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INVITED REVIEW

Oxalate-degrading microorganisms or oxalate-degrading enzymes: which is the future therapy for enzymatic dissolution of calcium-oxalate uroliths in recurrent stone disease?

Ammon B. Peck[1] · Benjamin K. Canales[2] · Cuong Q. Nguyen[1]

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Abstract Renal urolithiasis is a pathological condition common to a multitude of genetic, physiological and nutritional disorders, ranging from general hyperoxaluria to obesity. The concept of quickly dissolving renal uroliths via chemolysis, especially calcium-oxalate kidney stones, has long been a clinical goal, but yet to be achieved. Over the past 25 years, there has been a serious effort to examine the prospects of using plant and microbial oxalate-degrading enzymes known to catabolize oxalic acid and oxalate salts. While evidence is emerging that bacterial probiotics can reduce recurrent calcium-oxalate kidney stone disease by lowering systemic hyperoxaluria, the possible use of free oxalate-degrading enzyme therapy remains a challenge with several hurdles to overcome before reaching clinical practice.

Keywords Hyperoxaluria calcium oxalate (CaOx) · Microbiome · Enzymatic dissolution · Oxalate-degrading enzymes · Oxalate oxidase · Oxalate decarboxylase · Oxalyl-CoA decarboxlase

Introduction

Idiopathic calcium-oxalate (CaOx) nephrolithiasis in patients is commonly associated with hypercalciuria, hyperoxaluria and hypocitrauria [1]. Because oxalate levels are perceived to be the stronger controlling element in calcium crystal formation during kidney removal of water from urine leading to CaOx super-saturation, increasing attention has been placed on the role of hyperoxaluria in CaOx kidney stone disease. Oxalic acid is a natural and abundant by-product of metabolism, as well as a common constituent of most diets [2]. It is a highly oxidized organic compound with powerful chelating activity, therefore exists mostly in salt form with calcium, potassium, sodium, ammonium, etc. In high concentrations, oxalate can cause death in animals and occasionally humans due primarily to its corrosive effects. More commonly, however, accumulation of oxalic acid can cause a variety of pathological disorders known to associate and/or correlate with hyperoxaluria, including cardiomyopathy, cardiac conductance disorders, calcium oxalate stone disease, renal failure and even toxic death [3–11]. Furthermore, hyperoxaluria is observed with many pathological conditions, e.g., aspergillosis, cystic fibrosis, irritable bowel disease (Crohn's disease), primary hyperoxaluria type-I, pyridoxine deficiency, steatorrhea and possibly autism, as well as with certain medical interventions, e.g., ileal resection, ileal-bypass surgery and kidney dialysis [11–19]. Interestingly, evidence exists that animals, as well as humans, can respond to hyperoxaluria and adapt to diets high in oxalate through the selective increase in the numbers of oxalate-degrading bacteria (such as *Oxalobacter formigenes*, *Bifidobacterium* sp. *Porphyromonas gingivalis*, and *Bacillus* sp.) naturally present in the gut [20, 21].

Oxalic acid, when bioavailable, appears to be absorbed by all segments of the intestine with a significant portion of dietary oxalate absorbed through the upper part of the intestinal tract [5]. However, oxalate absorption is probably more prevalent in the normal large intestine, and this

✉ Ammon B. Peck
peck@ufl.edu

[1] Department of Infectious Diseases and Pathology, University of Florida College of Veterinary Medicine, P.O Box 100125, VAB, Bldg 1017, Gainesville, FL 32610, USA

[2] Department of Urology, University of Florida College of Medicine, P.O. Box 100247, 1600 SW Archer Rd, Gainesville, FL 32610, USA

is the location where greatly enhanced oxalate absorption occurs in patients with enteric hyperoxaluria due to ileal disease [6, 7], chronic inflammatory bowel disease [15], jejunoileal-bypass surgery [16], fat malabsorption, steatorrhea and sprue [17, 22]. This is also where oxalate-degrading bacteria tend to reside, especially *O. formigenes* that requires a strict anaerobic environment to survive. Recent studies by Hatch et al. [23] and others [17] have demonstrated that the colon has the capability of regulating absorption, as well as secretion of oxalate, and these studies suggest that this intestinal segment participates significantly in the mass balance of oxalate and subsequent oxalate homeostasis [18]. Both absorptive and secretory pathways for oxalate have been identified in the proximal and distal segments of the colon, regulated by neuro-hormones that direct net oxalate flux. The oxalate secretory pathways in the colon can potentially provide an important extra-renal route for oxalate excretion, especially in disorders like chronic renal failure which are known to be associated with hyperoxalemia and uremia [18]. Two published studies have confirmed extra-renal elimination of oxalate in rats with chronic renal failure [9, 10], and oxalate secretory pathways in the large intestine have been proposed to be functionally important in stone formers who are presumed to hyper-absorb dietary oxalate. Importantly, reduction in the colonic secretory component, rather than (or in addition to) an enhancement of absorptive component of oxalate transport, has been proposed to explain "dietary hyperoxaluria" in stone-formers [24]. Thus, the importance of this colonic segment in regulating oxalic acid homeostasis has focused attention on the role of oxalate-degrading microorganisms, such as *O. formigenes*, in oxalate-associated diseases. Already, several clinical studies have shown negligible or very low rates of oxalate degradation in fecal samples obtained from patients suffering from enteric hyperoxaluria secondary to jejunoileal-bypass surgery [16, 25], steatorrhea [26], Crohn's disease, inflammatory bowel disease [27], and these patients are often *O. formigenes* negative. Such studies have, for years, made a strong case for the importance of the gut microbiome in health and disease.

Considering current clinical data, hyperoxaluria with recurrent CaOx urolithiasis is a major health problem worldwide [19]. National Health and Nutrition Examination Surveys carried out in the USA assessing the health and nutritional status of US citizens have now shown that kidney stone prevalence increased from 3.2 % in 1980 to 8.4 % in 2010, thereby actually surpassing the prevalence of type-2 diabetes, estimated at 8.2 %. This increasing prevalence is observed for both males and females, as well as in children [28, 29]. Of serious note, however, there are no serious measures to predict who will fall victim to kidney stone disease, even though the recurrence rate in individuals having produced a stone is between 30 and 60 %. While urolithiasis has become the most costly urologic disease in the USA, more important is the quality of life factor, especially in patients with conditions that increase oxalate absorption as they are at increased risk of developing recurrent CaOx kidney stone disease [30, 31].

Circumstantial evidence points to the fact that one probable underlying cause of hyperoxaluria and subsequent CaOx urolithiasis is the wide spread use of antibiotic therapy that, along with diet and environmental factors, alters intestinal bacterial microbiomes. The overall role of microbiomes in human and animal health has become one of the most active fields in medical sciences with rapidly accumulating evidence strongly indicating that the gut, oral, skin, vaginal and ocular microbiomes are all important in health, immunity, and general physiological homeostasis of its host. Therefore, a better understanding of the relationships between the gut microbiome and enteric hyperoxaluria is needed, representing a wide range of opportunities for translational and clinical research, especially in light of conflicting data published in rodent animal models of induced CaOx renal pathology versus human CaOx kidney stone disease [32–34]. Thus, one must ask the question "Is the gut microbiome phenotype a risk factor for hyperoxaluria and CaOx urolithiasis?".

The gut microbiome and CaOx urolithiasis

To address this specific point, it is important to examine the nearly three decades of research and clinical studies investigating the gut-associated oxalate-degrading microorganism, *O. formigenes*. *O. formigenes* is now known to regulate the absorptive and secretory pathways for oxalic acid in the intestines, thereby influencing homeostatic levels of oxalate in plasma and urine [35–38]. *O. formigenes* (shown in Fig. 1), is a Gram-negative, obligate-anaerobic bacterium [39–41] that may be unique among oxalate-degrading organisms, having evolved a total dependence on oxalate metabolism for energy [40]. Although *O. formigenes* was first isolated by Allison et al. from the rumen contents of sheep [20, 42], it was soon found in fecal samples from rats, guinea pigs, and pigs [35, 43], in fecal samples from humans [25], and in anaerobic aquatic sediments [44].

Oxalobacter formigenes has been reported to be present in fecal specimens of healthy individuals at levels ranging from 10^7 to 10^8 colony-forrming units (CFU) per gram (g) wet sample. Based on the oxalate-degrading capacity of *O. formigenes*, a normal colonization of the intestines could result in the degradation of more than 1 g of oxalate per day. Attempts to culture this bacterium out of fecal specimens collected from different individuals have indicated that many individuals have colony counts much lower than 10^6 CFU per g wet sample [20] and some individuals are

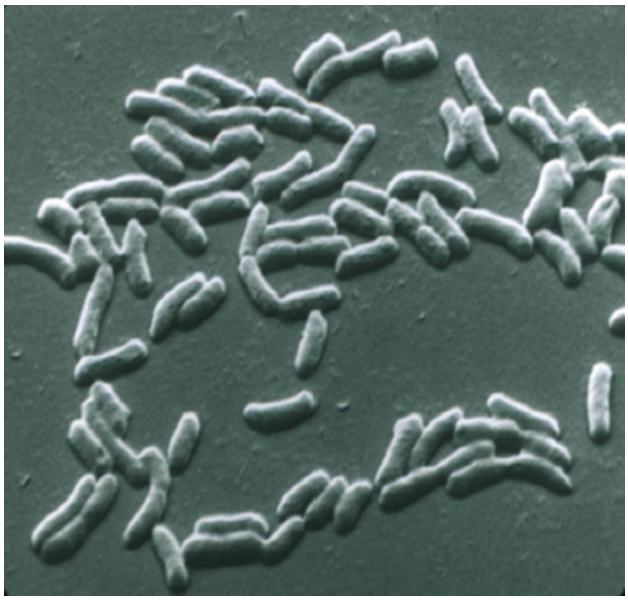

Fig. 1 *O. formigenes* bacteria (Courtesy of Dr. Milton Allison)

apparently *O. formigenes* negative. This suggests that part of the normal population is either not colonized or colonized with fewer bacteria than can be readily detected. Interestingly, our studies on the natural colonization of the gut with *O. formigenes* in healthy children and adult populations has shown that virtually 100 % of children do become naturally colonized between 1 and 6 years of age, but that 20–25 % lose their colonization during adolescence or early adulthood [41]. Additionally, children residing in countries with strong healthcare programs and/or higher economic life-styles tend to have significantly less *O. formigenes* colonization, an observation considered to be due to higher general use of antibiotics within these societies and populations [45].

In contrast to normal healthy children, the vast majority of patients with cystic fibrosis (CF) show a complete absence of *O. formigenes* or very low colonization [46]. CF patients have been found to be at increased risk for developing nephrocalcinosis and calcium oxalate urolithiasis [11, 12], with an incidence of urolithiasis in CF children reportedly 3.5 % over a 12-year period as compared to only 0.2 % for the same time period in the normal population. Medullary nephrocalcinosis is reported in more than 95 % of CF patients at post-mortem autopsy [13]. Furthermore, urolithiasis appears to be an increasingly common complication as life expectancy of CF patients increases [47]. Though the underlying cause for CaOx urolithiasis in CF patients remains speculative, data published on suspected urinary-lithogenic and stone-inhibitory parameters in CF patients suggest that hyperoxaluria may be the main risk factor [48], as we have reported urinary oxalate levels can be as high as those present in primary hyperoxaluria type-I patients [41, 49].

Enteric hyperoxaluria due to pancreatic insufficiency and fat malabsorption is also a well-documented entity observed in gastrointestinal diseases (e.g., colitis or Crohn's disease), or following ileal resection and jejuno-ileal bypass surgery [17, 19, 50–55]. First, the colon has been identified as a primary site for increased oxalate absorption, mostly attributable to an enhanced mucosal permeability. Second, these patients exhibit an increased oxalate solubility and bio-availability in fecal contents [19, 50, 54]. This is especially true for patients with small bowel resection, as this can lead to a steatorrhea that increases the permeability of the colon to oxalate and a subsequent increased concentration of oxalate due to calcium binding to free fatty acids. Similarly, patients with Crohn's disease or ulcerative colitis, plagued by recurrent inflammatory responses along the gastrointestinal (GI) tract, exhibit malabsorption due in part to a greater permeability of the colonic mucosa, although this is truly an oversimplification. While a majority of kidney stones in these patients are CaOx, many inflammatory bowel disease (IBD) patients present with uric acid stones, similar to diabetic patients with urolithiasis. Thus, it is not surprising that in a recent prospective study of Crohn's disease patients, of whom nearly 40 % were hyperoxaluric, there was a direct association of stone formation with observed lower concentrations of magnesium and citrate, relative to calcium, and higher urinary pH and levels of NH_4 ions. Although it is not known if these clinical observations are in any way attributable to altered gut bacterial microbiomes, an earlier study revealed that Crohn's patients with CaOx stone disease were generally *O. formigenes* negative, despite their partners living in the same environment being *O. formigenes* positive (personal communication). A logical conclusion might be that clinical manifestations result from loss of bicarbonate, water and salt in diarrheal stools in conjunction with decreased absorption of citrate and magnesium, then confounded by the lack of oxalate-degrading bacterial species either by these changes in gut environment or heavy use of prescribed drugs.

Probiotic intervention and future CaOx kidney stone disease therapies

The possibility of using oxalate-degrading micro-organisms for the prevention of human CaOx kidney stone disease was first suggested by Dr. Birdwell Finlayson after hearing a presentation by Dr. Milton Allison describing the isolation of *O. formigenes* from sheep and the importance of this single bacterium in reducing the toxic effects of high oxalate intake during spring grazing (personal communication). This quickly led to a multitude of epidemiology studies to determine correlations between the absence

and presence of *O. formigenes* and disease states associated with hyperoxaluria, especially kidney stone disease. A number of critical observations can be summarized from the results, including:(a) natural colonization of the gut with *O. formigenes* occurs primarily at the time children begin to crawl and play outdoors, suggesting horizontal transmission despite being an obligate anaerobe, (b) fecal specimens collected from patients with chronic hyperoxaluria-associated pathologies are often, but not always, negative for *O. formigenes*, (c) all individuals thus far tested are never colonized by more than one subgroup of *O. formigenes*, suggesting this bacterium actively prevents dual colonization, (d) the frequency of recurrent kidney stone disease is higher in non-colonized individuals, and (e) kidney stone patients who have been treated with antibiotics are more likely to have recurrent stone episodes than those not treated with antibiotics.

At the same time, studies performed in rodents, especially male rats, have provided strong support for the observations reported in human kidney stone patients, as well as the potential use of *O. formigenes* as a probiotic treatment to reduce hyperoxaluria. Results from these studies have shown that (a) laboratory rats housed in typical animal facilities and maintained on commercial rodent pellets remain *O. formigenes* negative, (b) neonatal rats born to mothers colonized with *O. formigenes* do not become colonized themselves until they begin crawling around their cages, (c) rats colonized with *O. formigenes* exhibit stable reductions in hyperoxaluria when fed an oxalate rich diet that would normally induce high levels of hyperoxaluria in non-colonized rats, and, most critical, (d) colonization is achieved by a maximum of a single subgroup of *O. formigenes*, even if gavaged with multiple substrains. In addition, a recent report by Canales et al. [56] indicated that obese rats having undergone bariatric surgery then colonized with *O. formigenes* maintained a significant (>70 %) reduction in urinary oxalate levels.

Considering the results from both human and animal studies, it is obvious that a great deal of attention has been placed on the role of *O. formigenes* in human (and animal) health despite the fact that the human bacterial microbiome contains multiple oxalate-degrading bacterial species, as stated earlier. Furthermore, rodent studies have clearly indicated a possible use of *O. formigenes* as a probiotic to reduce hyperoxaluria and subsequent kidney stone disease. However, clinical studies in humans have yet to produce consistent results, e.g., the study of Jairath et al. [57] versus that of Mayo Clinic [58], thus raising questions whether the underlying problem is technical, biological or patient sample. From a technical perspective, *O. formigenes* is an obligate anaerobe that utilizes a relatively complex biochemical pathway to catabolize oxalate, i.e., oxalyl-CoA decarboxylase coupled to formyl-CoA transferase, making it very difficult with which to work. From a biological perspective, *O. formigenes* is highly sensitive to its environment, susceptible to the use of antibiotics, and relatively ineffective in gaining a stable colonization of the gut, especially in adults. These facts suggest that investigations of other bacterial organism are needed, especially in light of the recent study by Mogna et al. [59] using *Lactobacillus* and *Bifidobacterium* strains. In contrast, many microorganisms have the ability to degrade oxalate using a far simpler system, i.e., oxalate decarboxylase, and are technically easier to handle. Thus, while attention has mostly focused on the possible development of *O. formigenes* as a probiotic therapy, greater attention should be placed on additional oxalate-degrading bacteria. Furthermore, a third oxalate-degrading enzyme system, i.e., oxalate oxidase, is present in many plant tissues and is well known since it has been used for several decades to measure urine oxalate levels via measurement of H_2O_2, one of the two products produced in its degradation of oxalate.

Use of oxalate-degrading enzymes for dissolution of urinary tract stones

While bacteria such as *O. formigenes* that express oxalyl-CoA decarboxylase enzyme systems have been shown to slowly degrade oxalate salts in agar, it is considered highly unlikely that the enzymes in free form are capable of a similar action due to spatial requirements. In contrast, both the oxalate decarboxylase and the oxalate oxidase enzymes act directly on oxalate and therefore represent biochemical factors useful in dissolving or reducing the size of CaOx stones already formed in the urinary tract. Application of such therapy would be especially pertinent for patients who are poor candidates for surgery, have rapidly recurrent formation of stones, and/or have received shockwave lithotripsy. Oxalate-degrading activity of these two latter enzymes could function in unique ways: first, catabolize free oxalate to lower the bioavailability of oxalate thereby reducing levels below supersaturation and permitting precipitated crystals to dissolve naturally, and/or secondly, act directly on CaOx crystals in formed kidney stones to slowly dissolve the CaOx mineral precipitates within the stone matrix. Similarly, treatment of patients with alkaline-citrate, shown to be relatively successful in reducing recurrent disease involving CaOx monohydrate stones or uric acid calculi [60], most likely encompasses multiple biochemical processes without actually participating in active dissolution of the stone.

In our most recent study [61], we examined the ability of oxalate decarboxylase and oxalate oxidase to dissolve CaOx crystals in an in vitro analysis. Results of this study revealed several important points including: (a) free oxalate decarboxylase enzyme is capable of dissolving CaOx

crystals in an enzyme concentration-dependent manner, (b) free oxalate oxidase enzyme proved far less efficient compared to oxalate decarboxylase in dissolving CaOx, (c) in a closed system, the rate at which oxalate decarboxylase enzyme dissolves CaOx crystals drops off due to a reversible inhibition of the enzymatic reaction by formate, a product of the oxalate breakdown, (d) long-term enzymatic activity of oxalate decarboxylase requires the presence of FDH-coupling reagents, and(e) oxalate decarboxylase derived from *Bacillus subtilis* may not be the ideal source for CaOx stone dissolution as the maximum obtainable velocity was <1.3 % of the true V_{max} of the enzyme. The latter conclusion suggests that oxalate decarboxylases from other organisms need to be examined for possible higher efficacy. Further considerations in trying to design oxalate-dissolving enzyme therapies is the fact that maximum enzymatic activities for both oxalate decarboxylase and oxalate oxidase currently used and studied in detail lie below pH 4.5. Furthermore, it must be remembered that both enzymes are proteins derived form non-mammalian sources and, as such, are immunogenetic molecules. It is not known how modifications such as pegylation could affect enzymatic activities. Clearly, there is much to clarify before these enzymes can be used in a clinical setting as adjuvants for stone dissolution.

Conclusion

Studies in both humans and animal models of hyperoxaluria-associated CaOx kidney stone disease indicate that oxalate-degrading microorganisms, in particular the more widely-studied *O. formigenes*, are both capable of and important in regulating urinary levels of oxalate. This regulation of oxalate levels reveal trends showing reductions in hyperoxaluria with subsequent lowering of recurrent stone formation. While there is a paucity of studies using free oxalate-degrading enzymes, preliminary in vitro investigations suggest that oxalate decarboxylase and oxalate oxidase possess the potential to actively dissolve CaOx crystals. However, how oxalate-degrading enzymes can be put into clinical practice will require substantial innovative measures, but a successful technology would clearly impact the treatment of recurrent stone disease. It seems reasonable to begin the thought process of how to partner the use of oxalate-degrading microorganisms with their free enzymes to enhance the speed at which CaOx stones dissolve naturally.

Compliance with ethical standards

Conflict of interest There are no authors of this report that currently have a conflict of interest with the subject matter.

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