

## Short Communication

# The Prevention of Calcium Oxalate with Probiotics in Kidney stone

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### Article Info

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### Abstract

Many edible plants generate oxalate, which is a toxin that is harmful to human health and is also produced by animals as a terminal metabolite in their liver. Both animals and humans have enzyme systems that break down oxalate. Kidney stone is a complex disease of worldwide prevalence that is influenced by both genetic and environmental factors. About 80% of kidney stones are predominantly composed of calcium oxalate and urinary oxalate. Bacteria may have a role in the pathogenesis and prevention of kidney stones and the involvement of the intestinal microbiome in this renal disease have been investigated. *Oxylobacter formigenes* is a gram negative bacteria that degrades oxalate in the gut decreasing urinary oxalate excretion. In this review, collection of the data studying the role of probiotic *Oxylobacter* forming genes in kidney stone disease in humans and animals.

**Keywords:** Probiotics; Nephrolithiasis; Urolithiasis, Kidney stone

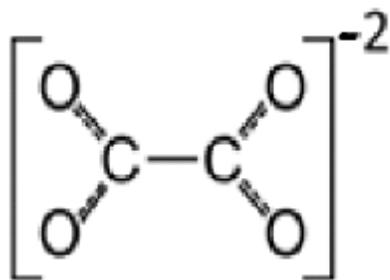
### Introduction

Environmental and genetic factors have a role in the complicated condition known as kidney stones. Research has indicated that factors such as location, work environment, food, and exercise may be involved [1]. The term "microbiome" refers to the enormous number of microorganisms that inhabit human bodies and organize into intricate ecosystems. It interacts with host human cells to carry out a number of biological functions. Concern over how changes in human lifestyle may impact the gut microbiome's genetic makeup and metabolic activity is growing. Increases in the prevalence of conditions including obesity, cardiovascular disease, allergies, and metabolic syndrome have been linked to these bacterial population alterations[2]. These effects make tenable the possibility that the gut microbiome also affects absorption and secretion of solutes relevant to kidney stone formation. A recent study has identified distinct differences in the gut microbiome of kidney stone patients compared to patients without stones [3]. 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.

### Chemistry of Oxalate

Oxalate is the anion of a dicarboxylic acid that is commonly found in many plant foods, including nuts, fruits, vegetable, grains and legumes. Different salts of oxalate are found in the plants, such as

sodium, potassium or magnesium oxalate, each with unique water solubility characteristics [17]. Enzymatic synthesis of oxalate occurs by hydrolysis of oxaloacetate in fungi, e.g., *Aspergillus niger*, and bacteria, e.g., *Acetobacter*. In mammals, oxalate is produced through the tricarboxylic acid cycle. The chemical structure of the anion is shown in Figure 1 [18].



**Figure 1.** Chemical structure of oxalate anion.

The oxalate in the body has two sources: from dietary sources or from endogenous synthesis [19]. The endogenous synthesis takes place mainly within the liver, from different dietary precursors, such as glyoxalase, ascorbic acid and some amino acids [20]. Oxalate synthesis in the body has essential impact on the rate of oxalate content in the urine and formation of calcium oxalate stone in kidney. Glyoxylate is the major precursor to oxalate production. The main sources of in vivo glyoxylate metabolism are phenylalanine, glycine, hydroxyproline, tryptophan, pentose sugars, glucose, fructose, ethanolamine and glycolate [21–23].

### Microbiota of lumen

#### *Oxylobacter formigenes*

The discovery of an oxalate degrading bacteria, *Oxylobacter 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 [5,6]. 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.

#### *Bifidobacterium lactis*

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 [7, 8].

#### *Lactobacillus species*

Studies have reported an extensive variation in the degree to which *Lactobacillus* species colonizes the normal human gut. In contrast, abundance of the organism decreased with increasing calcium intake, which would bind oxalate and reduce its availability [9].

### Association of microbiota and kidney stones

There are multiple epidemiological studies suggesting a protective role for microbiota. Human studies have also shown a strong inverse association between microbiota 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 microbiota and recurrent calcium oxalate stones with a 70% risk reduction [10]. 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.

### Antibiotic effect on *O. formigenes* in humans and mice

The hypothesis that antibiotic use could be responsible for the decrease in the prevalence of microbiota 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) [11]. Microbiota strains are susceptible to multiple antibiotics including quinolones, macrolides, tetracycline and metronidazole. In a prospective study, the prevalence of microbiota 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 microbiota on initial stool testing and were not administered antibiotics remained positive for microbiota on stool tests at 1 month and 6 months.

### Animal studies

Multiple experiments have investigated the role of microbiota 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

[12]. Likewise, in a mouse model of primary hyperoxaluria, a genetic disorder causing increased endogenous oxalate production, *O. formigenes* induces enteric oxalate secretion, ultimately reducing net urinary oxalate excretion [13]. The urinary oxalate was similarly reduced when lysate of the bacterium was used in lieu of whole bacterium [14]. 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 [15]. An alternative hypothesis is that microbiota 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 microbiota 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 [14]. This was shown by the studies on mice using two strains of microbiota, a human and rat strain.

#### **Potential role of probiotics and whole microbial communities**

Recent microbial transplants of oxalate-degrading bacteria into a laboratory rat from the mammalian herbivore *Neotoma albigula* produced a notable and long-lasting colonization of oxalate-degrading bacteria. In order to provide permanent oxalate degradation across species, this finding could point to a novel target for therapeutic intervention [15]. Urinary oxalate excretion has been seen to temporarily diminish in rats or humans whose guts have been treated with oral probiotic formulations containing oxalate-degrading bacteria. Various combinations of *Oxf*, *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and other oxalate degraders are present in these oral probiotic formulations. The probiotics evaluated in people and animals show that all formulations first reduce the excretion of oxalate in the urine.

#### **Conclusion**

While there is a dearth of evidence proving a direct causal link between changes in the gut microbiota and kidney stone occurrence, the literature review is somewhat suggestive. Even though this area of study is still in its infancy, the development of sequencing technologies and analytical tools presents a rare chance to investigate unsolved issues regarding the function of urine and gut bacteria in the pathophysiology of stones. It is possible to identify and take into account a few constraints from earlier research while designing new ones.

The microbiome of mice was altered in all animal experiments by adding bacteria and altering their diet. Since the human microbiota and diet varies greatly from those of rodents, it may be required to develop a more representative model 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. This brief message suggests that taking probiotics at the same time as oxalate can have a major impact on oxalate breakdown and kidney stones.

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