Oxalate handling in health and disease - crosstalk gut and kidney

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Oxalate is a naturally occurring molecule found in various foods, including certain types of fruits, vegetables, beans, nuts, and grains. Besides being absorbed from the diet, it is also generated as a metabolic end-product from numerous precursors in the liver. Its removal mainly relies on renal excretion, where the proximal tubule plays a critical role. The cross-talk between the proximal tubule and the intestine, where oxalate is also absorbed, has been the topic of research in chronic kidney disease (CKD) and cardiovascular disease patients. Certain conditions, such as primary hyperoxaluria or Crohn's disease, cause overproduction or overabsorption of oxalate thus leading to a variety of symptoms.

Renal oxalate handling

Oxalate management in the proximal tubule has been studied related to chloride transport in this tubular segment. The major fraction of chloride reabsorption in the proximal tubule is passive and paracellular. Recent investigations show that Claudin-10a is essential for paracellular chloride transport in the proximal tubule and its deletion causes chloride redistribution. Besides the paracellular pathway, chloride is also transported by a transcellular energy-dependent pathway. It is believed that this active transcellular absorption is mediated by the protein-coding gene SLC26A6. SLC26A6 is a transmembrane secondary transporter that mediates the exchange of pairs of anions, including chloride and oxalate, followed by the recycling of oxalate into the cell, to sustain a substantial amount of chloride absorption in this segment. Research showed that SLC26A6 knockout mice do not exhibit changes in volume or chloride reabsorption in the proximal tubule, but they do display a significantly reduced fractional excretion of oxalate in the urine. This finding supports the role of SLC26A6 in oxalate renal secretion but does not elucidate chloride pathways in the proximal tubules.

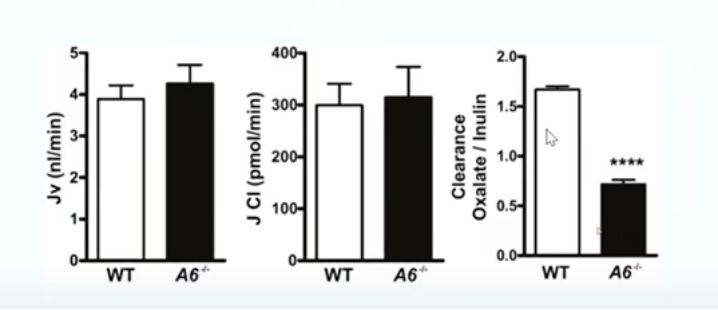

Figure 1. SLC26A6 mediates oxalate transport in the kidney

Intestinal oxalate handling

The oxalate transport pathways in the gut are similar to those in the kidneys. Oxalate interacts with calcium in the intestinal lumen to form a compound that cannot be passively absorbed via the tight junctions in the intestinal epithelium and is excreted by the feces. However, there is never enough calcium present in physiological conditions to combine with all the oxalate, thus the small free oxalate molecules readily pass from the intestinal lumen through tight junctions between adjacent epithelial cells along with salt and water. The SLC26A6 transporter in the intestines plays a key function in restricting net oxalate absorption by back-secreting it into the lumen. When this transporter is knocked-out in the intestine and the kidney, a phenotype prone to kidney stones occurs. Although it might be expected for urine oxalate to decrease due to loss of the renal SLC26A6 transporter, the reality is just the opposite. Because of the predominance of the intestinal phenotype, more oxalate is absorbed from the intestines and filtered into the urine, resulting in kidney stones.

The gut-kidney crosstalk

Persons with healthy kidney function maintain a state of oxalate homeostasis. However, in renal failure plasma oxalate concentration increases due to reduced glomerular filtration, as demonstrated in the German Chronic Kidney Disease cohort. The recent research on murine models focused on examining the intestinal oxalate handling processes in CKD. It showed a notable increase of SLC26A6 expression in the intestine of mice with CKD, including a significant up-regulation of the SLC26A6 transporter in the colon. Thus, in CKD there is a shift from renal to predominantly intestinal oxalate removal.

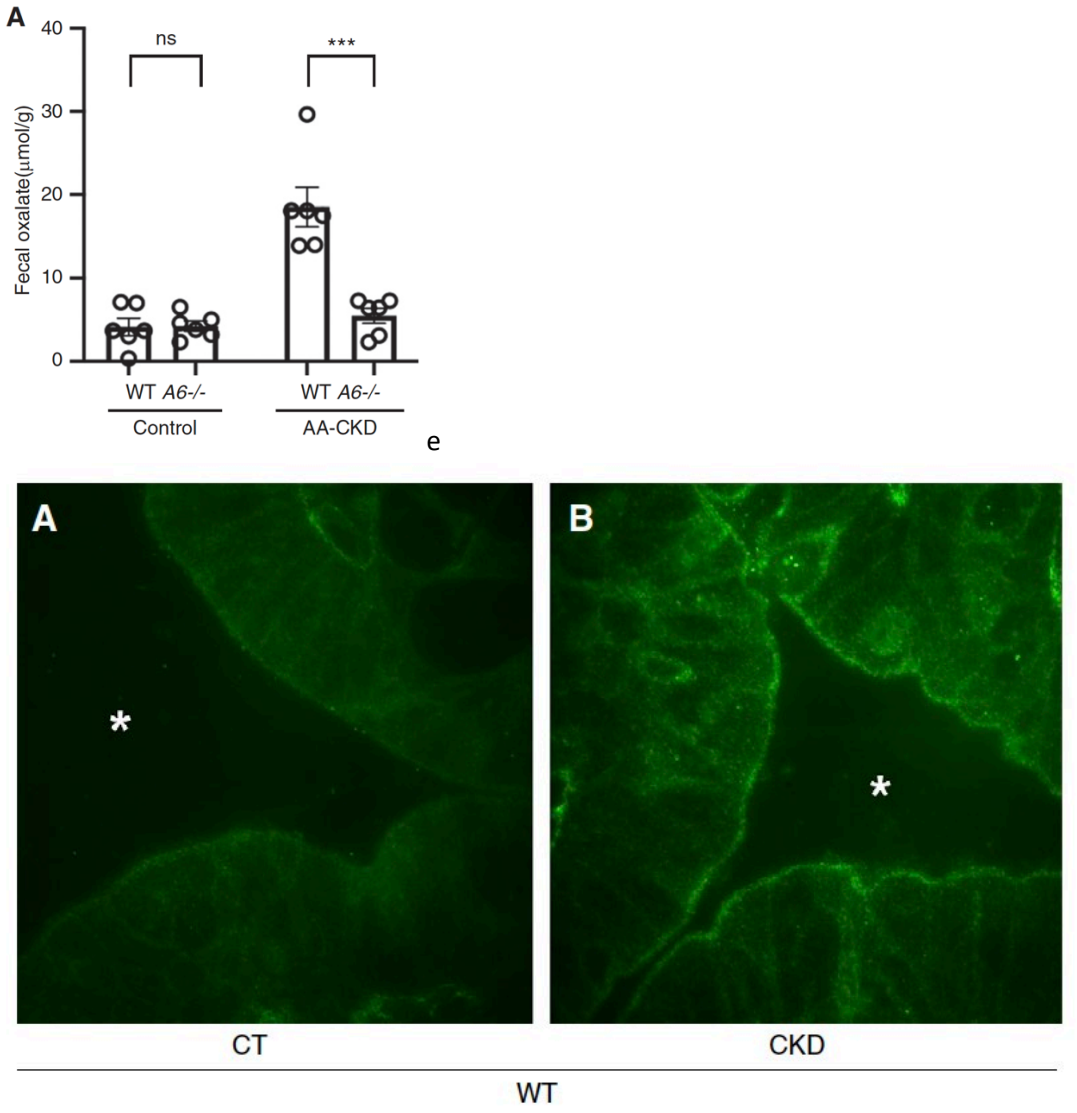

Figure 2. Enteric oxalate secretion is increased in CKD

In patients with end-stage renal disease, dialysis is the only option to substantially scale down plasma oxalate concentration. Dialysis efficiency is critical for lowering plasma oxalate levels in this population, but no significant benefit has been shown in oxalate removal related to different dialysis modalities or treatment duration. High oxalate is significantly associated with a lower survival rate and increased risk for cardiovascular events and sudden cardiac death in the dialyzed population. These findings are in line with observations in animal models, where mice fed a high oxalate diet exhibited increased rates of cardiac fibrosis, reduced ejection fraction, and diastolic dysfunction.

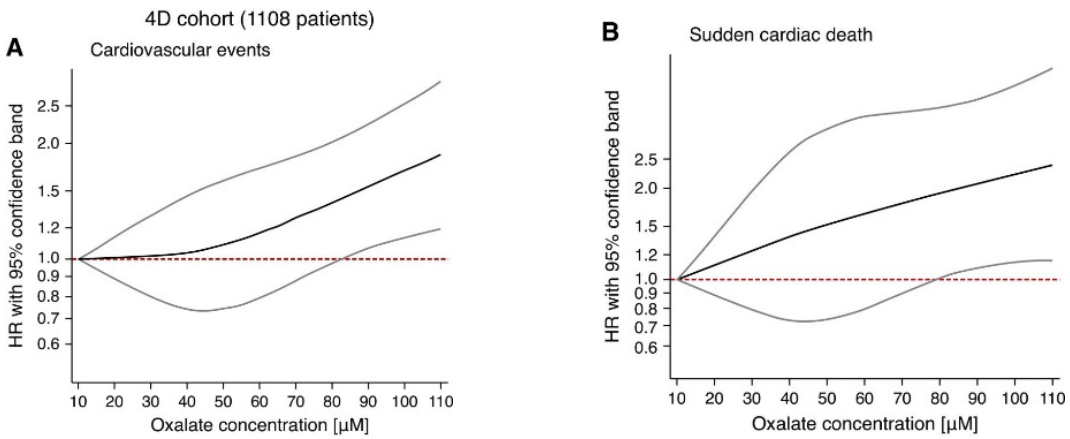

Figure 3. High oxalate correlates with increased cardiovascular events

Oxalate and inflammation

Basic research has demonstrated that oxalate is a potent trigger of systemic inflammation and cardiovascular complications. Since intestinal excretion cannot completely compensate for insufficient oxalate renal removal in CKD, accumulated plasma oxalate induces the 'reno-cardial vicious circle' causing increased cardiovascular mortality in this population. Oxalate crystals can activate inflammatory cells, dendritic cells, macrophages, and monocytes by the toll-like receptor 4 inflammasome signaling that leads to cytokine release and inflammation.

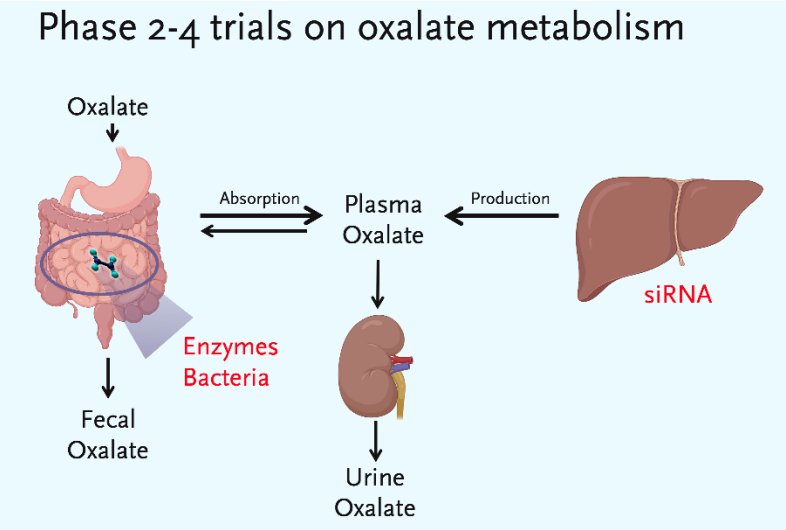

Figure created with BioRender.com.

Figure 4. Phase 2-4 trials on oxalate metabolism

There are several ongoing trials focused on targeting oxalate metabolism either via the Dicer-short interfering RNA (si-RNA) to inhibit glycolate oxidase (enzyme converting glycolate to glyoxylate, which is the primary substrate for the production of oxalate) or by directly targeting oxalate in the intestines. A recently conducted study investigated the effect of reloxaliase in patients with hyperoxaluria.

Reloxaliase is a recombinant oxalate decarboxylase enzyme from *Bacillus subtilis* expressed in *Escherichia coli* that catalyzes the conversion of oxalate to formate and carbon dioxide. Reloxaliase is orally administered with food, and its mechanism of action is to degrade oxalate along the gastrointestinal tract, thereby preventing its absorption. The patients with enteric hyperoxaluria were randomly assigned to reloxaliase or placebo for 4 weeks and followed for another 4. Reloxaliase decreased urine oxalate by 22,6%, however the group receiving placebo also demonstrated reduced urinary oxalate by 9.7%. Adverse events were relatively uncommon, but not dose-limiting. These data support the need for clinical trials to determine the impact of reloxaliase on nephrolithiasis in patients with enteric hyperoxaluria. In addition, bacteria harboring oxalate degrading enzymes have been engineered to consume oxalate in the gut. These bacterial therapeutics are currently being examined for their effectiveness to reduce urinary oxalate in ongoing clinical trials.

Key points

1. Despite its importance for oxalate homeostasis, the mechanisms for oxalate handling in the intestine and the kidney remain incompletely defined.
2. The amount of urinary oxalate depends on metabolic production, intestinal absorption and renal excretion.
3. New insight into the pathogenesis of hyperoxaluria has come from studies of anion transporter SLC26A6, which mediates active transcellular oxalate absorption in the proximal tubules and oxalate back secretion in the intestine.
4. In CKD, a shift from renal to predominantly intestinal oxalate removal appears.
5. New promising studies show that oxalate intestinal absorption can be successfully decreased by enhancing intestinal oxalate degradation.

Further reading

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