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REVIEW

Bernd Hoppe · Gerd von Unruh · Norbert Laube
Albrecht Hesse · Harmeet Sidhu

Oxalate degrading bacteria: new treatment option for patients with primary and secondary hyperoxaluria?

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Abstract Current treatment options in patients with primary and secondary hyperoxaluria are limited and do not always lead to sufficient reduction in urinary oxalate excretion. Intestinal oxalate degrading bacteria are capable of degrading oxalate to CO_2 and formate, the latter being further metabolized and excreted via the feces. It is speculated, that both endogenously produced, as well as dietary oxalate can be significantly removed via the intestinal tract. *Oxalobacter formigenes*, an obligate anaerobic microbe normally found in the intestinal tract has one oxalate degrading enzyme, oxalyl-CoA decarboxylase, which is also found in *Bifidobacterium lactis*. Other bacteria with possible oxalate degrading potency are lactic acid bacteria, as well as *Enterococcus faecalis* and *Eubacterium lentum*. However, specific therapeutic studies on humans are scarce and, except for *Oxalobacter*, data are not congruent. We found the oral application of *Oxalobacter* successful in patients with primary hyperoxaluria. However, long-term post-treatment follow-up of 1–2 years showed that constant intestinal colonization is not achieved in most patients. In one patient with constant colonization, urinary oxalate excretion normalized over time. Short-term studies with other bacteria such as lactic acid bacteria did not show a specific reduction in urinary oxalate excretion. *O. formigenes* might be a promising new therapeutic tool in patients with primary and secondary hyperoxaluria.

Keywords Primary · Secondary · Hyperoxaluria · Oxalate degrading bacteria · Treatment

B. Hoppe (✉)
University Children's Hospital Cologne,
Division of Pediatric Nephrology,
University of Cologne, Kerpenerstrasse 62,
50931 Cologne Germany
E-mail: bernd.hoppe@medizin.uni-koeln.de
Tel.: +49-221-4784391
Fax: +49-221-4785835

G. von Unruh
Department of Internal Medicine I,
University of Bonn, Germany

N. Laube · A. Hesse
Division of Experimental Urology,
Department of Urology, University of Bonn, Germany

H. Sidhu
Ixion Biotechnology Inc, Gainesville, FL, USA

Introduction

Hyperoxaluria is one of the main risk factors for recurrent urolithiasis and progressive nephrocalcinosis [1]. The current therapeutic drug treatment options for primary hyperoxaluria and/or the dietetic regimen for patients with secondary hyperoxaluria do not always lead to adequate success, e.g. sufficient reduction of urinary oxalate excretion. Hence, new treatment options are clearly needed. This is further substantiated, as less than a third of patients with primary hyperoxaluria experience a profound reduction in their urinary oxalate excretion under current therapy [2].

Treatment with oxalate degrading bacteria could be such a new therapeutic option in patients with either form of hyperoxaluria. Normally, the intestinal tract is colonized with such bacteria as *Oxalobacter formigenes*, *Enterobacter faecalis* or *Lactobacillus* species and others [3, 4]. However, environmental influences, frequent antibiotic treatment, e.g. in patients with cystic fibrosis [5], or therapeutic interventions for the underlying disease, e.g. in Crohn's disease, often lead to a loss of intestinal colonization, and, in addition to other reasons, to an increased risk for stone formation.

Intestinal oxalate handling

Normal intestinal oxalate handling

The oxalate content of the normal western diet is approximately 80–120 mg/day, of which around 10% is

normally absorbed via the intestinal tract [6, 7]. Later, together with the endogenously produced oxalate, this amount of exogenous oxalate has to be eliminated via the urine [6]. As most of the dietary oxalate is intestinally bound to calcium or intestinally degraded by oxalate degrading bacteria, only small amounts of dietary oxalate are finally available for absorption [3, 8].

Abnormal intestinal oxalate handling

In patients with chronic inflammatory bowel diseases, calcium is bound to malabsorbed fatty acids instead to oxalate, hence more unbound oxalate remains for absorption [3, 6]. A further risk factor is the lack or absence of intestinal oxalate degrading bacteria. Approximately 50–80% of the dietary oxalate is normally degraded by these bacteria to CO_2 and formate, which is later metabolized or directly excreted via the feces. In case of lack or absence of such bacteria, intestinal oxalate absorption is increased and consecutively urinary oxalate excretion is elevated [3]. Hence, an additive effect of both malabsorption and absence of oxalate degrading bacteria is the culprit for the secondary hyperoxaluria in patients with Crohn's disease, as well as in patients with cystic fibrosis [3]. Lack of intestinal oxalate degrading bacteria is also the background for elevated urinary oxalate excretion in most of the patients with secondary hyperoxaluria for other or unknown reasons [3].

Potentially oxalate degrading bacteria

Oxalobacter formigenes

O. formigenes is an obligate anaerobe, gram-negative microbe that utilizes oxalate as its sole carbon and major energy source, and which normally colonizes the intestinal tract in 70–80% of the healthy population [10]. It is widely distributed in nature, e.g. in the rumen and hindgut of herbivores, in the coecum of birds and in marine sediments. The normal colonization rate is approximately 7.6×10^6–2.3×10^8 colony forming units (CFU)/g feces, which leads to an oxalate degradation rate of 5–8 mmol/g/h [10]. *O. formigenes* possesses two enzymes using oxalate as the substrate for biosynthesis: formyl-CoA transferase and oxalyl-CoA decarboxylase. Hence, oxalate is degraded to CO_2 and formate, of which the latter will be further metabolized and excreted via the feces [10]. Taking this into consideration, treatment with *O. formigenes* should be a logical option for patients with either absorptive and/or dietary, hence secondary, hyperoxaluria [3, 11].

In addition, the background for treatment with *O. formigenes* in primary hyperoxaluria is the hypothesis that oxalate is secreted via a high transepithelial gradient over the enterocytes into the intestinal lumen [12]. Therefore, an additional and significant amount of endogenous oxalate would be eliminated via the intestinal tract instead of being unexceptionally excreted via the kidneys. In our own examination of patients with secondary or primary hyperoxaluria, we observed that only a few were colonized with *O. formigenes* [3, 13].

Enterococcus faecalis

It is postulated that *E. faecalis* possesses three potential oxalate-degrading enzymes [14]. Its oxalate degrading capacity has been demonstrated in vitro, but further studies to prove this hypothesis have not yet been performed. Hence, there is no specific experience with this bacterium, especially with regard to its application in humans.

Lactic acid bacteria

Whether or not lactic acid bacteria are definitively able to degrade oxalate is controversial [3, 15, 16]. Nevertheless, treatment with a mixture of lactic acid bacteria has led to a reduction of urinary oxalate excretion in different studies [15]. In addition, it was recently shown, that *Bifidobacterium lactis*, one of the microbes often enclosed in lactic bacteria preparations, possesses the same oxalate degrading enzyme as *O. formigenes* (oxalyl-CoA decarboxylase [16]). However, our own work with preparations of lactobacilli does not so far support the hypothesis that urinary oxalate excretion can be substantially reduced by such treatment. Ingestion of 600 mg oxalate per day made healthy subjects hyperoxaluric, but treatment with 8×10^{11} CFU of freeze dried lactic acid bacteria (*Lactobacillus acidophilus*, *L. plantarum*, *L. brevis*, *Streptococcus thermophilus*, *B. infantis*; Oxadrop, VSL Pharmaceuticals) was neither able to reduce the intestinal oxalate absorption nor to decrease urinary oxalate excretion [17].

Eubacterium lentum

One study from Japan shows a potential oxalate degrading capacity of *E. lentum* (WYH-1 strain) in an artificial intestinal system [18]. Dietary oxalate was degraded up to 100%, and, in consequence, the intestinal oxalate content was reduced. However, no further specific studies are available.

Clinical studies with oxalate degrading bacteria

O. formigenes was previously tested in animal studies. For example, ethylene glycol fed (and therefore hyperoxaluric) rats were either supplied or not supplied with *O. formigenes* [19]. This system is comparable to the situation in primary hyperoxaluria, as ethylene glycol ingestion leads to an increase in endogenous oxalate production. Hence, the finding that only the rats treated

with *O. formigenes* experienced a reduction in urinary oxalate excretion was an important stimulation for further studies in humans. A first evaluation in humans showed comparable results [11].

In a pilot study, we treated patients suffering from primary hyperoxaluria with *O. formigenes*, first with a frozen cell paste ($>10^{10}$ colony forming units) and later with *O. formigenes* capsules ($>10^{7}$ colony forming units [20, 21]). We were able to recolonize the patients with *O. formigenes* and, much more important, we achieved an up to 50% reduction of urinary oxalate excretion under oral application of this bacterium [20, 21].

However, only some of the patients remained colonized post-treatment and hence long-term studies are necessary. Nevertheless, stable colonization and normalization of urinary oxalate excretion in one patient with primary hyperoxaluria after a 4 week course of oral *O. formigenes* application leads us to speculate on the effectiveness of such a treatment: the patient is still colonized 2 years later and, without changing any other part of the therapeutic regimen, her urinary oxalate excretion has since gradually decreased from values above 1.2 mmol/1.73m^2/24 h to normal, e.g. 0.22 mmol/1.73m^2/24 h at the last examination. Studies in patients with secondary hyperoxaluria are currently being undertaken. So far, we have not seen any specific side-effects of the treatment with *O. formigenes*, which we did not expect for a microbe which normally colonizes the intestinal tract.

Are there any promising data for other bacterial preparations? Next to *O. formigenes*, data for *Lactobacillus* spp. preparations are available. One study in children with recurrent urolithiasis or nephrocalcinosis showed a reduction in urinary oxalate excretion under treatment [22]. A further study in six adult patients with secondary hyperoxaluria showed a decrease in urinary oxalate excretion during short-term administration of the Oxadrop preparation [15]. Long-term follow-up studies, however, are not available for either lactic acid bacterial preparations or *O. formigenes*. However, our own preliminary data on a 47-year-old patient with short bowel syndrome (30 cm small intestine remaining) and recurrent calcium oxalate urolithiasis (50–80 microliths/stones per year) under treatment with lactobacilli once a day for 8 months (5×10^{8} CFU of *L. acidophilus*, *B. bifidum*, *Lactobacillus casei*, and *Streptococcus lactis*) showed a reduction of urinary oxalate excretion from >2 to <1.2 mmol/1.73m^2/24 h, a decrease in stone frequency (no stone passage/colic for the past 3 months) and the patient is well.

Conclusions

Treatment with oxalate degrading bacteria could be a promising new therapeutic option for patients with either primary or secondary hyperoxaluria. *O. formigenes* use in patients with primary hyperoxaluria looks especially promising. However, there is, of course, the necessity to check the preliminary data in long-term, multicentre studies. It has to be shown that stable colonization can be achieved and that urinary oxalate excretion remains continuously reduced in follow-up. In addition, the question of whether or not any kind of antibiotic treatment directly hampers the therapeutic effect of bacterial treatment currently remains unanswered. According to our own short-term results, continuous treatment with such bacterial preparations seems to be necessary.

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