Hyperoxaluria: a gut–kidney axis?

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Hyperoxaluria leads to urinary calcium oxalate (CaOx) supersaturation, resulting in the formation and retention of CaOx crystals in renal tissue. CaOx crystals may contribute to the formation of diffuse renal calcifications (nephrocalcinosis) or stones (nephrolithiasis). When the innate renal defense mechanisms are suppressed, injury and progressive inflammation caused by these CaOx crystals, together with secondary complications such as tubular obstruction, may lead to decreased renal function and in severe cases to end-stage renal failure. For decades, research on nephrocalcinosis and nephrolithiasis mainly focused on both the physicochemistry of crystal formation and the cell biology of crystal retention. Although both have been characterized quite well, the mechanisms involved in establishing urinary supersaturation *in vivo* are insufficiently understood, particularly with respect to oxalate. Therefore, current therapeutic strategies often fail in their compliance or effectiveness, and CaOx stone recurrence is still common. As the etiology of hyperoxaluria is diverse, a good understanding of how oxalate is absorbed and transported throughout the body, together with a better insight in the regulatory mechanisms, is crucial in the setting of future treatment strategies of this disorder. In this review, the currently known mechanisms of oxalate handling in relevant organs will be discussed in relation to the different etiologies of hyperoxaluria. Furthermore, future directions in the treatment of hyperoxaluria will be covered.

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Oxalate ($C_2O_4^{2-}$) is the salt-forming ion of oxalic acid ($C_2H_2O_4$) that is widely distributed in both plants and animals. Oxalic acid may form oxalate salts with various cations, such as sodium, potassium, magnesium, and calcium. Although sodium oxalate, potassium oxalate, and magnesium oxalate are water soluble, calcium oxalate (CaOx) is nearly insoluble.[1] Excretion of oxalate occurs primarily by the kidneys via glomerular filtration and tubular secretion.[2–4] As oxalate can bind with calcium in the kidney, increased urinary oxalate excretion (hyperoxaluria) leads to urinary CaOx supersaturation, resulting in the formation and putative retention of CaOx crystals in renal tissue.[5] These CaOx crystals may contribute to the formation of diffuse renal calcifications (nephrocalcinosis) and stones (nephrolithiasis). Moreover, when the innate renal defense mechanisms[6,7] are suppressed, injury and progressive inflammation caused by these CaOx crystals,[8–14] together with secondary complications such as tubular obstruction, may lead to decreased renal function[15,16] and in severe cases even to end-stage renal failure.[6,17,18]

In the last decades, mechanistic research on nephrocalcinosis and nephrolithiasis mainly focused on understanding both the physicochemistry of intratubular (urinary) crystal formation and the cell biology of renal crystal retention[19–25] (as this falls beyond the scope of this article, the reader is referred to some recent reviews on this matter[18,25–27]). Although this research contributed significantly to our understanding of renal biomineralization, until now many (if not all) preventive or therapeutic strategies fail in their compliance or effectiveness. Hence, stone recurrence is still very common.[28] As the condition *sine qua non* of renal calcification is crystal formation driven by supersaturation, preventing the latter would be an effective approach. Although supersaturation and crystal formation in tubular fluid and urine have been characterized quite well, the mechanisms involved in establishing this supersaturated state *in vivo* are insufficiently understood, particularly with respect to oxalate. In this regard, a good understanding of how oxalate is transported throughout the body and how this transport is regulated is crucial. In this review, the current knowledge of the mechanisms of renal and gastrointestinal oxalate transport will be discussed in relation to the different etiological types of hyperoxaluria. Furthermore, potential interventional strategies to prevent urinary oxalate supersaturation will be covered.

SOURCES OF OXALATE

Urinary oxalate is derived from both exogenous and endogenous sources that, depending on dietary intake, may equally contribute to urinary oxalate excretion.[29] Oxalate is an unavoidable component of the human diet as it is a ubiquitous component of plants and plant-derived foods.[29–31] Endogenous oxalate synthesis (see Figure 1) primarily occurs in the liver[32] with glyoxylate as an immediate oxalate precursor.[33,34] Glyoxylate is derived from oxidation of glycolate by glycolate oxidase or by catabolism of hydroxyproline, a component of collagen.[35–38] Transamination of glyoxylate with alanine, by alanine/glyoxylate aminotransferase (AGT), results in the formation of pyruvate and glycine. Excess glyoxylate, however, will be converted to oxalate by glycolate oxidase or lactate dehydrogenase, of which the latter most likely catalyzes the bulk of this reaction.[6,33,39] It has been suggested that increased fructose intake may increase endogenous oxalate synthesis[33] and hence urinary oxalate excretion, thereby increasing the risk of incident kidney stones.[40] However, conflicting results have been reported about the relationship between fructose and oxalate synthesis.[41,42] Very recently, it was shown that in healthy individuals consuming controlled diets, increasing fructose concentrations had no effect on the excretion of oxalate, calcium, or uric acid. Moreover, cultured liver cells incubated with ^{13}C-labeled sugars did not convert fructose to oxalate *in vitro*.[43] The contribution of ascorbate catabolism to urinary oxalate is controversial.[44–49] An important reason for this may be the fact that ascorbate converts to oxalate nonenzymatically (pH >4.0) during sample processing, leading to an overestimation of the urinary oxalate concentration.[50,51] Other oxalate precursors are xylitol[52] and a number of amino acids.[5,53]

ETIOLOGY OF HYPEROXALURIA

Depending on dietary intake, daily urinary oxalate excretion in healthy individuals ranges between 10 and 40 mg per 24 h (0.1–0.45 mmol per 24 h). Concentrations over 40–45 mg per 24 h (0.45–0.5 mmol per 24 h) are considered as clinical hyperoxaluria.[5,6,39] Hyperoxaluria can be generally divided into two categories: primary and secondary hyperoxaluria. Primary hyperoxaluria is the result of inherited (mostly) hepatic enzyme deficiencies leading to increased endogenous oxalate synthesis. Secondary hyperoxaluria results from conditions underlying increased intestinal oxalate absorption, such as (1) a high-oxalate diet, (2) fat malabsorption (enteric hyperoxaluria), (3) alterations in intestinal oxalate-degrading microorganisms, and (4) genetic variations of intestinal oxalate transporters. Furthermore, it is worth mentioning that hyperoxaluria may also occur following renal transplantation because of rapid clearance of accumulated oxalate (see below).

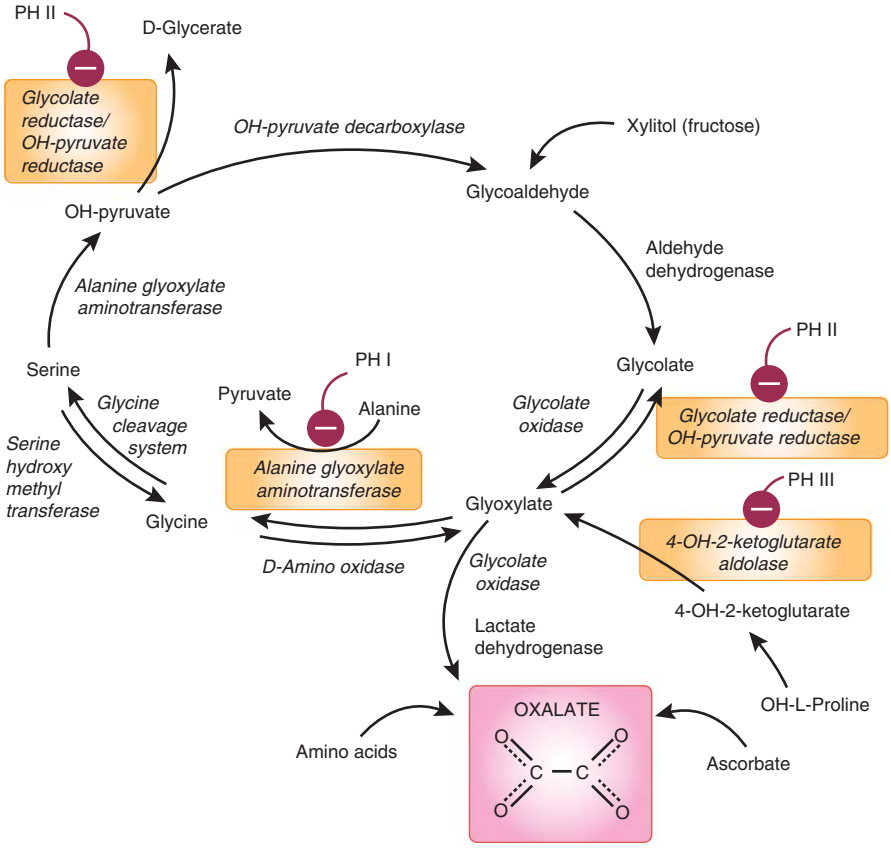

Figure 1 | Overview of endogenous oxalate synthesis pathways. PH I–III, primary hyperoxaluria types I–III.

Primary hyperoxaluria

The primary hyperoxalurias type I–III (PH I–III) are relatively rare autosomal recessive disorders of glyoxylate metabolism, resulting in markedly increased endogenous oxalate synthesis. All three types are characterized by the inability to remove glyoxylate (see Figure 1). PH I, accounting for the majority of all cases (70–80%),[17] results from the absence or deficiency of the peroxisomal liver enzyme AGT, of which the activity depends on pyridoxal phosphate. As AGT catalyzes the transamination of glyoxylate to glycine, its deficiency in PH I allows glyoxylate to be reduced to glycolate and to be oxidized to oxalate. PH II is a somewhat milder variant[54] resulting from the deficiency of the cytosolic liver enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR).[6,17,55,56] Severe hyperoxaluria is the clinical hallmark of these two types of PH, with reported values ranging between 88 and 352 mg per 24 h (1–4 mmol per 24 h) for PH I and 88 and 176 mg per 24 h (1–2 mmol per 24 h) for PH II.[6,17,54,56] Recently, a third form of PH was described, in which patients present with normal AGT and GRHPR enzyme activities.[17,57] Studies to define the etiology of this type of PH ruled out SLC26A6 (an oxalate transporter; see below) as the monogenic cause in a non-PH I/PH II cohort of eight patients,[58] whereas a very recent study indicated that mutations in DHDPSL are responsible for PH III. It is assumed that DHDPSL encodes 4-hydroxy-2-oxoglutarate aldolase, catalyzing the final step in the metabolism of hydroxyproline[59] (see Figure 1). However, little is known about the long-term outcome of this form of PH, as very few patients have been characterized to date. Furthermore, there still are patients presenting clinical symptoms of PH, but with negative mutation analysis for the known PH subtypes, suggesting another or even more subtypes of PH.

PHs are among the most severe disorders causing progressive nephrocalcinosis and/or nephrolithiasis, often leading to early end-stage renal disease. As renal function declines to a glomerular filtration rate of <45 ml/min per 1.73 m^2, oxalate excretion becomes compromised, such that plasma oxalate levels rise markedly (>30 μmol/l), thereby exceeding the CaOx supersaturation threshold. Hence, systemic deposition of CaOx (systemic oxalosis) occurs in extrarenal tissues, which lead to early death when left untreated.[17,55,56]

All types of PH become symptomatic in early childhood to adolescence, with about half of PH I patients exhibiting their first symptoms by the age of 5 years, while the median age of onset of PH II is 15 years.[56] PH III patients tend to develop severe recurrent nephrolithiasis in the first years of life, with clinical improvement over time and a lower risk of renal failure (personal experience). However, because of the systemic nature of the symptoms and the heterogeneity of disease expression in PH I, at least 35% of PH I patients remain undiagnosed until advanced renal failure has developed, or after early failure of a kidney graft.[17] This number may even be higher for patients with PH II and III based on the lack of significant symptoms in the long run and the lower risk of end-stage renal disease.

Secondary hyperoxaluria

High-oxalate diet. Estimates of the average daily oxalate intake of the western population are highly variable, ranging between 44 and 351 mg/day (0.5–4.0 mmol/day).[30,60–62] Daily intake may even exceed 1000 mg/day (11.4 mmol/day) when oxalate-rich foods, such as spinach or rhubarb, are consumed.[60] Values of up to 2000 mg (22.7 mmol) have been reported in seasonal rural diets in India.[63] However, the fraction of dietary oxalate that will effectively be absorbed by the intestine is highly influenced by the amount of oxalate-binding cations, such as calcium and magnesium, in the gut. In this context, several studies demonstrated that the concomitant ingestion of calcium (or magnesium) with oxalate can reduce oxaluria by forming insoluble oxalate complexes in the gut (thereby decreasing intestinal oxalate absorption),[64–69] a process that is disturbed in the pathology of enteric hyperoxaluria due to fat malabsorption (see below). Among other highly variable parameters, oxalate bioavailability, amount of oxalate precursors, inherited oxalate absorption capacity, gastric emptying, intestinal transit time, and the presence of oxalate-degrading microorganisms can be named.[5,60–64] Using standardized ^{13}C-labeled oxalate absorption tests,[70–75] the reference range for intestinal oxalate absorption in healthy individuals was reported to be between 2.2 and 18.5% of an administered load, with values >15% considered as oxalate hyperabsorption,[73] which is a risk factor for idiopathic CaOx nephrolithiasis.[70,71,74,76] This is supported by the observation that idiopathic CaOx stone formers absorb more oxalate than normal individuals.[70,74,77]

For a long time, the contribution of dietary oxalate to urinary oxalate was thought to be minimal (10–20%),[78] as a linear relationship between dietary oxalate intake and urinary oxalate excretion was assumed. However, Holmes *et al.*[29,30] identified a curvilinear relationship in normal individuals because of higher oxalate absorption at low intakes and established a dietary contribution of $\sim$50%, making it an important determining factor in urinary oxalate excretion.[29] A recent cross-sectional study of 3348 stone-forming and non-stone-forming individuals challenged the impact of dietary oxalate on 24 h urinary oxalate excretion.[79] However, in that study no postprandial urinary oxalate excretions were investigated, which may be important as it was shown that an oxalate load results in transiently increased plasma and urine oxalate levels peaking 2 to 4 h post load, implying that an oxalate-rich meal is able to induce temporary states of hyperoxaluria, not to be noticed in 24 h urine samples.[31,80]

Fat malabsorption (enteric hyperoxaluria). Hyperoxaluria due to fat malabsorption refers to a condition in which intestinal oxalate absorption is increased as a result of two different mechanisms: (1) both dihydroxy bile acids and fatty acids increase the permeability of the intestinal mucosa to oxalate and (2) complexation of fatty acids with luminal calcium increases the amount of soluble oxalate that is available for absorption as insoluble CaOx complexes are no longer formed.[81] It is also postulated that inhibition of

intestinal oxalate-degrading bacteria in patients with bile acid malabsorption might contribute to the increased intestinal oxalate absorption, which may range from 35 to 50% of an administered oxalate dose.[81] Hyperoxaluria due to fat malabsorption is typically seen in patients suffering from inflammatory bowel disorders,[81] after bariatric surgery (potentially leading to kidney failure[82–84])[85,86] or after the use of gastrointestinal lipase inhibitors.[87,88] Daily urinary oxalate excretion ranges between that of healthy individuals and PH patients (44–70 mg per 24 h; 0.5–0.8 mmol per 24 h).[6,17,81]

Alterations in intestinal oxalate-degrading microorganisms. One of the best-known oxalate-degrading organisms is *Oxalobacter formigenes,* a Gram-negative anaerobic bacterium that is found in the colon of humans and other vertebrates and that exclusively relies on the conversion of oxalate to formate as its energy source. Oxalate enters the bacterium through an oxalate–formate antiporter on the cell membrane, where it is metabolized to formate and CO_2 by the activities of two enzymes (that is, formyl-CoA transferase and oxalyl-CoA decarboxylase), resulting in a proton gradient used to drive ATP synthesis. Subsequently, the formed CO_2 diffuses out of the bacterium and formate exits through the antiporter.[89,90] The discovery of this bacterium led to the hypothesis that colonization with *O. formigenes* would reduce intestinal oxalate absorption, and hence decrease urinary oxalate excretion. This hypothesis has been confirmed in several animal and human studies.[91–94] Moreover, a recent study using male Sprague–Dawley rats showed that *O. formigenes*, in addition to its luminal oxalate-degrading capacities, is able to derive oxalate from systemic sources by inducing enteric oxalate secretion.[95]

Genetic variations of intestinal oxalate transporters. Recently, it was shown that deletion of the slc26a6 oxalate transporter gene in mice, a species virtually insensitive to lithogenic agents, results in hyperoxalemia, hyperoxaluria, and CaOx urolithiasis due to a defect in intestinal oxalate secretion.[96,97] It was also suggested that differences in affinity and electrogenicity of this transporter may partially explain differences in species susceptibility (mice less susceptible than humans) to nephrolithiasis.[98] Furthermore, it has been reported that polymorphisms of this transporter (V185M) in the human population may explain accelerated lithogenesis in distinct subpopulations.[98] Taken together, these observations suggest that alterations in intestinal oxalate transporters might be associated with reduced intestinal oxalate secretion and increased prevalence or severity of nephrocalcinosis and/or nephrolithiasis, highlighting the importance of a good understanding of oxalate transport for future treatment and/or prevention of these disorders.

Hyperoxaluria following renal transplantation

When glomerular filtration rate declines, oxalate clearance becomes compromised, resulting in elevated plasma oxalate levels that may be up to 10 times above normal in predialysis patients: 90 ± 6 vs. 9 ± 2 μmol/l.[99,100] As CaOx supersaturation may already occur at plasma oxalate levels of 30 μmol/l, uremic plasma is often supersaturated, potentially leading to systemic oxalosis.[101] Moreover, a significant correlation between plasma oxalate and time on dialysis has been demonstrated.[102] Hence, following renal transplantation or combined liver/kidney (PH patients) transplantation, the accumulated oxalate is rapidly released from the body, resulting in transient hyperoxaluria and risk of CaOx precipitation within the allograft tissue,[103] especially in the presence of allograft dysfunction.[104,105]

OXALATE TRANSPORT

Insights in the mediators of epithelial oxalate transport gained a significant boost with the identification of the solute-linked carrier 26 (SLC26) anion exchangers, which consist of 11 members capable of transporting several anions, including sulfate (SO_4^{2-}), chloride (Cl^-), hydroxyl (OH^-), iodide (I^-), bicarbonate (HCO_3^-), formate, and oxalate (see Table 1).[106–109]

The first member of this family that was identified is SLC26A1 (sulfate anion transporter 1 (SAT-1)). This transporter is expressed in the sinusoidal membrane of rat hepatocytes,[106,107,109–112] the basolateral membrane of renal proximal tubules,[106,107,109–111,113] and enterocytes of several mammalians.[114,115] SLC26A1 has been reported to mediate SO_4^{2-}, Cl^-, HCO_3^-, glyoxylate, and oxalate transport.[106,107,109–111,113,115,116]

SLC26A2 (diastrophic dysplasia sulfate transporter (DTDST)) is the closest paralog of SLC26A1 and is located at the apical membrane of rat small intestine, rat proximal tubule, and human colon, where it appears to function as a SO_4^{2-}, Cl^-, and oxalate exchanger.[106,107,109,117]

SLC26A3 (downregulated in adenoma (DRA)) is capable of Cl^-, HCO_3^-, OH^-, and oxalate transport and has been shown to be present at the apical membrane of enterocytes of humans and laboratory animals.[106,107,114,118]

SLC26A6 (chloride/formate exchanger (CFEX) or putative anion transporter 1 (PAT-1)) mediates SO_4^{2-}, Cl^-, HCO_3^-, OH^-, formate, and oxalate transport and is expressed at the apical membrane of several tissues including the gastrointestinal tract and along the nephron.[119–122]

SLC26A7 is reported to transport SO_4^{2-}, Cl^-, HCO_3^-, and oxalate[123–125] and may also function as an intracellular pH-sensitive Cl^- channel as was shown in *Xenopus* oocytes and HEK293 cells.[126] In mammalian kidney, this transporter is expressed in proximal tubule (subapical), thick ascending limb (basolateral), principal cells of the distal tubule (basolateral), and intercalated cells of outer medullary collecting duct (basolateral).[123–125,127] In the gastrointestinal tract, SLC26A7 is expressed in gastric parietal cells (basolateral) of mice.[128]

SLC26A8 (testis anion transporter 1 (TAT1)) and SLC26A9 demonstrate Cl^-, SO_4^{2-}, and oxalate transport activities when expressed in *Xenopus* oocytes.[125] Both transporters show distribution in renal tissue, whereas SLC26A9 is also expressed in rodent stomach.[106,108,109]

Table 1 | Renal, hepatic, and gastrointestinal SLC26 oxalate transporters

Transporter	Substrates	Tissues	Apical	Basolateral	Species
SLC26A1 (Sat-1)	SO_4^{2-}, HCO_3^-, Cl^-, oxalate[106–111,113,120,144]	Hepatocyte[106,107,109–111,113,144] Ileum[96,144], cecum,[144] colon[144] Proximal tubule[106–111,113,120,144]		X	Rat[107,110,111,113] Human[107,109] Mouse[96,107,109,120,144]
SLC26A2 (DTDST)	SO_4^{2-}, Cl^-, oxalate[106–109,117,137]	Ileum,[96] colon[107,108,117] Proximal tubule[117,137]	X		Rat[107,117,137] Human[107,109,117] Mouse[96,109,117]
SLC26A3 (DRA)	SO_4^{2-}, Cl^-, HCO_3^-, OH^-, oxalate[106–108,171]	Duodenum,[107,171] ileum,[96,118,171] cecum,[171] colon[107,171]	X		Rat[107,171] Human[106,107] Mouse[96,106,107,118]
SLC26A6 (PAT-1) (CFEX)	SO_4^{2-}, Cl^-, HCO_3^-, OH^-, oxalate, formate[96-98,106–109,119,120,122,136,151,152,172–174]	Stomach (parietal cells)[107,108,136,173] Duodenum,[97,107,136,152] jejunum,[97] ileum[96,97,109,136] Proximal tubule[97,107–109,119,120,127,136,152,172,174] TAL, DCT, and collecting duct[108,113]	X		Rat[174] Human[58,97,106–109,127,136,151,175] Mouse[96–98,106–109,119,120,136,151,152,172,173]
SLC26A7	SO_4^{2-}, Cl^-, HCO_3^-, oxalate[106–109,123,125,126,128]	Stomach (parietal cells)[106,108,109,128] Proximal tubule and TAL[106,108,109,124] OMCD[106–109,123,127]	X	X	Rat[108,123,124] Human[109,125,127] Mouse[108,109,124,128]
SLC26A8 (Tat1)	SO_4^{2-}, Cl^-, oxalate[107–109,125]	Kidney[109]	?	?	Human[108,109,125] Mouse[109]
SLC26A9	SO_4^{2-}, Cl^-, OH^-, HCO_3^-, oxalate[106–108,125]	Stomach[106,108] Kidney[108]	X		Rat[108] Human[108,125] Mouse[108]

Abbreviations: CFEX, chloride/formate exchanger; Cl^-, chloride; DCT, distal convoluted tubule; DRA, downregulated in adenoma; DTDST, diastrophic dysplasia sulfate transporter; HCO_3^-, bicarbonate; I^-, iodide; OH^-, hydroxyl; OMCD, outer medullary collecting duct; PAT-1, putative anion transporter 1; Sat-1, sulfate anion transporter 1; SLC26, solute-linked carrier 26; SO_4^{2-}, sulfate; TAL, thick ascending limb; Tat1, testis anion transporter 1; X, present; ?, unknown.

Furthermore, besides the SLC26 transporters, other anion exchangers may also be involved in oxalate transport. For example, SLC4A1 (AE1; band 3), which is found in renal and intestinal epithelia, as well as in erythrocyte plasma membranes of both laboratory animals and humans,[129] has been shown to exhibit Cl^-/oxalate exchange in human erythrocytes.[130] Moreover, this transporter seems to exhibit altered exchange properties in CaOx stone formers.[131,132] Its contribution to renal and gastrointestinal oxalate transport, however, needs further investigation. Finally, nonoxalate exchanging transporters may also have a critical role in oxalate handling by contributing to ion gradients that influence oxalate exchangers, adding an extra level of complexity to a full understanding of oxalate handling. In addition, it should be noted that much information regarding oxalate transport is derived from *in vitro* studies, of which several seem to show conflicting results, likely depending on species and experimental conditions used. Therefore, further studies are required to get better insights in transport properties and (pathological) physiological contribution of these transporters in humans.

Renal oxalate handling

It has been shown in rat and humans that renal oxalate handling comprises glomerular filtration, tubular secretion, and tubular reabsorption.[2,133] Whereas glomerular filtration of oxalate directly depends on plasma oxalate levels, tubular oxalate handling is mediated by several SLC26 transporting proteins: that is, SLC26A1, A2, A6, and A7 (see Figure 2).

SLC26A1 is reported to mainly exchange oxalate for intracellular SO_4^{2-} and to have a role in tubular oxalate

Figure 2 | Proposed mechanism of renal oxalate handling. Cl^-, chloride; DCT, distal convoluted tubule; OMCD, outer medulla collecting duct; Ox^{2-}, oxalate; PCT, proximal convoluted tubule; PST, proximal straight tubule; SLC26, solute-linked carrier 26; SO_4^{2-}, sulfate; TAL, thick ascending limb.

uptake across the basolateral membrane.[110,111] Krick *et al.*[111] calculated that with normal plasma oxalate concentrations (usually in the 1–6 μmol/l range[17]), the binding site of SLC26A1 is theoretically 1.8–8.6% occupied by oxalate, so that SLC26A1-mediated tubular oxalate uptake is likely negligible. In PH patients in whom plasma oxalate levels may be >100 μmol/l,[17] however, SLC26A1 occupancy increases to 65.3% and oxalate is taken up into the tubular cell, so that tubular oxalate secretion (facilitated by SLC26A6 at the apical membrane; see below) may occur.

In mammalian kidney, SLC26A7 is expressed in the proximal tubule (subapical), thick ascending limb (basolateral), principal cells of the distal tubule (basolateral), and intercalated cells of outer medullary collecting duct (basolateral).[123,124,127] Its role in renal oxalate transport remains unknown. Oxalate transport has also been reported across the rabbit papillary epithelium,[134] where it may be involved in the deposition of CaOx crystals on Randall's plaques.[135] However, the transporter involved herein has not yet been identified.

Studies in slc26a6$^{-/-}$ mice showed that SLC26A6 is the dominant Cl^-/oxalate exchanger at the apical membrane of the proximal tubule, mediating the only known physiological function of oxalate, namely oxalate-dependent tubular Cl^- reabsorption (tubular oxalate secretion). Cl^-/oxalate exchange occurs in parallel with a second process, namely $3Na^+/SO_4^{2-}$ exchange. A third process, that is, oxalate/SO_4^{2-} exchange, functions as a mechanism to recycle oxalate back into the cell and sulfate from the cell to the lumen.[136] This exchange mode is (partly) mediated by an exchanger other than SLC26A6 as oxalate/SO_4^{2-} exchange is only partially defective in slc26a6$^{-/-}$ mice.[97] As SLC26A2 is expressed at the apical membrane of proximal tubules and reported to transport oxalate and SO_4^{2-}, as shown in humans and rodents,[117,137] this transporter would be a candidate for apical oxalate/SO_4^{2-} transport.

Apical exchange of intracellular oxalate for luminal Cl^- has also been reported in rat distal tubule.[138] Human SLC26A6 is also reported in Henle's loop, distal tubule, and intercalated cells of collecting ducts.[127]

CFTR (cystic fibrosis transmembrane conductance regulator), a Cl^- channel expressed in the apical membrane of epithelial cells, shows reciprocal regulatory activity with several SLC26 anion exchangers, including SLC26A6.[139] Defective expression of this channel in the proximal tubule of cystic fibrosis patients might drive SLC26A6-induced tubular oxalate secretion, which together with increased intestinal oxalate absorption[140] might explain the mild hyperoxaluria and increased incidence of CaOx nephrolithiasis in these patients.[141]

Under physiological conditions, oxalate is predominantly excreted by glomerular filtration. Furthermore, given that oxalate is a metabolic waste product, it would reasonably be expected that tubular reabsorption does not occur. However, in rat kidney, it was found that the S1 and S2 (convoluted) segments of the proximal tubule show net oxalate absorption, whereas the S3 (straight) segment shows net oxalate secretion.[2,39] Tubular oxalate reabsorption may be a way to reduce urinary CaOx supersaturation along the early sensitive parts of the nephron. More important than reducing urinary CaOx supersaturation, however, seems to be maintaining relatively constant plasma oxalate levels as increased plasma oxalate concentrations may give rise to life-threatening systemic oxalosis.[17] In this context, Bergsland *et al.*[142] very recently identified tubular oxalate secretion, next to glomerular filtration, as a key mediator in the regulation of plasma oxalate levels in calcium stone formers, as a strong correlation was observed between (high) urinary oxalate excretions and tubular oxalate secretion, whereas plasma oxalate was similar between stone formers and controls. The role of tubular oxalate secretion as mediator of plasma oxalate levels is further supported by the observation that tubular oxalate secretion is generally elevated in PH patients.[143] Moreover, the phenotypes of slc26a1$^{-/-}$ (see ref. 144) and slc26a6$^{-/-}$ (see ref. 97) also show increased plasma oxalate levels, next to hyperoxaluria, due to reduced intestinal oxalate secretion (see below). As SLC26A1-mediated oxalate uptake (basolateral) and SLC26A6-mediated oxalate efflux (apical), hence tubular oxalate secretion, is absent in these knockout mice, it can be suggested that under conditions of increased intestinal oxalate supply, oxalate elimination solely via glomerular filtration is insufficient to maintain stable plasma oxalate levels.

Hepatic oxalate handling

As already mentioned above, endogenous oxalate synthesis primarily occurs in hepatocytes, with glyoxylate as the principal precursor. Under physiological conditions, the majority of glyoxylate is converted to glycine or glycolate by AGT and GRHPR, respectively, whereas excess glyoxylate is metabolized to oxalate,[32,33] which is secreted into the blood across the hepatocyte sinusoidal membrane by SLC26A1, mainly in exchange for SO_4^{2-} and HCO_3^- (see refs 110,111) (see Figure 3). In PH patients, glyoxylate concentration rises because of AGT, GRHPR, or 4-hydroxy-2-oxoglutarate aldolase deficiency, leading to increased hepatic oxalate synthesis.[17,59] Interestingly, a molecular link between the mechanism of cellular oxalate release and oxalate metabolism has recently been described by Schnedler *et al.*,[116] showing that oxalate and its precursor glyoxylate increase mRNA and protein expression of several splice variants of SLC26A1 in hepatocytes (HepG2 cells). This appears to be a logical observation as oxalate is a metabolic end product with cellular toxicity of which the intracellular concentration needs to be lowered as soon as possible. In this context, the presentation of primary hyperoxaluria might be viewed as the direct result of self-preservation of the hepatocyte. However, whether glyoxylate and oxalate upregulate SLC26A1 activity in PH patients remains to be determined.

Gastrointestinal oxalate handling

Paracellular vs. transcellular. Gastrointestinal oxalate transport can be generally divided into two components:

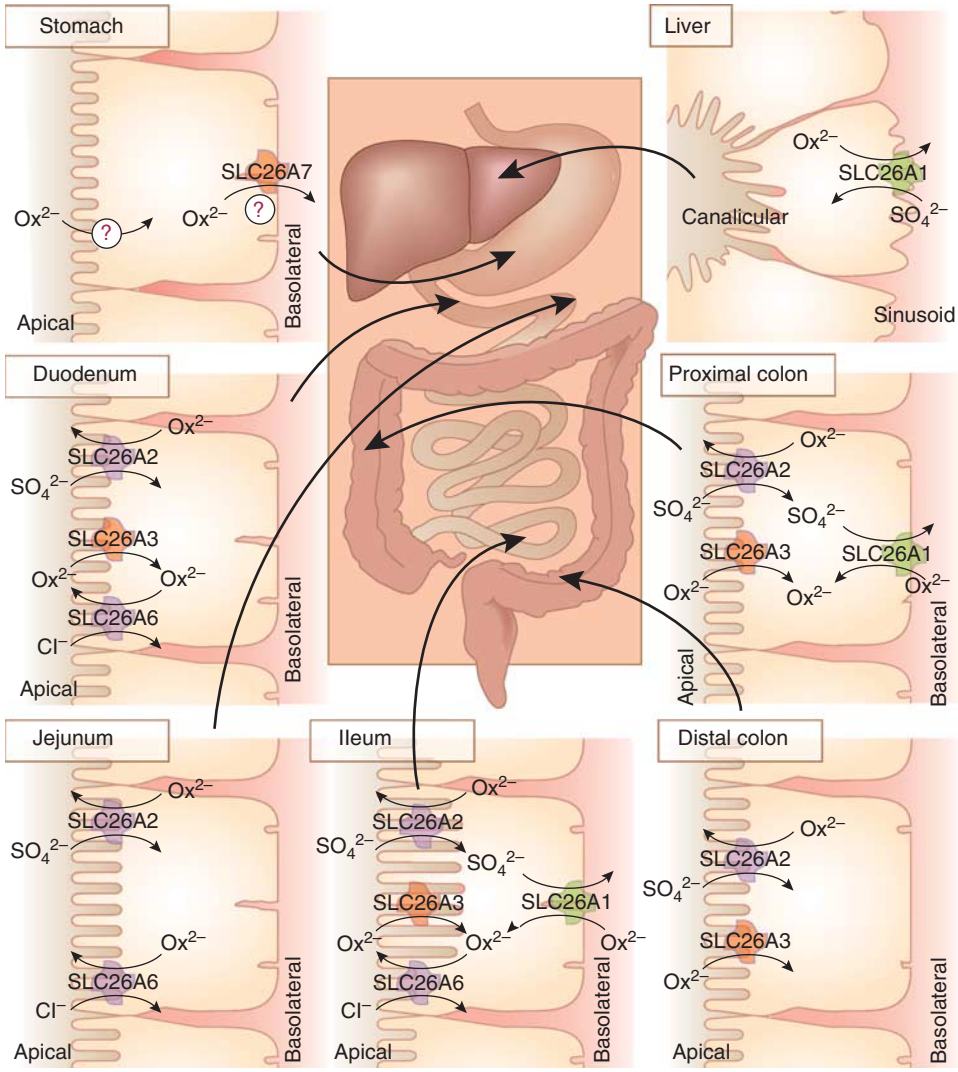

Figure 3 | Proposed mechanism of oxalate handling across liver, stomach, and intestinal tract. Cl^-, chloride; Ox^{2-}, oxalate; SLC26, solute-linked carrier 26; SO_4^{2-}, sulfate.

paracellular and transcellular oxalate transport, so that the resulting unidirectional oxalate flux is the sum of both pathways. Whereas the paracellular route is passive and driven by electrochemical gradients across the intestinal epithelium, transcellular transport is usually mediated and coupled to secondary active processes providing the potential for transport independent of the prevailing electrochemical gradient. The relative importance of these two routes varies per intestinal segment and with disease state. It is expected that the paracellular route contributes more significantly to oxalate absorption in the small intestine where junctional resistance is low and luminal oxalate concentration is expected to be high, in contrast to more distal intestinal segments. Furthermore, it is known that both dihydroxy bile acids and fatty acids increase the permeability of the intestinal mucosa to oxalate in the setting of enteric hyperoxaluria[81] so that paracellular oxalate absorption may become the dominant route in this pathology.[114,118]

Stomach. Given the acidic environment and tight epithelium of the stomach, it is presumed that gastric oxalate uptake occurs mainly via (transcellular) nonionic diffusion, whereas oxalate efflux across the basolateral membrane may occur by an as yet unidentified mediated transcellular mechanism.[114] As SLC26A7 is expressed in the basolateral membrane of gastric parietal cells,[128] this transporter may be responsible for this basolateral oxalate efflux (see Figure 3). However, it should be noted that studies on gastric oxalate transport are very limited. To our knowledge, only two studies describe the contribution of the stomach to gastrointestinal oxalate absorption. Hautmann *et al.*[145] administered a 5 mmol oxalate load via a nasogastric tube to six patients while blocking gastric emptying by an intrapyloric balloon. With increasing gastric loading time, a linear increase in urinary oxalate excretion was observed. Therefore, it was concluded that the stomach seems to be an important site for oxalate absorption and that a prolonged gastric transit

time of an oxalate load may lead to hyperabsorption and subsequent periods of hyperoxaluria. In line with this research, Chen *et al.*[146] investigated urinary oxalate excretion after an oral spinach load (~30 mmol oxalate) in 8 patients who underwent a total gastrectomy and compared it with that of 10 healthy adults. Urinary oxalate excretion in the healthy individuals showed a biphasic pattern with peaks occurring at 40 min and 2 h after oxalate loading. Interestingly, the first peak was absent in the patients with total gastrectomy, indicating a significant contribution of the stomach to oxalate absorption.

Intestinal tract. As in the organs mentioned above, transcellular intestinal oxalate transport is mediated by members of the SLC26 anion exchanging family (see Figure 3). SLC26A1 is expressed on the basolateral membrane of human small intestine and colon. SLC26A2 is relatively abundant on the apical membrane of human colonocytes and less in small intestine. In mice and rats, SLC26A3 is expressed on the apical membrane of colon and less in small intestine, which is the opposite of SLC26A6 being abundant on the apical membrane of small intestine but less in colon.[118]

For a long time it has been thought that oxalate transport across the intestinal tract could only function in absorptive mode and that the kidney was the sole route for oxalate excretion. However, it has been shown in rabbits,[147,148] rats,[149] and mice[96,97] that oxalate handling across the intestine is segment specific with net oxalate secretion in the small intestine and proximal colon and net oxalate absorption in the distal colon. In humans, intestinal oxalate secretion seems to be less pronounced as fecal excretion of an intravenously administered ^{14}C-oxalate dose was negligible in dialysis patients.[150] However, it was shown in PH patients that net intestinal oxalate secretion can be induced by *O. formigenes*, possibly by contributing to a transepithelial gradient favoring intestinal secretion of endogenous oxalate.[91]

Segment and species differences in oxalate handling across the intestine have been related to spatial distribution (abundant in small intestine but less in colon) and transport characteristics of SLC26A6. Recently, it was observed that slc26a6$^{-/-}$ mice present a reduced ileal[96] and duodenal[97] serosa-to-mucosa oxalate flux compared with wild-type mice, leading to the conversion of net oxalate secretion to net absorption and subsequent increased plasma oxalate levels and hyperoxaluria. This corroborates the fact that SLC26A6 is a major oxalate-secreting transporter and that intestinal secretion may have an important role in the prevention of hyperoxaluria and related CaOx stone disease. Interestingly, it was shown that human and mouse SLC26A6 show different anion transport properties. In contrast to mice, human SLC26A6 has lower affinity for extracellular Cl^-, and Cl^-/oxalate exchange appears to be electroneutral, suggesting that human intestinal oxalate secretion is less efficient relative to that of mice.[98,151] These variations might explain why humans are more susceptible to nephrocalcinosis/nephrolithiasis when compared with mice.

Furthermore, the recent finding that slc26a1$^{-/-}$ (Sat1$^{-/-}$) mice also exhibit hyperoxaluria with hyperoxalemia, nephrocalcinosis, and CaOx stones added new insights in transepithelial oxalate transport.[144] These animals show reduced oxalate transport in basolateral membrane vesicles of distal intestinal segments (distal ileum, cecum, and proximal colon), suggesting that the hyperoxalemia and hyperoxaluria are the result of reduced intestinal oxalate secretion, as is observed in slc26a6$^{-/-}$ mice.[96,97,152] As SLC26A1 is expressed on the basolateral membrane, these data suggest that SLC26A1 mediates basolateral oxalate uptake, which together with apical oxalate efflux via SLC26A6 facilitates intestinal oxalate secretion.

SLC26A3 is currently thought to be responsible for apical oxalate uptake in the intestine as it was preliminarily observed that both slc26a3$^{+/-}$ and slc26a3$^{-/-}$ mice present a significantly reduced mucosa-to-serosa oxalate flux in distal ileum and distal colon and significantly lower urinary oxalate excretions when compared with wild-type mice.[118]

The role of SLC26A2 in intestinal oxalate transport is not yet clear; however, this transporter may be responsible for the residual intestinal oxalate secretion observed in slc26a6$^{-/-}$ mice.[117,122]

Interestingly, it is known for rodents that intestinal oxalate secretion can be enhanced when renal function is compromised or in other conditions characterized by elevated plasma oxalate levels.[149,153] Whereas the distal colon in rats with normal renal function shows net oxalate absorption, this is reversed to angiotensin II-mediated net oxalate secretion in chronic renal failure rats. An elevated plasma oxalate level alone (in the absence of chronic renal failure) may lead to angiotensin II-independent intestinal oxalate secretion, possibly mediated by cAMP-dependent pathways.[148,154,155] The exact mechanism by which net intestinal oxalate secretion in humans is induced remains unknown.

TREATMENT OF HYPEROXALURIA

Lowering urinary CaOx supersaturation, enhancing AGT activity, and dietary restrictions

Treatment should be initiated as soon as the underlying pathology of hyperoxaluria is known, with a large daily fluid intake (>3 l per 1.73 m^2) being essential in all types of hyperoxaluria. The placement of a gastrostomy tube should be considered to ensure adequate fluid administration in small children with PH.[17] In case of fever, vomiting, diarrhea, or other significant fluid losses, patients should receive intravenous fluids.

Alkali citrate treatment aims to reduce urinary CaOx supersaturation.[156] Citrate is metabolized to bicarbonate in the liver and this alkali load reduces intratubular citrate reabsorption and therefore increases urinary citrate excretion. Citrate forms a complex with calcium, thereby reducing precipitation of calcium with other substances such as oxalate.[157] The therapeutic effect of orthophosphate is comparable to that of alkali citrate, and long-term follow-up reports of orthophosphate treatment suggest efficacy for PH patients.[158]

A second treatment strategy is to enhance the reduced activity of AGT in PH I patients. Pyridoxal phosphate is an essential cofactor of AGT, and pharmacological doses of pyridoxine reduce hyperoxaluria in ~30% of PH I patients.[56] Pyridoxine responsiveness can be predicted with mutation analysis.[159,160] The ultimate strategy to restore hepatic AGT activity is of course liver transplantation. Combined liver/kidney transplantation is performed in patients with an already compromised renal function.

Dietary oxalate restriction is of limited benefit in PH as only a very small proportion of urinary oxalate is derived from the diet in these patients.[71] Patients with secondary hyperoxaluria should be recommended to avoid food with very high oxalate content (for example, spinach, rhubarb), in order to avoid disturbances of the intestinal interplay of ions resulting in increased intestinal calcium absorption. In addition, a diet high in calcium or oral administration of calcium supplements to bind oxalate in the intestine theoretically might be an efficient strategy to lower oxalate absorption; however, this should be administered with caution because of the potential risk associated with absorption of excess free calcium.[161]

Strategies to alter intestinal oxalate handling

As the role of the intestine in oxalate metabolism is becoming better understood (see paragraph intestinal oxalate transport), modern treatment strategies focus on manipulating intestinal oxalate handling.

A first strategy is the use of oxalate-degrading bacteria, such as *O. formigenes*, that harbor the colon and reduce luminal oxalate concentrations and thus absorption. Moreover, it was shown in rats that *O. formigenes* is able to promote intestinal oxalate secretion.[95] Promising results of a pilot study showing a reduction of plasma oxalate levels and urinary oxalate excretion in the majority of PH patients treated orally with *O. formigenes*[91] could not be unequivocally confirmed in a recent multicenter trial in 42 PH patients;[162] *ad hoc* analyses of a subset of the most compliant ones, however, suggested an effect on oxalate/creatinine ratio.

It was shown that a mixture of freeze-dried lactic acid bacteria is also able to degrade oxalate, as it reduced urinary oxalate excretion in patients with idiopathic CaOx stone disease and mild hyperoxaluria,[163] as well as in patients with enteric hyperoxaluria.[164] However, a recent study showed no effect on urinary oxalate excretion and CaOx supersaturation in patients with mild hyperoxaluria on controlled diets. Hence, it is speculated that the diet has a more important role than administration of a probiotic in reducing urinary oxalate excretion.[165]

Although treatment with oxalate-degrading enzymes instead of using intact bacteria could also be beneficial, as was shown in laboratory animals,[166,167] a phase-1 trial of such a preparation (ALTU-237) in healthy volunteers on a high-oxalate diet did not result in significant reduced urinary oxalate excretions (http://www.medicalnewstoday.com/articles/109956.php; 22 March 2011).

It is hypothesized that patients with secondary hyperoxaluria may also benefit from orally administered oxalate-binding compounds, analogous to the phosphate binders used to correct for hyperphosphatemia in patients with chronic renal failure. One study reported a significant decrease in urinary oxalate excretion in patients with chronic kidney disease,[168] which was greater after calcium carbonate ($41.2 \pm 17.4\%$) than after sevelamer hydrochloride treatment ($30.4 \pm 23.8\%$), whereas another study using the latter compound only showed a nonsignificant reduction of urinary oxalate excretion (17%) in patients with enteric hyperoxaluria without reduction in urinary CaOx supersaturation.[169] In this context, lanthanum carbonate showed promising results in a rat model of hyperoxaluria (S Robijn, BA Vervaet, PC D'Haese, A Verhulst, unpublished results).

Finally, a future treatment target for patients with secondary hyperoxaluria may be the inhibition of oxalate absorption by using specific inhibitors of the major oxalate-absorbing transporters (SLC26A3?), as is currently being investigated for sodium-dependent phosphate cotransport inhibitors in the treatment of hyperphosphatemia.[170]

CONCLUSION

Insights in the manner in which oxalate is handled throughout the body have gained a significant boost over the last decade, especially after the discovery of the SLC26 oxalate exchangers. It is important, however, to be aware of species differences upon interpretation of transport properties. Therefore, further studies are required to get better insights in transport properties and (pathological) physiological contribution of these transporters in humans. Furthermore, an intriguing question remains as to whether oxalate handling is merely the consequence of concentration gradients across an epithelium or the result of oxalate-mediated regulation of anion exchangers. The observation that intestinal oxalate secretion may be induced or enhanced to divert endogenous oxalate to the feces instead of to the urine may have important consequences for future hyperoxaluria treatment strategies.

DISCLOSURE

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