

Probiotics for prevention of urinary stones

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Background: Urinary supersaturation is one key determinant of calcium oxalate (CaOx) urinary stone formation, and urinary excretions of oxalate and citrate are two key determinants. Each is influenced by gastrointestinal processes.

Methods: Open label and randomized placebo studies have examined the effect of oral probiotic preparations on urinary supersaturation and oxalate excretion. Cross sectional studies in humans have studied the association of *Oxalobacter formigenes* colonization status and urinary oxalate excretion and prevalence of urinary stones. The intestinal microbiome of representative animals adapted to a high oxalate diet has been defined.

Results: The fecal content of *O. formigenes*, the best studied oxalate-degrader, varies depending on stone status. However, trials with probiotics designed to degrade oxalate including those containing *O. formigenes*, *Lactobacillus*, and/or *Bifidobacterium spp.*, have been disappointing. Multiple intestinal segments of animals on a high oxalate diet contains diverse communities of microorganisms that can function together to degrade and detoxify a large oxalate load.

Conclusions: Although the intestinal microbiome seems likely to play a role to modify gastrointestinal absorption of lithogenic substances and hence urinary stone risk, whether we can develop tools to manipulate it and decrease this kidney stone risk remains to be determined.

Keywords: Calcium oxalate (CaOx); *Lactobacilli*; microbiome; nephrolithiasis; *Oxalobacter formigenes*

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Introduction

Biology of calcium oxalate (CaOx) kidney stones

The urine of most humans is supersaturated and favors CaOx crystallization. Thus, perhaps it is not surprising that 70% or more of kidney stones are composed of CaOx (1). Given that the urine of most persons is supersaturated for CaOx, one might indeed wonder why everyone does not form stones. However, although supersaturation is key and requisite for stone formation, other biologic events are also implicated. These include the formation of anchored precursors within the kidney including Randall's plaque and collecting duct plugs (2-5), macromolecules that control the rates of crystal growth and aggregation (6,7), and crystal internalization

and processing by cells (8). These secondary factors are only partially understood, and not subject to therapeutic interventions at the present time.

Fortunately, relatively more is known about the control of the urinary composition of stone forming salts. Key factors that determine urinary supersaturation include the urinary excretion of calcium, oxalate, citrate and water. Of these, evidence is strong that genetics greatly influence urinary calcium excretion (9), although diet is also an important modifier (10). Evidence also suggests that there are heritable components of the amount of urinary oxalate, citrate and even water (the latter likely mediated by thirst) (11). However, most likely environment (diet and fluid intake/losses) are relatively more important for determining the urine composition.

Oxalate biology

Oxalate is a small dicarboxylic acid formed as an end product of metabolism by humans, largely in the liver (12). Oxalate is also found in certain plants, largely as CaOx crystals in the stems and leaves. Whatever oxalate is generated or absorbed from the diet, it must be eliminated in the urine (13). At least three genetic defects are known to cause primary hyperoxaluria (PH), which leads to over-generation of oxalate in the liver (12). Whether or not other genetic variation in these or other genes underlies milder hyperoxaluria in the general population remains unknown.

Because oxalate exists in plants in the form of CaOx crystals, only a small amount is bioavailable for absorption (typically about 10% or less) (14). The majority of anionic oxalate is thought to be absorbed via a paracellular route (Figure 1) (15). Apical and basolateral transporters have also been demonstrated to have oxalate-transporting activity *in vitro*. Conversely, the role of transcellular oxalate transport in normal human biology remains unclear. Interestingly, however, knockout of *SLC26A6* (the gene that encodes PAT1) results in hyperoxaluria due to decreased secretion of oxalate into the gut lumen in mice (16,17). Thus it has been hypothesized that increased degradation of oxalate by the intestinal microbiome could create a driving force for oxalate secretion into the gut, and hence reduce

urinary excretion. Furthermore, certain bacteria might release soluble factors that increase PAT1 activity (18).

The majority of oxalate is eliminated by the kidney via filtration. A smaller amount can be secreted in the proximal tubule. The amount of oxalate secretion can increase in CKD, perhaps in response to increasing blood concentrations (19). Oxalate is not secreted or reabsorbed past the proximal tubule. Thus the oxalate concentration increases as water is reabsorbed along the nephron, reaching critical thresholds by the collecting duct where it can crystallize with calcium (19). This is undoubtedly a key factor in urinary stone risk, especially in regards to growth upon a preexisting nidus, since a urinary stone cannot develop in the absence of supersaturation.

The gastrointestinal tract is a key player in oxalate biology. In normal individuals, only about 10% of ingested oxalate is absorbed, presumably because it is tightly complexed with calcium within the plant matter ingested (14). Factors that influence oxalate absorption include the amount of calcium and fat in the diet (20). It is thought that fatty acids bind calcium, and thus increase unbound anionic oxalate that can then be absorbed paracellularly. Free calcium in the gut lumen can in turn bind up this anionic oxalate and prevent its absorption. Patients with any cause of fat malabsorption are thus at risk

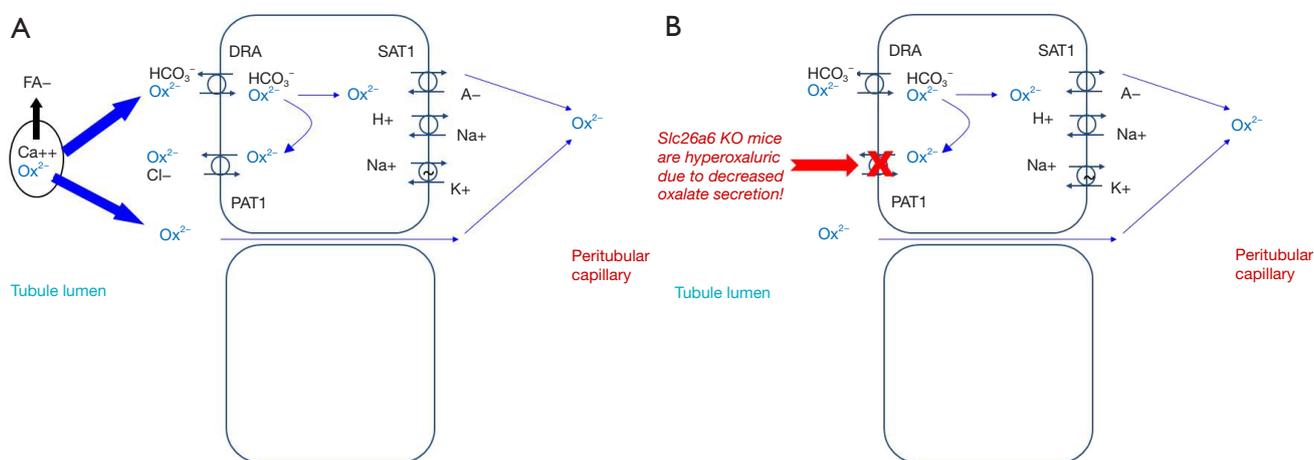


Figure 1 Oxalate transport in the intestine. (A) It is thought that the majority of oxalate is absorbed paracellularly. In states of fat malabsorption, increased fatty acids can bind calcium resulting in more oxalate ion free for absorption. Paracellular transporters to facilitate transcellular oxalate absorption include DRA (*SLC26A3*) on the apical surface that can exchange oxalate for bicarbonate, and SAT1 (*SLC26A1*) on the basolateral surface that can exchange oxalate for sulfate and other anions; (B) PAT1 (*SLC26A6*) in the apical surface can facilitate oxalate secretion into the lumen in exchange for chloride. *SLC26A6* knockout mice are hyperoxaluric, presumably due to loss of this intestinal secretory pathway.

of enteric hyperoxaluria on this basis.

On average, CaOx stone formers appear to absorb slightly higher percentage of oxalate from their food (14). The reasons are not known. Could this be due genetic alterations in oxalate transport, a tendency towards fat malabsorption, or changes in the intestinal microbiome? To date there are no clear answers. Typical treatments for stone patients with mild hyperoxaluria include a lower oxalate diet with adequate amounts of calcium. Preferably the calcium should be in food sources like dairy products, since calcium supplements might slightly increase stone risk (21). Lower fat intake is also a good idea, although not extensively studied outside of the group with clear enteric hyperoxaluria. It has been hoped that manipulation of the intestinal microbiome might also alter oxalate absorption.

Citrate biology

Citrate is thought to be an important crystallization inhibitor (22). Citrate complexes with filtered calcium and also has independent effects at the crystal surface to inhibit CaOx and brushite crystal growth (22,23). Some filtered citrate is reabsorbed in the proximal tubule, largely regulated by proximal tubule cell pH, with lower intracellular pH increasing citrate reabsorption (24). In the absence of renal tubular acidosis the net absorption of alkali by the gastrointestinal tract is thought to be the most important determinant of net urinary citrate excretion (25). Thus a diet weighted towards protein, chronic malabsorption states, hypokalemia, or distal renal tubular acidosis are the most common causes of hypocitraturia, which is found in 20–60% of calcium stone formers (24). Treatment is of the underlying disorder and/or administration of potassium citrate are the available options (24). Given the key role of gastrointestinal function in citrate homeostasis, it seems likely that the microbiome might influence net alkali absorption, and hence urinary citrate excretion. However, no evidence to this effect has yet been published. Indeed, urinary citrate excretion did not increase in the kidney stone probiotic studies where this value was reported (26–28).

Methods

In this systematic review we present the results of open label and randomized placebo studies that have examined the effect of oral probiotic preparations on urinary CaOx supersaturation and oxalate excretion. We also discuss

cross sectional studies in humans that have studied the association of *O. formigenes* colonization status and urinary oxalate excretion, and prevalence of urinary stones. Finally, we review what is reported regarding potential oxalate-degrading organisms in the intestine of humans and animals.

Results

Trials of Lactobacillus-containing probiotics for stone disease

Investigators have conclusively demonstrated that components of the endogenous digestive microflora can utilize oxalate, potentially limiting its absorption from the intestinal lumen (29). Probiotics containing *Lactobacilli spp.* have been commonly used to treat gastrointestinal symptoms such as antibiotic-induced diarrhea. Thus one might hope they would have favorable effects on urinary oxalate and/or citrate excretion. Oxadrop[®] was formulated specifically for potential treatment of hyperoxaluria (28). Each gram of the mix (Oxadrop[®]) contains 2×10^{11} bacteria (*Lactobacillus acidophilus*, *L. brevis*, *Streptococcus thermophilus*, and *Bifidobacterium infantis*). The different strains are mixed in a 1:1:4:4 weight and prepared as a granulate. The organisms were chosen on the basis of their ability to degrade oxalate *in vitro*.

In an initial pilot study, Oxadrop[®] reduced urine oxalate excretion by 40% in a group of mildly hyperoxaluric CaOx stone formers (30) (Table 1). The hypo-oxaluric effect even lasted after a 1 month wash out period. In a subsequent study, a group of ten patients with various causes of enteric hyperoxaluria and stones were also treated with Oxadrop[®] (28). This study was also unblinded and thus lacked a placebo arm. Patients sequentially received 4 g Oxadrop[®], 8 g Oxadrop[®], and 12 g Oxadrop[®] for 1 month each. These data suggested a small effect at 4 and 8 g, with a fall in urine oxalate excretion of about 20–25% (Table 1). The third month on 12 g of Oxadrop[®] the urine oxalate excretion was again close to baseline, after which it fell slightly after another washout month. Thus this study suggested there might be a dose-dependent effect of the preparation, or perhaps that the differences observed in urine oxalate excretion at the lower (and/or higher) doses were nonspecific and not related to the study drug at all.

Based upon these intriguing data, albeit inconclusive, a more rigorous randomized trial was completed in a population of 40 enteric hyperoxaluria stone formers (26).

Table 1 Trials of *Lactobacillus*-containing probiotics for hyperoxaluria

Author	Population	Design	Outcome
Campieri <i>et al.</i> (30)	Mildly hyperoxaluric stone formers (n=6)	Unblinded; 4 g Oxadrop® for 30 days	Urine oxalate dropped 40% at 30 days and remained down 50% at 60 days
Lieske <i>et al.</i> (28)	Patients with enteric hyperoxaluria (n=10)	Unblinded; 4 g Oxadrop® for 30 days; then 4 g for 30 days; then 12 g for 30 days	Urine oxalate dropped 19% at 30 days; 24% at 60 days; 2% at 30 days; and 20% after a 30-day washout
Lieske <i>et al.</i> (26)	Patients with enteric hyperoxaluria (n=40)	Patients on controlled diet randomized to Oxadrop®, AKSB, or placebo for 4 weeks	No change from baseline (controlled diet alone) for any group
Goldfarb <i>et al.</i> (31)	Stone patients with mild hyperoxaluria (n=20)	Randomized to placebo vs. Oxadrop® for 56 days	No change in urine oxalate in either group at 28 or 56 days
Ferraz <i>et al.</i> (27)	Stone patients (n=14)	Sequentially on high oxalate diet then high oxalate diet plus <i>Lactobacilli</i> and <i>Bifidobacterium</i> preparation	Urine oxalate increased on high oxalate diet with no effect of the probiotic

AKSB, Agri-King Synbiotic.

Patients were randomized to Oxadrop®, placebo, or an alternative probiotic, Agri-King Synbiotic (AKSB) (Agri-King Inc., Fulton, IL, USA). AKSB is a candidate synbiotic preparation extensively studied at Mayo Clinic that was hoped to have beneficial effects on gastrointestinal health, although there was no direct evidence it should influence oxalate metabolism directly (26). Subjects were given two AKSB capsules per day for a total of 10¹⁰ organisms containing: (I) fructooligosaccharide (115 mg), manufactured as Ultra-FOS ST by Encore Technologies, Minnetonka, MN, as food-grade quality and is a prebiotic component of AKSB; (II) *Enterococcus faecium* [*E. faecium*] SF68; 4.5 billion] produced by Cerbios-Pharma SA (Barbengo, Switzerland); (III) *Saccharomyces cerevisiae* *subsp. boulardii* (300 million), a yeast produced as Levucell SB by Lallemand Biochem International, Ontario, Canada, as ‘food-grade’ quality; and (IV) *Saccharomyces cerevisiae* (200 million), a food-grade yeast produced as active dry yeast by SAF Corporation in Milwaukee, WI, USA. AKSB was developed by Agri-King with the primary aim of improving gut performance in animals so that the routine use of antibiotics in animal feeds could be reduced or eliminated. Studies in farm animals by Agri-King have confirmed that the preparation improves intestinal health and reduces the risk of illness when animals are challenged with food- or water-borne pathogens, and overall growth rates improve.

In this randomized, placebo-controlled trial study patients were placed on a controlled metabolic diet with normal calcium (1,000 mg) and reduced oxalate

(80–100 mg), appropriate for their CaOx urinary stone diagnosis. The diet itself was effective, reducing urine oxalate excretion by an average of 36%, with an overall improvement in urinary CaOx supersaturation. However, urine oxalate not fall further from this baseline on controlled diet with either probiotic or placebo. It is possible that the diet was “too effective”, in essence not leaving enough free oxalate within the gut lumen for the probiotics to degrade. Nevertheless, the more rigorous design than the previous studies suggests general use of currently available *Lactobacillus*-containing preparations may not work as well as initially hoped in patients with enteric hyperoxaluria.

Subsequently, a 56-day randomized, placebo controlled trial of Oxadrop® was completed in 20 mildly hyperoxaluric stone formers, without known enteric hyperoxaluria and on a free choice diet (31). In this study, like the placebo-controlled enteric hyperoxaluria study (26), no effect on urinary oxalate excretion was observed in either arm at 28 or 56 days.

As noted above, it has been hypothesized that oxalate-degrading bacteria may require a certain amount of free oxalate to survive and/or thrive in the intestinal lumen. Thus Ferraz and colleagues studied a population of 14 stone formers (7 men and 7 women) on a low calcium (400 mg) and high oxalate (200 mg) diet (27). Under these dietary conditions urinary oxalate excretion did increase by 30% from the previous baseline on a free choice diet. However, addition of a *Lactobacillus/Bifidobacterium* preparation had no further effect on urinary oxalate levels.

Thus, on balance one can conclude that evidence from the more rigorous studies does not suggest that currently available *Lactobacillus* or other probiotic products and/or regimens of their administration can consistently reduce urinary oxalate excretion.

Oxalobacter and oxalate metabolism

O. formigenes is an interesting organism. This obligate anaerobe utilizes oxalate as its sole energy source. The three key genes are the oxalate/formate antiporter (*OxIT*), a formyl coenzyme A transferase (*frc*), and oxalyl-coenzyme A decarboxylase (*Oxc*). Most humans become colonized with *O. formigenes* during childhood, but colonization can be lost later in adulthood, perhaps in response to antibiotics. The balance of dietary calcium and oxalate (and hence free oxalate in the gut lumen) appears to influence the amount of *O. formigenes* recovered from the stool (32). Thus, *O. formigenes* might be an inducible defense against ingestion of a high oxalate diet.

Observational studies support a role for *O. formigenes* colonization in CaOx urinary stone risk. For example, in a large cross sectional study only 17% of 247 stone patients were colonized with *O. formigenes*, while 38% of 259 control patients were (33). Previous antibiotic usage was associated with colonization status. However, although the stone patients had higher urine oxalate excretion, colonization status did not correlate with urine oxalate excretion in these patients who were on a self-choice diet.

In a smaller cross sectional study, eleven *O. formigenes*-colonized stone formers were found to have a lower urine oxalate excretion (0.31 ± 0.10 mM/day) compared to 26 non-colonized stone formers (0.40 ± 0.13 mM/day) (34). Non colonized stone formers were more likely to have a history of multiple stone events. Interestingly, the percent of absorption of an oral radiolabeled oxalate load did not vary between the two groups, despite the fact the plasma oxalate was significantly higher in the *O. formigenes* colonized group. Together, these observations are consistent with decreased gastrointestinal secretion of oxalate by the patients not colonized with *O. formigenes*.

Because of evidence that oxalate can be secreted by rodents into their gut lumen (17), there has been great interest to test whether oral administration of *O. formigenes* might increase oxalate degradation within the gut lumen and possibly promote oxalate secretion amongst hyperoxaluric patients, even those with PH. The hoped-for net effect is to increase gut and decrease

urinary oxalate elimination. Studies in a mouse model of type 1 PH support the possible effect of this strategy (35). Indeed, in a small unblinded pilot study of four PH patients, urine oxalate excretion fell up to 50% during 4 weeks on an oral preparation of *O. formigenes* (36). In this pilot study, three out of five patients with preserved renal function demonstrated a 22–48% reduction of urinary oxalate excretion while taking the first oral formulation of *O. formigenes*. Two other patients in the study with chronic kidney disease on dialysis experienced a significant reduction in plasma oxalate and amelioration of clinical symptoms. While taking a second *O. formigenes* formulation, four out of six patients with normal renal function demonstrated a reduction in urinary oxalate ranging from 38.5% to 92%. Although *O. formigenes* could be detected in the vast majority of subjects on active treatment, fecal recovery dropped at follow up (off therapy), indicating only transient gastrointestinal-tract colonization while subjects were still taking the preparation.

Despite these promising preliminary data, in the decade since no evidence from a follow up controlled trial has been published to further support the use of oral *O. formigenes* therapy in PH. Potential issues with the therapeutic use of oral *O. formigenes* include formulation of pharmacologic amounts of this obligate anaerobe, as well as the long term viability of this obligate anaerobe in paste or freeze dried preparations. Furthermore, no studies using oral *O. formigenes* in groups of patients with enteric or idiopathic hyperoxaluria have yet appeared in the literature. Thus, the role of pharmacologic use of this intriguing bacteria to reduce urinary oxalate excretion, and hence kidney stone risk, remains unclear.

Other oxalate degraders

In vitro studies suggest that *O. formigenes* is the most efficient oxalate-degrading organism found in the human intestinal tract. For example, under controlled conditions *O. formigenes* degraded up to 98% of available oxalate (37). On the other hand, in the same studies *Lactobacillus* and *Bifidobacterium spp.* also effectively degraded oxalate, albeit somewhat less effectively (11–68%). Furthermore, the key oxalate degrading genes *Oxc* and *frc* have been sequenced from *Lactobacillus* and *Bifidobacterium spp.* One potentially unique feature of *O. formigenes* is that this organism can utilize oxalate as a carbon and energy source, and thrives in the presence of the anion (38). Other oxalate-degrading

species such as *Lactobacilli* can detoxify oxalate and survive in its presence, but not necessarily thrive. Thus, the relative importance of various bacteria in oxalate-homeostasis in humans remains ill-defined.

Along these lines, recent studies in the white-throated wood rat *Neotoma albigula* are of interest (39). This mammal consumes a diet comprised almost entirely of the oxalate-rich *Opuntia* cactus. These animals have a complicated segmented gut that harbors a diverse microbiome along its length. The foregut microbial community in particular shifts in composition in response to dietary toxins, and may be important for their degradation. When the microbiome was characterized by segment of the intestinal tract, isolates spanned three genera: *Lactobacillus*, *Clostridium*, and *Enterococcus*. Over half the isolates exhibited oxalate-degrading capacity *in vitro*, and *Lactobacillus* isolates contained the *Oxc* gene. *Oxalobacter spp.* were also identified throughout the intestinal tract, but were much less abundant and were more concentrated in the more distal regions (cecum and large intestine). Other oxalate-degrading genera (especially *Lactobacilli spp.*) were more concentrated in the foregut, the point where oxalate first enters the gastrointestinal tract. The authors hypothesized that each gut region supplied a niche for diverse functional taxa and communities of microorganisms that can function together to degrade and detoxify a large oxalate load as it is made bioavailable by digestive processes. The analogies, or lack thereof, in humans remain to be determined.

Conclusions

Diet and gastrointestinal function play a key role in determining the composition of the urine. It also seems quite likely that the gastrointestinal microbiome would greatly influence how key components of the diet are metabolized and absorbed. Key urinary parameters that the microbiome might influence include oxalate and citrate. Indeed, the intestinal microbiome contains numerous obligate and generalized oxalate degraders. Evidence suggests that the fecal content of *O. formigenes*, the best studied oxalate-degrader, varies depending on stone risk and urinary oxalate excretion. However, to date trials with probiotics designed to degrade oxalate, including those containing *Oxalobacter*, *Lactobacillus*, and/or *Bifidobacterium spp.*, have all been disappointing. Thus, although the intestinal microbiome likely plays a role to modify urinary stone risk, whether we can develop tools to manipulate it and decrease this risk remains to be determined.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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