The Role of Oxalate in Urolithiasis

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Abstract

Urolithiasis is a frequent urological condition and oxalate plays an important role in kidney stone formation. Since hyperoxaluria seems to be one of the main risk factors for developing recurrent kidney stones and progressive nephrocalcinosis, many researches are focused on lowering the urinary oxalate. For now, treatment of hyperoxaluria consists of dietary oxalate restrictions and/or therapeutic drug treatment. These are rather limited options and a sufficient reduction in urinary oxalate is not always achieved. In this review, oxalate absorption, its excretion, hyperoxaluria, as well as some treatment options for hyperoxaluria will be discussed.

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Introduction

Urolithiasis is a frequent urological condition. The incidence for developing urolithiasis in Europe and USA is estimated at 0.5% per year, whereas the prevalence is estimated around 5.2% of the population per year (1,2). It has been proposed that calcium oxalate composites approximately 80% of all kidney stones (3). Intestinal absorption of dietary oxalate and renal handling of it are believed to be risk factors for calcium oxalate stone formation, which implies the very important role of oxalate in the formation of kidney stones (4).

Despite the fact that urinary stones can form anywhere in the urinary tract between the kidney and the bladder, the majority of the stones in the western cultures are formed in the kidneys. The biochemical processes involved in stone formation are (a) supersaturation, (b) crystallization, (c) crystal nucleation, (d) crystal retention, (e) formation of stone nidus and (f) finally development of stone (5). Supersaturation of the urine with calcium oxalate creates a perfect environment for crystallization. We need to understand that the urinary calcium oxalate supersaturation, and consequently crystallization, not only depends on urinary calcium and oxalate concentrations, but is also influenced by several other factors: (a) the presence of low molecular weight compounds, such as magnesium, citrate, pyrophosphate and bisphosphonate, (b) presence of high molecular weight compounds, such as glycosaminoglycans and proteins, (c) lipids and cellular membranes. These form complexes with calcium and oxalate and as a consequence act as modulators of urinary stone formation. The urinary concentration of these modulators can be influenced by many metabolic disorders, that originate either in the nephron or other tissues (5,6).

The source of urinary oxalate is divided into endogenous and exogenous, e.g. dietary, whereas endogenous represents two thirds, and exogenous one third of the total urinary oxalate. Healthy individuals produce around 80-90% of their oxalate endogenously, as a metabolic product in the degradation of glycine, glyoxylate and ascorbic acid in the liver (7,8). Contrary to that, findings from Holmes et al. suggest that approximately half of urinary oxalate should be derived from the diet (9). Based on these data it is clear that exact numbers are hard to determine and further research will be needed.

In a normal western diet, the oxalate content was estimated to approximately 80-120 mg per day (0.89 mmol - 1.33 mmol) (10). According to different authors, it is estimated that only around 6-14% of the digested oxalate is normally absorbed through the intestinal tract (8,10–12). However, Liebman et al. showed that a dietary oxalate intake, greater than 180 mg per day (2 mmol per day) could lead to a higher absorption of oxalate, extending to values reaching 50% of digested oxalate being absorbed (13).

Oxalate absorption and its modulation

Most of the ingested oxalate binds in the intestinal tract to calcium, if available, or it is degraded by oxalate degrading bacteria (14). Thus as already stated above, only small amounts of dietary oxalate are absorbed from the intestinal tract. It appears that the absorption of oxalate occurs in 50% along the small intestine and another 50% in the large intestine (15).

The amount of ingested oxalate that has been absorbed in the intestinal tract and then entered the circulation is difficult to measure directly. This is the reason, why most of the researches measure the absorbed oxalate with an indirect method, through the amount of oxalate, being excreted in the urine. This way of measuring can be seen as valid, if significant
amounts of the absorbed oxalate are not taken up by tissues, are not metabolized in the body, or are not secreted back into the intestine or other fluids such as sweat (11). As these assumptions appear to be valid in healthy individuals, there are growing evidence supporting a theory, that significant amount of circulating oxalate may be secreted back into the large intestine in some pathological conditions, such as hyperoxalemia or renal dysfunction (16). Recently, Voss et al. compared oxalate absorption between 120 healthy volunteers and 120 recurrent calcium oxalate stone formers on controlled diets. The study showed a significant higher oxalate absorption in stone formers. Furthermore, it showed that a small number of stone formers absorbed more than 20% of the oxalate load (17). Also Hesse et al. found differences in oxalate absorption reviewing several studies. They compared healthy individuals and patients with kidney stones and found evidence, which indicates that stone formers may on average absorb up to 50% more oxalate than healthy individuals (18). One of the possible explanations for such differences in absorption could have a genetic basis. It has been suggested that anion exchange proteins from the SLC26 family, and especially SLC26A6, play an important role not only in renal but also in small intestine oxalate transport (19,20).

An also important aspect is how ingested oxalate influences its excretion. Holmes et al. found out that apparently there is a much higher absorption of oxalate at low oxalate intakes then at high intakes. In their opinion the reason for this curvilinear relationship is that a much higher proportion of ingested oxalate is being ionized and available for absorption at low oxalate intakes. On the other hand at high oxalate intakes, a large fraction of oxalate will form complexes or get crystallized, thus unavailable for absorption. Based on these findings, the authors suggest, that on average, around 50% of the urinary oxalate excreted has its dietary origins, but this percentage may vary regarding different amounts of calcium and oxalate being ingested (9).

As already mentioned before, there are factors that can modulate the absorption of oxalate from the intestine. These include the co-ingestion of calcium and magnesium and the presence of oxalate degrading bacteria. Curhan et al. preformed a large prospective study on 45,619 men, 40 to 75 years old, who had no history of kidney stones. While observing the correlation between dietary calcium intake and the risk of symptomatic kidney stones, they have come to the conclusion that an inverse relationship between calcium intake and stone formation exists (21). They also suggested that the responsible mechanism for this effect was due to calcium biding to oxalate, thus reducing its availability for absorption. These findings were confirmed by other studies as well (13,18).

Curhan et al. also performed another prospective study among 96,245 female participants, aged 27 to 44 years, with no history of kidney stones. For 8 years they were examining the association between dietary factors and the risk of incident symptomatic kidney stones. They confirmed the assumption that a higher intake of dietary calcium decreases the risk of kidney stone formation (22).

The other important factor influencing the absorption modulation is presence of oxalate degrading bacteria in the intestinal tract, which may lower the amount of oxalate available for absorption by utilizing it for their metabolically needs. Research has been mostly focus on Oxalobacter formigenes. A study performed by Troxel et al. linked the absence of oxalobacter colonization with increased urinary oxalate excretion in patients with kidney stone disease (23), and another two studies linked the absence of oxalobacter colonization with increased stone formation (24,25).

An increase in absorption of oxalate has also been associated with chronic inflammatory bowel diseases and intestinal resections. Normally the ingested calcium forms complexes with oxalate and consequently makes it unavailable for absorption. In these patients, calcium is bound to malabsorbed fatty acids instead to oxalate, thus more oxalate remains unbound and available for absorption (26). Another condition, leading to increased absorption of oxalate from the intestinal tract, is the deficiency or complete absence of intestinal oxalate degrading bacteria. Normally these bacteria would degrade approximately 50-80% of the dietary oxalate into carbon dioxide and formate, but in their absence or diminished number, more oxalate is available for absorption and consequently more oxalate is being excreted through urine (14).

**Oxalate excretion**

The kidneys excrete almost the entire oxalate, absorbed from the gastrointestinal tract. In the kidney, oxalate is freely filtered through glomeruli, followed by partial passive back-diffusion into peritubular capillaries, from where the residual oxalate is excreted by active tubular transport back into the lumen. The ratio between oxalate clearance and glomerular filtration rate is around 1,2, which implies the importance of tubular secretion of oxalate (11). The proposed mechanism of oxalate secretion has been observed in a number of species, including...
humans. The oxalate secretion process in rat kidneys occurs in the proximal tubule, where also secretory pathways for other ions take place. Therefore it has been proposed, that the human oxalate secretory pathway occurs there as well. Although the transport processes and individual steps of the oxalate secretory pathway are still not fully understood, it has been suggested that anion exchange proteins from the SLC26 family are involved in this process. It is believed, that oxalate is directly removed from the blood as it flows through the kidneys, supposedly by a member of SLC26 family, sat-1 (SLC26A1) exchanger, which has been identified on the basolateral membrane of the proximal tubule cells. It exchanges oxalate for either sulfate or bicarbonate, thus acting as an oxalate transporter, which transfers oxalate from blood into the tubular cells. Following transcellular flux, oxalate is then released into the nephron lumen and excreted through urine. Among SLC26 exchangers family, A6, A7, A8 and A9 exchangers have been identified on the plasma membrane of the cells that can transport oxalate. Especially SLC26A6 is believed to play a role in secreting oxalate from the proximal tubule into urine, since it has been localized in the luminal membrane of proximal tubular cells (27–31).

After an oxalate rich meal, kidneys tend to secrete oxalate for an extended period of time. A study performed by Knight et al. compared intestinal and renal handling of oxalate loads in normal individuals and stone formers. Results showed that plasma oxalate levels, urinary oxalate excretion, and clearance ratio all increase similarly with increasing doses of oxalate in both, stone formers and control group. The same study also showed that renal oxalate secretion was evident up to 8 hours after a single oxalate load (4). Although several authors reported that high oxalate loads in animal models led to cell injury, detected through elevated urinary enzyme markers, that imply damage to renal tubular epithelial cells, there has been a lack in evidence for oxalate-induced tubular damage in humans (32).

A study, performed on healthy individuals, ingesting large doses of oxalate (up to 8 mmol or 720 mg), showed no increase in oxidative stress or renal injury markers, thus calling into question the importance of oxalate-induced cell membrane damage in calcium oxalate stone formation (11). Also another study, performed by Knight et al. showed no difference in excretion of oxidative stress or renal injury markers, even after highest oxalate loads in healthy subjects as well as in stone formers (4). The authors conclude that transient exposure of kidneys to high levels of oxalate may not be overtly harmful, however renal damage cannot be ruled out in more chronic exposures, like it was reported by others in animal model systems (4,5,33).

### Hyperoxaluria and its treatment

Hyperoxaluria is one of the risk factors for developing kidney stone disease and is described as urinary excretion of more than 40 mg (0,44 mmol) of oxalate per day. It is associated with higher urinary saturation of calcium oxalate, which consequently promotes formation of calcium oxalate stones. Causes of hyperoxaluria can be divided into three categories: (a) primary hyperoxaluria, a rare autosomal recessive disorder in glyoxylate metabolism, (b) enteric hyperoxaluria, which is associated with chronic diarrheal states and intestinal malabsorptive states, accompanying inflammatory bowel disease, celiac sprue or intestinal resection, and (c) dietary hyperoxaluria, which follows an excessive dietary oxalate intake or high substrate levels, such as ascorbic acid (32).

Laminski et al. suggest that hyperoxaluria is present in approximately 20 to 40% of stone formers, thus making it an important risk factor for developing kidney stone disease. They also identified that if we rule out primary hyperoxaluria as a source of urinary oxalate, the reason for increased oxalate urinary levels could be either increased dietary oxalate intake, increased endogenous production by metabolism or increased enteral oxalate absorption (34).

Specific treatment options for hyperoxaluria are rather limited. Treatments are mostly limited to dietary restrictions and may not be appropriate for people, who have difficulties in defining causative dietary constituents in their own diet (35). Typical treatment strategies include: (a) dietary oxalate restriction to limit its delivery to the colon, (b) low fat diets to limit malabsorption and effects of fatty and bile acids describe above, (c) oral calcium administration to bind oxalate and form complexes with it, and (d) bile acids sequestrants like cholestyramine (8). In addition to that it is possible to administer some drugs like thiazide diuretics, potassium citrate, cellulose phosphate or pyridoxine, which are all more or less successful in lowering the urinary oxalate (36). It has been also tried to degrade oxalate present in diet with help of an enzyme, called oxalate oxidase, but it is rather difficult to achieve satisfying results as these enzymes are likely to be inactivated by proteolytic enzymes during its passage through the gastrointestinal tract (37).

Recently it has been proposed, that it would be possible to treat hyperoxaluria with oxalate degrading...
bacteria, since these bacteria have been identified in human feces (38). Usually, oxalate degrading bacteria colonize our intestinal tract and use the ingested oxalate as a source of energy. As such, they are representatives of normal microflora in our intestine and could serve as a natural defense mechanism against urolithiasis (14).

Conclusion

Oxalate plays an important role in kidney stone formation, since calcium oxalate composites approximately 80% of all kidney stones. Understanding oxalate absorption, its modulation and oxalate excretion is important in developing therapeutical approaches in treatment of kidney stone disease. Although genetic and biochemical research on oxalate absorption and excretion has already revealed some of the important underlying pathways, the biochemical processes of different oxalate pathways and its influence on stone formation need further research, to fully understand this molecule, which is responsible for the formation of the majority of kidney stones.

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