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ORIGINAL PAPER

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Chitosan does not reduce post-prandial urinary oxalate excretion

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Abstract Chitosan is a positively charged non-absorbable cellulose-like fibrillar biopolymer derived from shellfish which forms films with negatively charged surfaces. We hypothesized that negatively charged oxalate in the intestinal lumen could attach to the positively charged tertiary amino group of chitosan. We studied the effects of chitosan on intestinal oxalate absorption by measuring urinary oxalate excretion following an oral oxalate load with and without accompanying oral chitosan. The subjects consumed a fixed diet and collected urine for 24 h, in divided periods, during control and experimental protocols. Urine was collected with HCl and thymol as a preservative. For the control period, the subjects consumed an oxalate load, 50 g of cooked spinach, with water for lunch; the post-prandial urine collection was divided into three periods of 2 h. For the experimental period, 1 week later, the subjects consumed the same diet as that during the control period, but added 2 g of chitosan to the oxalate load. Post-prandial urinary oxalate excretion was expressed as mg oxalate/g creatinine. The spinach load was associated with a significant post-prandial increase in urinary oxalate during the control period of 25.7 ± 12.8 mg/g creatinine. Accompanying the oxalate load with chitosan was well tolerated. There was no decrease in post-prandial urinary oxalate excretion during the experimental period: oxalate excretion rose by 31.3 ± 16.9 mg/g creatinine ($P = 0.57$, NS). We conclude that chitosan does not reduce acute intestinal oxalate absorption and therefore does not affect post-prandial urinary oxalate excretion.

Keywords Renal calculi · Chitin analogs and derivatives · Diet · Kidney stones · Polysaccharides · Urolithiasis

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Introduction

Urinary oxalate excretion is an important contributor to calcium oxalate kidney stone formation [1]. Its contribution to calcium oxalate supersaturation, relative to calciuria, in calcium stone formers with mild hyperoxaluria may be debated [2, 3]. That it is likely to play a role in such patients is made clear by its unquestioned contribution to stone formation in enteric hyperoxaluria and the genetic disorder primary hyperoxaluria. One factor that hinders the development of a consensus on the importance of oxalate excretion in patients lacking these latter two disorders is the absence of any randomized controlled trials of a therapeutic reduction in urinary oxalate excretion [4]. In turn, this absence stems from the relatively unsatisfactory nature of the modalities available to reduce urinary oxalate.

In this study, we evaluated chitosan as a potential binder of intestinal oxalate. Chitosan is a positively charged macromolecule that has been promoted as an over-the-counter weight loss preparation [5]. Its effect is attributed to its ability to bind negatively charged fats in the intestinal lumen and diminish their absorption. We hypothesized that chitosan would bind oxalate in the intestinal lumen, thus decreasing the urinary oxalate excretion.

Materials and methods

Subjects

Five healthy male volunteers participated in the study. The subjects provided informed consent regarding study participation and the study was approved by the local institutional review board.

During the control period all subjects recorded what they ate for dinner on day 0. On day 1, the subjects initiated a 24-h urine collection, separated into five separate urine collections. The post-awakening void was discarded. Collection 1 began post-awakening and extended until noon. For breakfast, each subject consumed one measured bowl of cereal with 8 ounces of 1% fat milk and coffee or water; juice was excluded. After the conclusion of collection 1 at noon, a high-oxalate meal was consumed, consisting of 50 g of frozen, microwaved Birds Eye brand chopped spinach. Water intake was encouraged and no other food was permitted. After the high oxalate meal, urine was collected every 2 h (collection 2 from 12–2 p.m., collection 3 from 2–4 p.m., and collection 4 from 4–6 p.m.). Finally, collection 5 extended from 6 p.m. until the void upon waking the following morning. Participants recorded dinner that evening.

Exactly 1 week later, the subjects repeated the entire protocol with one exception: they accompanied the noon high-oxalate meal with four tablets of Chitosense, an OTC preparation of chitosan. Dinners on the nights before and after the collections were identical to those consumed during the first control collections.

In order to demonstrate that the absorption of the oxalate delivered by this spinach meal could be diminished by an orally ingested preparation other than the chitosan, one subject repeated the experimental period accompanying the spinach with 500 mg of calcium as calcium carbonate.

Urine collections were maintained at room temperature and preserved with thymol and 4 N hydrochloric acid to achieve a pH of less than 2.0. The subjects recorded the volume of each individual urine collection and then placed 10 ml aliquots from each collection into sealed tubes that were sent by overnight mail to Litholink Corp (Chicago, IL) for analysis.

Urine chemistry studies

All urine samples were analyzed for calcium, oxalate, creatinine, and sodium concentrations by standard laboratory techniques using a Beckman-Synchron CX5 (Beckman Instruments, Brea, California) [6]. Oxalate was measured by enzyme assay using oxalate oxidase (Sigma Chemical Co., St. Louis, Missouri).

Statistics

Urine values obtained during the experimental and control periods were compared by the paired Student *t* test and considered statistically different at $P < 0.05$. Statistical data were generated and analyzed with a commercially available software package, Systat (Point Richmond, CA). Results were expressed as mean ± SD.

Results

Accompanying the spinach load with chitosan was well tolerated in all subjects, without any adverse effects. The protocol was successful in achieving a significant peak post-prandial mean increase in urinary oxalate excretion of 25.7 ± 12.8 mg/g creatinine during the control period. However, there was considerable variation in individual oxalate excretion with the spinach load. Figure 1 shows mean urinary oxalate excretion during the five collection periods in both the control and experiment periods. There was no effect of oral chitosan to reduce urinary oxalate excretion. The peak increase in urinary oxalate excretion was 31.3 ± 16.9 mg/g creatinine ($P = 0.57$, NS). During the first six post-prandial hours, the increment in oxalate excretion from baseline was 18.8 ± 9.5 mg/g creatinine during the control periods and 22.8 ± 12.5 mg/g creatinine during the chitosan periods ($P = 0.58$, NS).

Figure 2 shows the same data presented as a percentage. It shows the percent increase in oxalate excretion from baseline during the five collections in both the control and experimental periods. Again, in this analysis, there was no decrease in post-prandial urinary oxalate excretion caused by chitosan.

The protocol was successful in controlling the excretion of other urinary solutes. There was no significant change between the control and experimental periods in excretion of calcium (50.6 ± 17.1 vs. 53.6 ± 20.8 mg/g creatinine for the 6 h post-prandial periods; $P = 0.81$, NS) or sodium (91.4 ± 48.8 vs. 69.6 ± 55.3 mmol/g creatinine; $P = 0.52$, NS).

Figure 3 demonstrates the result in an individual participant by repeating the experimental period with a dose of calcium to accompany the high-oxalate meal. Calcium ingestion successfully reduced the increase in urinary oxalate excretion from 18.4 mg/g creatinine in

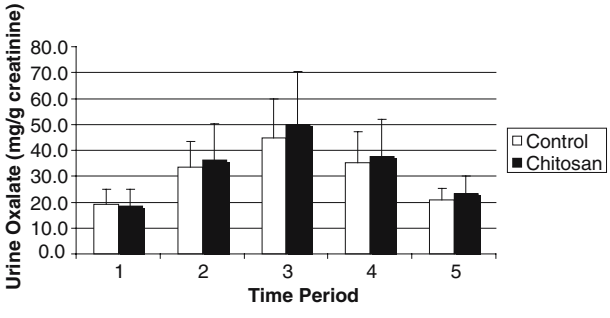

Fig. 1 Chitosan did not reduce urinary oxalate excretion when accompanying an oral oxalate load (means ± SD)

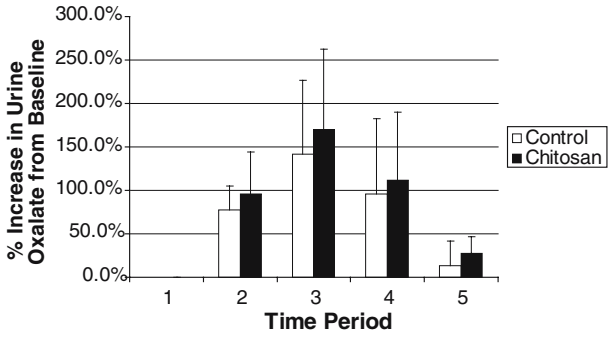

Fig. 2 Chitosan did not reduce the proportional increment in urinary oxalate excretion caused by the oral oxalate load in comparison to baseline (period 1) (mean ± SD)

the control period to 6.5 mg/g creatinine in the calcium carbonate period.

Discussion

The contribution of urinary oxalate excretion to calcium oxalate stone formation is presumed to be substantial [7]. Mild hyperoxaluria, as distinguished from the well-characterized genetic condition primary hyperoxaluria, may be present in between roughly 20 and 40% of patients with calcium oxalate stones [8, 9]. Areas of recent research and debate in the role of oxalate have included the relative proportion of urinary oxalate arising from endogenous metabolism versus diet; the relative importance to urinary lithogenicity of oxalate versus calcium excretion; the effect of ingested calcium on intestinal oxalate absorption and a variety of other topics [10]. In part, the reason these subjects remain of interest is that a consensus regarding an effective means of lowering urinary oxalate excretion has not yet been developed. In addition, despite the ability of diverse therapeutic maneuvers to lower urinary oxalate, no randomized controlled trial has demonstrated a reduction in stone formation attributable to lowering urinary oxalate excretion in patients with idiopathic hyperoxaluria.

In this study, we sought to develop a new therapy to reduce urinary oxalate excretion. We reasoned that chitosan, a positively charged non-absorbable cellulose-like fibrillar biopolymer derived from shellfish, would bind negatively charged oxalate in the intestinal lumen and thereby decrease urinary oxalate excretion. Increasing calcium or magnesium intake has been shown to lower urine oxalate excretion, but the use of these products is limited by increased calcium excretion and diarrhea, respectively [11, 12]. We chose to study chitosan as an alternative cation that might reduce oxalate excretion without undesirable side effects. Chitosan has recently been promoted as aiding in weight loss via binding of lipids, though its efficacy is not unequivocally established [5]. We were not able to demonstrate an effect of chitosan to reduce urinary oxalate excretion after an oral oxalate load.

There are some limitations to this study. First, we did not perform a dose-response study. It is possible that the spinach-derived oxalate may have been excessive for this dose of chitosan. Perhaps an effect of chitosan would be revealed by using more chitosan or a smaller oxalate load. We chose a dose of chitosan that has been recommended for weight loss and thought that most stone-formers would not want to take more than four large pills at a time. We did demonstrate that the oxalate load was not large enough to prevent an effect of oral calcium to lower urinary oxalate excretion. As a positive control, a single participant experienced a reduced oxalate excretion after accompanying the spinach meal with a modest dose of 500 mg of calcium carbonate. Second, it may be possible that chitosan had a higher affinity for other ingested anions, such as phosphates. We did not examine other means of delivery of an oxalate load, such as feeding our subjects with sodium oxalate or another source of dietary oxalate. Finally, we did not examine whether chitosan is capable of binding oxalate in vitro.

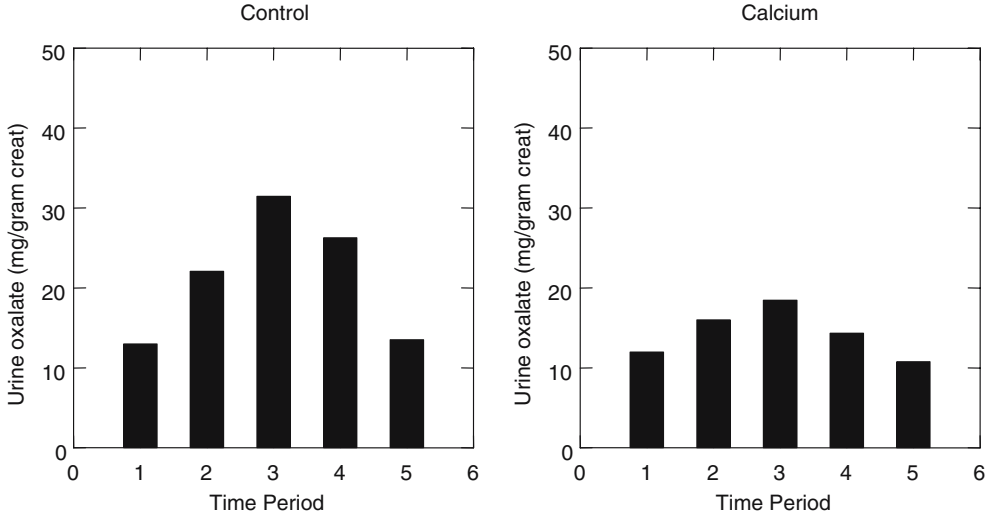

Fig. 3 An individual participant repeated the high-oxalate meal with calcium carbonate and demonstrated a significant reduction in urine oxalate excretion

The means by which urinary oxalate can be lowered are limited. Dietary oxalate restriction is often prescribed and may be successful in many patients, but many other patients cannot identify sources of oxalate in their diets and do not have changes in urinary excretion despite restriction [8]. Ox-Absorb is a ''marine hydrocolloid'' which binds intestinal oxalate diminishing absorption but which is not in widespread use [13]. Increasing dietary calcium ingestion lowers urinary oxalate excretion but may be effective for calcium stone prevention only if dietary sodium is concomitantly restricted and may otherwise lead to exacerbations of hypercalciuria [14].

The potential for microorganisms to lower oxalate excretion has received recent attention. Oxalobacter formigenes, an organism whose main substrate for ATP generation is oxalate, has been administered with a sodium oxalate load to reduce urinary oxalate excretion [15]. It has also demonstrated some efficacy in patients with primary hyperoxaluria but is not yet commercially available [16]. Lactic acid bacteria, administered to patients with enteric hyperoxaluria, have also been associated with some beneficial reduction in oxalate excretion [17]. However, this same preparation had no effect on urinary oxalate excretion in calcium stone formers with mild hyperoxaluria (authors' unpublished results).

In summary, chitosan did not lower urinary oxalate excretion after an orally administered oxalate load. Development of new oxalate binders would be of great clinical relevance in prevention of recurrent calcium stone formation.

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