



Review of the Role of Enteral Factor in the Development of Secondary Hyperoxaluria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Objectives: Discuss the role of the enteric factor in the hyperoxaluria development.

Methods: Using the Internet and written materials, the relevant factors of enteral factor; hyperoxaluria; oxalotrophia; *Oxalobacter formigenes*; kidney stones, and with 36 references, were comprehensively analyzed and studied.

Results: Under the condition of excessive intake of oxalate and its precursors, increased intestinal absorption of oxalate and imbalance of intestinal flora, resulting in increased urine oxalate and calcium oxalate crystal, which lead to hematuria, proteinuria, recurrent kidney stones and nephrocalcinosis.

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Discussion: Hyperoxaluria is a disease caused by metabolism disorder of oxalic acid and intestinal factors have significant influence on its progression. This disease can occur under the condition of excessive intake of oxalate and its precursors, increased intestinal absorption of oxalate and imbalance of intestinal flora, resulting in increased urine oxalate and calcium oxalate crystal, which lead to hematuria, proteinuria, recurrent kidney stones and nephrocalcinosis. Some patients may further progress to the AKI and CKD. With progressive decline in renal function, oxalate is reduced and deposits in the body can affect other tissues and organs. And adjustment of enteral factors is helpful for the treatment of hyperoxaluria.

In this article we discuss the role of the enteric factor in the hyperoxaluria development. Hyperoxaluria is a metabolic disease characterized by excessive urinary oxalic acid excretion and calcium oxalate crystal deposition, whose intestinal factors affecting its onset includes the increased intake of oxalic acid and its precursors, the increased intestinal absorption of oxalate and the imbalance of intestinal flora, etc. Severe hyperoxaluria can lead to kidney stones. At present, the influence of intestinal factors on hyperoxaluria has become a research focus, this paper will give a comprehensive description of its related research.

Keywords: Enteral factor; hyperoxaluria; oxalotrophia; *Oxalobacter formigenes*; kidney stones.

1. INTRODUCTION

Hyperoxaluria is a multifactorial metabolic disease caused by excessive urinary oxalic acid excretion and calcium oxalate crystal deposition due to the metabolism disorder of oxalic acid. Recently, in many countries, studies have returned to the issues of determining the causes of hyperoxaluria associated with enteral factors [1,2,3], including celiac disease, malabsorption syndrome, cystic fibrosis, steatorrhea and inflammatory bowel disease [4,5,6,7]. Intestinal diseases with their sufficiently long course contribute to the disorder of oxalate metabolism, cause the development of enterooxaluric syndrome and nephrolithiasis. Initially, it was believed that nephrolithiasis develops as a sequential condition in individuals who have undergone resection of the small intestine [8,9]. Later it was found that secondary hyperoxaluria occurs not only after the removal of the small intestine, but also in other diseases. In a study of 875 patients with inflammatory diseases of the small intestine (TC) [10], the presence of hyperoxaluria with nephrolithiasis was found in 7.2% of patients, while the average incidence of nephrolithiasis in inpatients in the United States does not exceed 1%. The development of secondary hyperoxaluria in children with celiac disease was noticed many years ago [11]. Fluid loss due to diarrhea plays a major role in the pathogenesis of crystalluria in celiac disease. This leads to a decrease in the volume of urine and, accordingly, an increase in its concentration. In turn, the loss of bicarbonates leads to acidosis and acidification of the urine, resulting in a decrease in urine stability, and favorable conditions are created for the

occurrence of crystalluria. Therefore, from a theoretical and practical point of view, the problem of combined damage to the organs of the urinary and digestive systems, which are characterized by the same type of morphological structures and the similarity of their functions, is of considerable interest. This paper focuses on the influence of intestinal factors, such as the increased intake of oxalic acid and its precursors, the increased intestinal absorption of oxalate and the imbalance of intestinal flora, on hyperoxaluria.

2. HYPEROXALURIA CAUSED BY INCREASED INGESTION AND INTESTINAL ABSORPTION

The combination of acquired pathology of the digestive and urinary organs, which, according to various sources, reaches 40–90% [12], negatively affects the course and prognosis of the pathology of both systems. One of the reasons for the development of secondary hyperoxaluria, in addition to impaired reabsorption of oxalates from the renal tubules, is increased absorption of oxalates in the intestine. In an extensive review by S. V. Belmer and T. V. Gasilina, a wide list of transporters common to the intestines and kidneys, which carry out the absorption and reabsorption of carbohydrates, amino acids, sodium, potassium, phosphorus, and xenobiotics, is given. Therefore, one can understand why the term dysmetabolic nephropathy has not been widely used for secondary hyperoxaluria, and at present, more and more researchers use the term enteral secondary hyperoxaluria. This is because the increased intake of oxalic acid and its precursors

and intestinal dysfunction lead to the increased intestinal absorption of oxalate.

2.1 Increasing Intake of Oxalic Acid and Its Precursors

Because of the current dietary changes, the daily intake of oxalic acid and its precursors has increased. Salads, fruit juices and vitamin C are widely consumed, which provide exogenous oxalic acid. Studies have shown that patients who consume lots of oxalates from food (about 800 mg oxalates daily) have significantly higher urinary oxalic acid excretion than others, and reducing oxalate intake can effectively relieve symptoms of hyperoxaluria and maintain the oxalic acid concentration in urine at normal levels. Studies have shown that taking vitamin C, a precursor of oxalic acid, 500 mg per week for 18 months significantly increases people's plasma oxalate levels and leads to secondary hyperoxaluria. Additionally, ethylene glycol can be converted to glycolic acid, glyoxylic acid and eventually oxalic acid in the liver by alcohol dehydrogenase, thus secondary hyperoxaluria can also occur when patients have ethylene glycol poisoning.

2.2 Increasing Intestinal Absorption of Oxalate

Intestinal dysfunction such as fat malabsorption causes calcium ions in the intestine to bind preferentially with fatty acids rather than oxalate, which leads to an increase in soluble oxalates. In addition, fat malabsorption can lead to vitamin B6 deficiency, and glyoxylic acid can't be converted normally, so oxalic acid is formed instead. Besides, intestinal inflammation leads to an increased intestinal permeability to oxalic acid, which finally leads to an increase in oxalates that are absorbed into the blood and cannot be excreted by the kidneys.

3. EFFECTS OF INTESTINAL FLORA

In recent years, the role of gut microbiota in affecting urine composition has been studied, resulting in evidence suggesting that it influences the incidence of nephrolithiasis. To date, relatively little is known about the overall role of gut microbiota in the pathophysiology of nephrolithiasis. A recent study revealed clear differences in the gut microbiota of patients with kidney stones compared to patients without

stones [13]. Fecal and urine samples collected from both groups of patients revealed 178 genera, of which the five most common enterotypes or single bacterial communities in each group accounted for more than 50% of the identified bacterial count. The genus *Prevotella* was the most common in the control group, while the genus *Bacteroides* was the most common in the nephrolithiasis patient group. *Eubacterium* is inversely correlated with oxalate levels and *Escherichia* is inversely correlated with citrate levels.

3.1 Protective Effects of *Oxalobacter formigenes*

In our opinion, the fact that the influence of the representative of the intestinal flora *Oxalobacter formigenes* on the concentration of oxalate in the urine deserves special attention. *Oxalobacter formigenes* was first identified from sheep rumen by scientists Dawson K. and Allison M. The discovery of the bacterium in 1980 gave rise to numerous studies that were conducted to study the role of *Oxalobacter formigenes* in the development of oxalate nephropathy. The main goal of the initial studies was to reduce urinary oxalate excretion and prevent the formation of calcium oxalate stones [14]. *Oxalobacter formigenes* exhibits a symbiotic relationship with the human body by reducing the absorption of oxalates in the intestinal lumen with a further decrease in their concentration in plasma and urine. *O. formigenes* is a Gram-negative, obligate anaerobic, non-motile, non-spore-forming bacterium that belongs to the genus *Betaproteobacteria* class and *Burkholderial*. Fatty acids provide the resistance of the microorganism to the negative effects of the environment, as well as to acid resistance [15]. Anaerobic bacterium colonizes the large intestine of all mammals, including humans, using oxalic acid as an energy source for its life activity [16]. In experiments on rats, M. Hatch et al. proved that, in addition to affecting the absorption of oxalate, *O. formigenes* induce its secretion in the lumen of the colon, thereby causing a decrease in the concentration of endogenous and alimentary oxalate in the urine [17]. The prevalence of *O. formigenes* ranges from 46% to 77% in the adult population [18,19]. Colonization occurs during life, not from birth. It is still unclear how the colonization of the intestine by this microorganism occurs. Almost all stool tests of 6-8 year old boys are positive for *O. formigenes*.

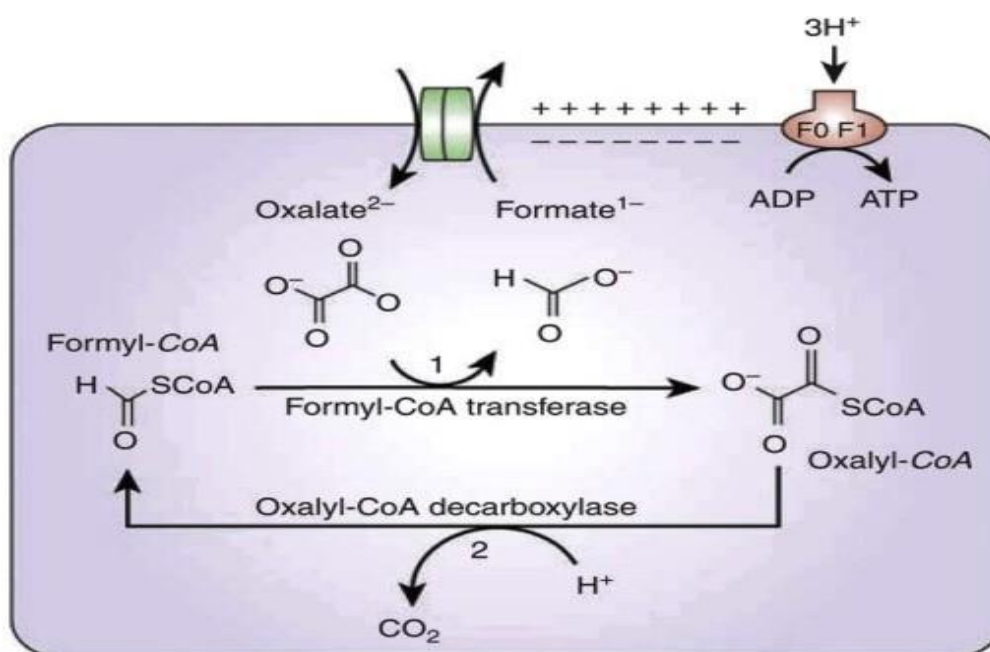


Fig. 1. Metabolism of oxalate by the bacterium *Oxalobacter formigenes* [16]

3.2 The Imbalance of Intestinal Flora Caused by Antibiotics

A number of studies have shown that antibiotic therapy can lead to loss of colonization. This is confirmed by the low prevalence of the bacterium in patients with cystic fibrosis (cystic fibrosis) [7] and with nephrolithiasis who have received repeated antibiotic therapy [20-23]. Patients with nephrolithiasis often receive antibiotic therapy during lithotripsy, with secondary infection. The researchers carried out the determination of sensitivity to antibiotics, 4 strains of *O. formigenes*. Resistance to amoxicillin, amoxicillin/clavulanic acid (augmentin), ceftriaxone (rocephin), and vancomycin has been identified [24]. In a study by Kharlamb V. et al. demonstrated the effect of antibiotic treatment on *O. formigenes* colonization in patients with *H. pylori*-associated infection. In patients treated with the antibiotic combination amoxicillin/clarithromycin for two weeks, colonization decreased from 100% to 37.5% after one month and recovered to 43.1% at month 6. In another group of patients, after a course of taking metronidazole / tetracycline, after a month there was a loss of colonization of about 50% and a complete loss by the 6th month, while after the appointment of a combination of antibiotics metronidazole / clarithromycin, there was no colonization of *O. formigenes*, after 1 and 6 months respectively [20]. In addition, it was found

that the intake of calcium and oxalate with food affects both the colonization of *O. formigenes* and the severity of hyperoxaluria. Jiang J et al. [25] confirmed that with a daily intake of an increased amount of calcium (2 g), the level of urinary oxalate excretion was significantly reduced compared with the same group, where calcium intake was lower (1 g and 0.4 g) [26].

3.3 The Influence of Oral Administration *O. formigenes*

In patients with primary hyperoxaluria, oral administration of *O. formigenes* for one month resulted in a decrease in urinary oxalate excretion [27]. And the use of this microorganism in children with hereditary oxalosis showed that hyperoxaluria was significantly reduced [28]. The clinical significance of colonization of the intestine by *O. formigenes* is primarily important for patients with calcium oxalate urolithiasis. Kaufman D.W. et al. showed in their studies that there is a strong inverse relationship between *O. formigenes* colonization and recurrence of calcium oxalate kidney stones. The risk of recurrence was reduced by 70% when colonized with this bacterium. In this study, *O. formigenes* was found in 17% patients, and in 38% of the control group [29]. A number of studies have shown that other gut microbiota also have the ability to absorb oxalates [30,31,32]. Campieri C. in his studies in 2001 showed that lactic acid

bacteria, when taken orally, degrade oxalate under in vitro conditions, thereby reducing its excretion in the urine [33].

4. HYPEROXALURIA LEADS TO KIDNEY STONES

The process of development of oxalate nephropathy, and eventually calcium oxalate nephrolithiasis, is a complex process in which more than one body system is involved [34]. Hyperoxaluria leads to supersaturation of urinary calcium oxalate (CaOx), which leads to the formation and retention of CaOx crystals in the kidney tissue. CaOx crystals may contribute to the formation of diffuse renal calcifications (nephrocalcinosis) or stones (nephrolithiasis). When the kidney's innate defense mechanisms are suppressed, the trauma and progressive inflammation caused by these CaOx crystals, together with secondary complications such as renal tubular obstruction, can lead to decreased renal function and, in severe cases, end-stage renal disease.

For decades, research on nephrocalcinosis and nephrolithiasis has mainly focused on both the physicochemistry of crystallization and the cell biology of crystal preservation. Although both are fairly well characterized, the mechanisms involved in establishing urinary supersaturation in vivo are not well understood, especially with respect to oxalate. Therefore, current therapeutic strategies often fail in adherence or effectiveness, and recurrence of CaOx stones is still common. Because the etiology of hyperoxaluria is diverse, a good understanding of how oxalate is absorbed and transported throughout the body, as well as a better understanding of the regulatory mechanisms, is critical to identifying future treatment strategies for this disorder.

Considering the chronic nature of the course and complications, it is necessary to develop new effective ways to treat and prevent nephrolithiasis already in childhood. Frequent and/or prolonged antibiotic therapy may contribute to the loss of *Oxalobacter formigenes* from the intestinal microbiota, and thereby increase the rate of oxalate elimination with increased hyperoxaluria and increased calcium oxalate stone formation in children with secondary hyperoxaluria. Therefore, it is necessary to expand clinical research on colonization of the intestine with bacteria *Oxalobacter formigenes* and other microbiota,

perhaps the most effective method for the prevention and treatment of nephropathy.

5. CONCLUSION

Hyperoxaluria is a disease caused by metabolism disorder of oxalic acid and intestinal factors have significant influence on its progression. This disease can occur under the condition of excessive intake of oxalate and its precursors, increased intestinal absorption of oxalate and imbalance of intestinal flora, resulting in increased urine oxalate and calcium oxalate crystal, which lead to hematuria, proteinuria, recurrent kidney stones and nephrocalcinosis. Some patients may further progress to the AKI and CKD. With progressive decline in renal function, oxalate is reduced and deposits in the body can affect other tissues and organs. And adjustment of enteral factors is helpful for the treatment of hyperoxaluria.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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