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The role of the microbiome in kidney stone formation

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Abstract

Nephrolithiasis is a complex disease of worldwide prevalence that is influenced by both genetic and environmental factors. About 75% of kidney stones are predominantly composed of calcium oxalate and urinary oxalate is considered a crucial risk factor. Microorganisms may have a role in the pathogenesis and prevention of kidney stones and the involvement of the intestinal microbiome in this renal disease has been a recent area of interest. *Oxalobacter formigenes* is a gram negative bacteria that degrades oxalate in the gut decreasing urinary oxalate excretion. In this review, we examine the data studying the role of *Oxalobacter formigenes* in kidney stone disease in humans and animals, the effect of antibiotics on its colonization, and the potential role of probiotics and whole microbial communities as therapeutic interventions.

Keywords

Microbiota; Nephrolithiasis; Urolithiasis

1. Introduction

Nephrolithiasis is a complex disease influenced by genetic and environmental factors. Twin studies have revealed a 56% heritability risk for stones while other implicated factors include diet, exercise, work environment and geography [1]. In recent years, the role of the

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intestinal microbiome in influencing the composition of the urine has been explored resulting in data suggesting that it affects kidney stone incidence. We will review here the evidence supporting this hypothesis. Not reviewed here is the well described role of infections of the urinary tract with *Proteus* species and other urease-producing organisms associated with struvite stone formation.

The enormous number of microorganisms that colonize the human body and form complex communities are referred to as the microbiome. Functionally, it communicates with host human cells and performs various biological processes. There is increasing concern that the 'Western' diet and lifestyle have altered the genetic composition and metabolic activity of the intestinal microbiome. The effects of these changes in the bacterial populations have been associated with the increasing incidence of diseases such as obesity, coronary vascular disease, allergies, and metabolic syndrome [2]. These effects make tenable the possibility that the gut microbiome also affects absorption and secretion of solutes relevant to kidney stone formation.

To date, relatively little is known about the general role of the gut microbiome in the pathophysiology of nephrolithiasis. A recent study has identified distinct differences in the gut microbiome of kidney stone patients compared to patients without stones [3]. Fecal and urine samples collected from both groups of patients revealed 178 genera, of which the five most abundant enterotypes, or distinct bacterial communities, within each group made up greater than 50% of the bacterial abundance identified. *Prevotella* genus was most abundant in the control group while the *Bacteroides* genus was most abundant in the kidney stone group. *Eubacterium* was inversely correlated with oxalate levels and *Escherichia* inversely correlated with citrate levels. Whether these differences in bacterial abundance seen in stone formers and controls are causative in the pathway of stone formation, or secondary to other variables such as antibiotic exposure or diet, is uncertain. Such broad characterizations of the microbiome will need more extensive investigations to link to specific solutes that compose kidney stones and specific agents affecting the crystallization process.

2. Oxalobacter formigenes

2.1. Genetic and microbiological characteristics

The discovery of an oxalate degrading bacteria, *Oxalobacter formigenes* (*Oxf*), by Allison and coworkers in 1985 has attracted considerable attention regarding its involvement in calcium oxalate stone disease [4]. Clinical findings have suggested that there is a direct correlation between the organism's absence and hyperoxaluria and oxalate stone formation. *Oxf* is a Gram negative, obligate anaerobic bacterium, that is part of the normal bacterial flora in the large intestine of humans and other mammalian species. It is unique in that it requires oxalate both as a carbon source and for ATP generation, which it finds in the intestinal lumen [5]. It has been found in the gut of humans, rodents, dogs, pigs, and cattle. If present, it could degrade ingested oxalate and reduce intestinal absorption, and stimulate oxalate secretion from the colon, offering protection from hyperoxaluria.

Oxalate metabolism by *Oxf* requires uptake of extracellular oxalate in exchange for formate by the membrane transporter called OxlT, encoded by the *oxlT* gene (see Fig. 1). The *frc*

gene encodes formyl CoA transferase, *Frc*, which activates oxalate by adding a coenzyme A molecule to form oxalyl-CoA. Oxalyl-CoA is then decarboxylated to CO_2 and formate, and the latter is then utilized by *oxlT* to take up more oxalate. The decarboxylation reaction is catalyzed by the enzyme oxalyl-CoA-decarboxylase, encoded by the gene *oxc* [6]. An inward gradient for protons results, driving ATP production.

While, *O. formigenes* is thought to be the most effective oxalate-degrader, the role of other oxalate-degrading microbiota in the human intestine is not fully elucidated. Multiple bacterial species have both *oxc* and *frc* and demonstrate oxalate-degrading activity in vitro [7]. Recently, Hatch et al. demonstrated that *Bifidobacterium lacti*s colonization decreases urinary oxalate by degrading dietary oxalate and reducing its intestinal absorption in a mouse model [8]. In a study of South African men, *Lactobacillus* species with high oxalate degrading capacity have been identified and associated with a lower prevalence of calcium oxalate kidney stones [9].

Comparison of the profiles of cellular fatty acids of 17 strains of *Oxf* has separated these strains into two main groups, currently designated as Group 1 (e.g. strain OXCC13) and Group 2 (e.g. strain HOxBLS). The sequencing of the genomes of these 2 strains as part of the Human Microbiome Project has provided an opportunity to increase our understanding of the important biological properties of the organism [10]. Additional proteomic analysis of *Oxf* in log and stationary growth phase cultures has allowed for the identification of specific proteins that are important for its growth and survival [11].

The development of a PCR-based detection assay specific for the *oxc* and/or *frc* genes in *Oxf* has allowed for the study of the role of this organism in oxalate metabolism. The rapid detection of *Oxf* in fecal cultures and fresh stool specimens is possible with a high degree of sensitivity and specificity [12]. Measurement of the oxalate-degrading capacity of the stool is another way to determine indirectly the presence or absence and activity of the organism [13].

Studies have reported an extensive variation in the degree to which *Oxf* colonizes the normal human gut. There may be undetectable levels of the bacterium or it may be present with as many as 10^7 per gram of feces. The levels of *Oxf* in fecal samples increased about 10 fold with a 10 fold increase of dietary oxalate. In contrast, abundance of the organism decreased with increasing calcium intake, which would bind oxalate and reduce its availability [14].

We recently described the prevalence, relative abundance and stability of *Oxf* in the human gut microbiome as revealed by Human Microbiome Project (HMP) data [15]. Fecal samples from 242 healthy young adults were analyzed using whole-genomic shotgun (WGS) sequencing and V13 or V35 16S rRNA sequencing. Analysis of the WGS dataset showed that 29 (31%) of 94 subjects were *Oxf*-positive while analysis of the V13 and V35 data showed *Oxf* prevalence at 15% (22/155) and 11% (23/210), respectively. Thus, detection of *Oxf* by the HMP investigators very much depended on methods used: WGS was more sensitive than 16S rRNA sequencing. We found that all 29 of the *Oxf*-positive subjects in the WGS analysis were colonized with strain OXCC13. However, of these 29, 59% were simultaneously colonized with strain HOxBLS. Thus, co-colonization with both strains was

common. It has not been established whether the two strains have differing clinical significance.

3. Human studies

3.1. O. formigenes prevalence in humans

A large percentage of the population is colonized with *Oxf*. In US adults, the colonization rate of *Oxf* has been estimated to vary between 38 and 62%, but worldwide, the colonization rate is higher in populations with limited exposure to antibiotics. For instance, in India, the prevalence was reported at around 60%; in Korea, prevalence was at 77% [16,17]. Low *Oxf* colonization rates have been noted in several pathologic conditions, including inflammatory bowel disease, recurrent nephrolithiasis, morbid obesity, cystic fibrosis and idiopathic calcium nephrolithiasis, all of which are associated with calcium oxalate stones (Table 1).

Colonization by *Oxf* has been investigated in a cross sectional study examining children from Ukraine [18]. This population was chosen due to the limited access to routine use of antibiotics during childhood. The organism could not be detected in infants less than 6–9 months of age and began appearing in the intestinal tracts of children around 1 year of age. By 3–4 years of age, all children showed colonization, with the number of children colonized declining between 8 and 12 years of age. Another group of patients of particular interest is those with cystic fibrosis (CF), who are known to have an increased prevalence of kidney stones. Patients with CF are subjected to multiple courses of antibiotics as a result of their increased susceptibility to pulmonary infections. In a study of urinary oxalate excretion in patients with CF, 71% of 21 non-CF control patients were colonized by *Oxf* compared with only 16% of 43 patients with CF [19]. All 7 patients with CF colonized by the bacterium had normal urinary oxalate excretion, whereas 53% of 36 patients not colonized had hyperoxaluria supporting the hypothesis that the presence of the organism protected against hyperoxaluria.

3.2. Association of O. formigenes and kidney stones

There are multiple epidemiological studies suggesting a protective role for *Oxf*. Human studies have also shown a strong inverse association between *Oxf* colonization and recurrent calcium oxalate renal stones. A case control study of 247 patients with recurrent episodes of calcium oxalate stones and 259 subjects without stone disease matched by age, gender and region found a strong inverse association between colonization with *Oxf* and recurrent calcium oxalate stones with a 70% risk reduction [20]. Among control subjects, an increase in the prevalence of *Oxf* was seen with increased oxalate consumption; the inverse was seen with antibiotic use. 24-h urine collections revealed a strong trend in the risk of stones with increasing urinary oxalate excretion. However there was no difference in median urinary oxalate excretion in patients who tested positive or negative for *Oxf*.

A key unanswered question is whether the absence of *Oxf* increases the risk of calcium oxalate stone formation by increasing urinary oxalate excretion. Under a controlled and standardized diet, urinary oxalate excretion has been shown to be lower in *Oxf* positive patients than in *Oxf* negative patients [21]. Results of a diet controlled study in 22 non-stone

forming patients who were naturally colonized or noncolonized with *Oxf* suggests that differences in urinary oxalate excretion may be affected by differences in dietary calcium and oxalate intake [14].

Duncan et al. showed that the oral ingestion of a single dose of *Oxf,* followed by a dietary oxalate load, resulted in reduced urinary oxalate excretion, recovery of oxalate-degrading activity in feces, and prolonged colonization in 3 of 3 participants. A randomized, multicenter study of patients with primary hyperoxaluria failed to show a clear treatment effect of *Oxf* to reduce urinary oxalate excretion. The dose and viability of the administered bacterial treatment were questioned though the results did suggest a treatment effect when urine oxalate was normalized for creatinine [22].

3.3. Antibiotic effect on O. formigenes in humans and mice

The hypothesis that antibiotic use could be responsible for the decrease in the prevalence of *Oxf* in adults has been investigated in recent studies. The effect of antibiotics on *Oxf* colonization was evaluated in patients receiving oral antibiotic treatment for *Helicobacter pylori* (*HP*) [23]. *Oxf* strains are susceptible to multiple antibiotics including quinolones, macrolides, tetracyclines and metronidazole. In a prospective study, the prevalence of *Oxf* colonization was compared between an *HP-positive* group who were treated with either clarithromycin or metronidazole and an *HP-negative* control group who did not receive antibiotics. 92% of the control group of 12 patients who were positive for *Oxf* on initial stool testing and were not administered antibiotics remained positive for *Oxf* on stool tests at 1 month and 6 months. In comparison, only 38% the 19 subjects who were positive for *Oxf* and who were administered antibiotic therapy for *HP*, remained positive for *Oxf* in the stool at both follow-up points. Only one of the participants whose colonization with *Oxf* was eliminated with antibiotics regained *Oxf* colonization at 6 months. These findings suggest that the lasting elimination of *Oxf* after antibiotic exposure may be a risk factor for kidney stone formation [23].

Another study examined the effect of antibiotic pulses in addition to dietary modifications in mice to understand the resulting physiologic perturbations [24]. In the pulsed antibiotic treatment (PAT) in early life mouse model, mice were divided into 3 groups. The control group did not receive antibiotics while the other two received 3 pulses of tylosin (a macrolide) or amoxicillin. To see the effect of the PAT model on oxalate degradation, the mean relative abundance of each of the three genes involved in oxalate metabolism was measured over time. The *oxc*, *frc*, and *oxlT* were not specific to *Oxf* but could be from other oxalate-degrading bacteria. Fig. 2 shows that antibiotic pulses and dietary modifications caused significant changes in the relative abundance of gene expression of *oxc, frc,* and *oxlT* during development; however the direction of the change was not uniform. This might indicate a differential effect of these variables on oxalate-degrading bacteria including *Oxf*.

4. Animal studies

Multiple experiments have investigated the role of *Oxf* in reducing urinary oxalate excretion in animal models. Sidhu et al. showed that in rats, colonization with *O. formigenes* resulted in reduction of urinary oxalate excretion [25]. Likewise, in a mouse model of primary

hyperoxaluria, a genetic disorder causing increased endogeneous oxalate production, *O. formigenes* induces enteric oxalate secretion, ultimately reducing net urinary oxalate excretion [26]. The urinary oxalate was similarly reduced when lysate of the bacterium was used in lieu of whole bacterium [27]. Chen et al. transfected mouse stem cells with *oxc* and *frc* genes, encoding the oxalate decarboxylase and the formyl Co-A transferase, and demonstrated reduction in oxalate levels in the media [28].

An alternative hypothesis is that *Oxf* possesses a unique characteristic that allows it to reduce urinary oxalate excretion not only by reducing intestinal absorption, but also by enhancing enteric oxalate secretion. Hatch et al. reported that *Oxf* interacts with colonic epithelium by inducing distal colonic secretion with a net secretive flux of oxalate from serosa to mucosa, leading to reduced urinary excretion [27]. This was shown by the studies on mice using two strains of *Oxf*, a human and rat strain. There was no change in colonic expression of the chloride/oxalate exchange protein, *Slc26a6*, in mice colonized by *Oxf* as compared with non-colonized wild type mice.

Characterization of the apparent secretagogue made by *Oxf* strengthening the plausibility of *Oxf*-stimulated oxalate secretion has recently proceeded. While the responsible molecule has not yet been identified, culture media exposed to *Oxf*, administered rectally to knockout mice with primary hyperoxaluria type 1, reduced urinary oxalate excretion (>32.5%) and stimulated distal colonic oxalate secretion (>42%) in Ussing chamber-mounted bowel cross-sections [29]. The mechanism of action included activation of the *SLC26A6* transporter by protein kinase A without any increased expression of the protein. These effects have not yet been recapitulated in human colon but described in human intestinal Caco-2-BBE cells. Since maintaining sustained *Oxf* colonization in the absence of high exogenous oxalate remains difficult, the identification of *Oxf*-derived bioactive factors that induce colonic oxalate secretion, thereby reducing urinary oxalate excretion, may be of important therapeutic potential.

The recent successful mono-colonization of germ free mice with *Oxf* suggests that *Oxf* does not require other organisms for its survival. Experiments showed that these mono-colonized mice had significantly reduced urinary oxalate excretion compared to germ free mice. This finding may play an important role in the development of *Oxf* as probiotic [30].

4.1. Potential role of probiotics and whole microbial communities

The recent microbial transplants of oxalate-degrading bacteria from the mammalian herbivore *Neotoma albigula* into a laboratory rat resulted in a significant increase and persistent colonization of oxalate-degrading bacteria. This result may represent a new target for therapeutic intervention to confer persistent oxalate degradation across species [31].

Attempts to introduce oxalate-degrading microbes though oral probiotic formulations into the human or rat gut have temporarily resulted in a decrease in urinary oxalate excretion. These oral probiotic preparations include *Oxf* alone, or different combinations of *Lactobacillus, Bifidobacterium*, *Enterococcus*, and other oxalate degraders. With all formulations, the probiotics tested in both humans and rodents initially lead to a reduction in

urinary oxalate excretion; however the bacteria and their oxalate-degrading function were usually undetectable as early as 5 days after oxalate is removed from the diet [7,32].

5. Conclusion

Although research establishing a direct causal relationship between alterations in the gut microbiome and the incidence of kidney stones is lacking, the reviewed literature is highly suggestive. While research in this field is still in its early stages, the advancement of sequencing technologies and analytical tools offer a unique opportunity to explore previously unanswered questions on the role of gut and urine bacteria in stone pathophysiology. (To date, there are no studies linking the presence of non-pathogenic bacteria in the urine, as opposed to the intestinal lumen, with kidney stones).

A few limitations in previous studies can be identified and considered in developing further studies. All the animal studies manipulated rodents' microbiome with the addition of *Oxf* and changes in diet. We know that the human microbiome and diet are significantly different than the rodent's, so finding a more representative model might be necessary in order to translate this work to humans. In addition, the understanding of the gut microbiome as a network of bacterial species performing a function, e.g. oxalate degradation, instead of as a single species, will likely be of important therapeutic implications.

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HIGHLIGHTS

- *Oxalobacter formigenes*.
- Genetic and microbiological characteristics.
- *O. formigenes* prevalence in humans.
- Association *of O. formigenes* and kidney stones.
- Antibiotic effect on *O. formigenes* in humans and mice.
- Potential role of probiotics and whole microbial communities.

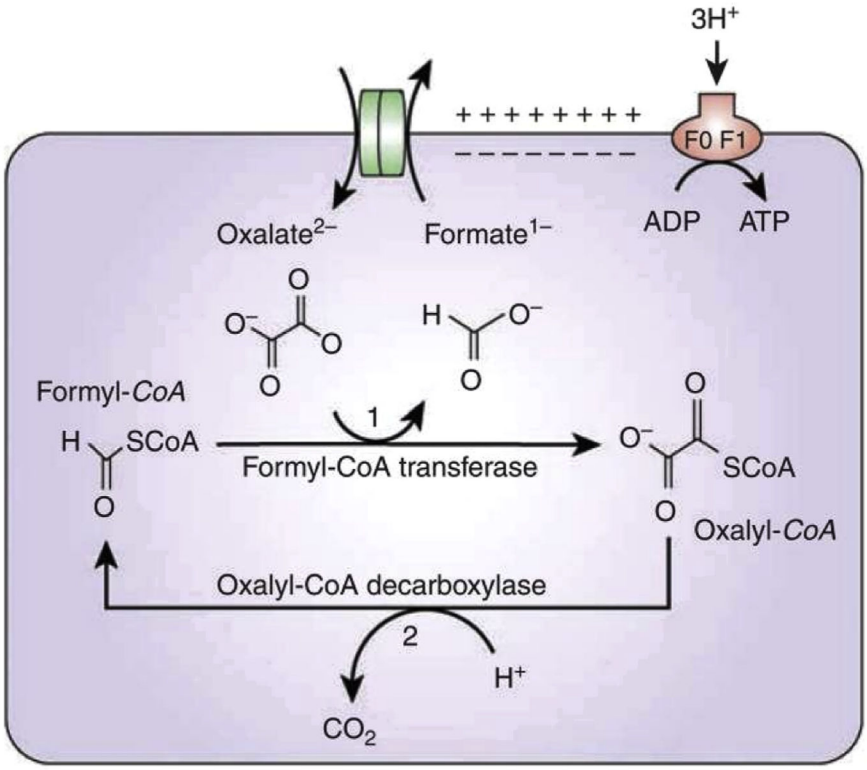

Fig. 1.
Metabolism of oxalate by *Oxf* [6]. Reproduced with permission.

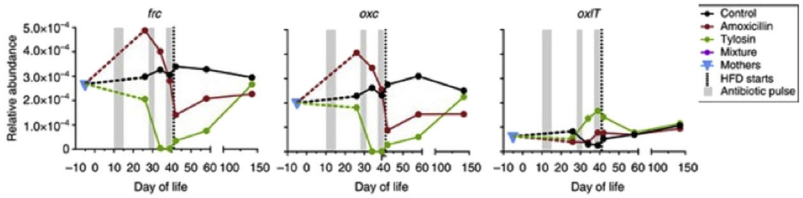

Fig. 2.

Changes in the relative abundance of gene expression of *oxc, frc,* and *oxlT* during development with pulsed antibiotic treatment [24] (HFD: high fat diet reproduced with permission.

Table 1

Reported *Oxf* colonization rates in various adult populations.

Reported Oxf colonization rates in various adult populations			
Country	**Population**	**Number of subjects**	**% colonization**
India	Normal	48	56
	Inflammatory Bowel Disease	48	10
USA	Normal	26	62
	Inflammatory Bowel Disease	16	9
USA	Normal	259	38
	Recurrent CaOx Stone formers	247	17
Germany	Normal	61	69
	CaOx Stone formers	145	43
Korea	Normal	233	77
	CaOx Stone formers	103	46