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Review

The role of the microbiome in kidney stone formation

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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.

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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.

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 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

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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 lactis* 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].

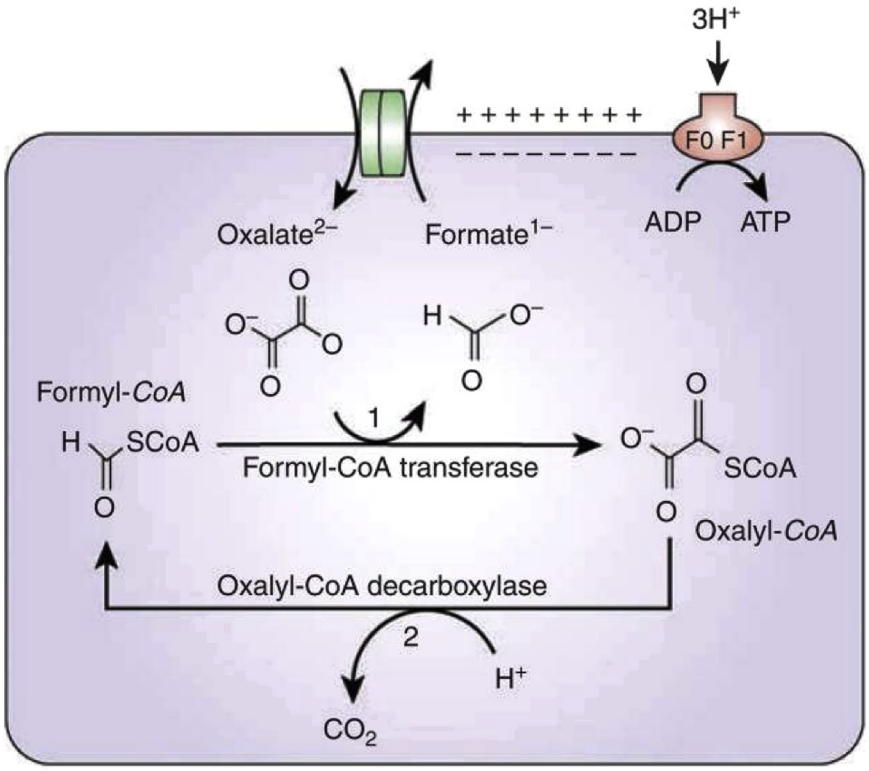

Fig. 1. Metabolism of oxalate by *Oxf* [6]. Reproduced with permission.