid excretions in our controlled-diet study suggests that environmental factors significantly influence excretion of this urinary analyte.

We recognize several limitations of our study. First, a larger percentage of the non-stone forming subjects were women. Evaluation of our controlled diet cohorts prior to the institution of the formula diet would have allowed more definitive conclusions to be drawn regarding the effect of the intervention. Additionally, the potential exists that the similarity in urinary uric acid excretion in the stone-forming and control populations is artifactual. The low prevalence of hyperuricosuria in the stone-forming group could simply reflect a difference in sampling compared with studies yielding contrary results. It would thus be of interest to pursue the same line of investigation in a population with previously demonstrated hyperuricosuria while on self-selected diet. Nevertheless, our findings demonstrate similar uric acid excretion in stone formers and non-stone-forming controls when dietary purine intake is controlled. These data are therefore suggestive of an important environmental role in urinary uric acid excretion.

CONCLUSIONS

When diet is controlled, urinary uric acid excretion is not higher in calcium oxalate stone formers than in non-stone-forming controls. The absence of a statistically or clinically significant difference in urinary uric acid excretion in these groups should discourage the nonselective use of agents such as allopurinol for calcium oxalate stone formers. Rather, intervention should be considered mainly in those with hyperuricosuria unresponsive to dietary modifications.

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ABBREVIATIONS USED

Cr, creatinine.

FIG. 1.
Distribution of 24-hour uric acid excretion in stone formers and non-stone formers.

TABLE 1Urinary Uric Acid Excretion On Controlled Diets (Mean $\pm$ Sd) In Stone-Forming And Non-Stone-Forming Subjects

	Urinary uric acid (mg/g of Cr)
Stone formers (<i>N</i> = 65)	337 $\pm$ 64
Male (<i>N</i> = 51)	325 $\pm$ 47
Female (<i>N</i> = 14)	381 $\pm$ 94
Non-stone formers (<i>N</i> = 61)	379 $\pm$ 76
Male (<i>N</i> = 12)	315 $\pm$ 44
Female (<i>N</i> = 49)	394 $\pm$ 75
P value	
All	<0.05
Male	0.52
Female	0.59

TABLE 2Urinary Uric Acid Excretion (Mean $\pm$ Sd) In Male And Female Subjects On Controlled Diet

	Stone formers	Non-stone formers	Both groups
Male subjects	325 $\pm$ 47	315 $\pm$ 44	323 $\pm$ 45
Female subjects	381 $\pm$ 94	394 $\pm$ 75	392 $\pm$ 78
<i>P</i> value	<0.01	<0.001	<0.001