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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).

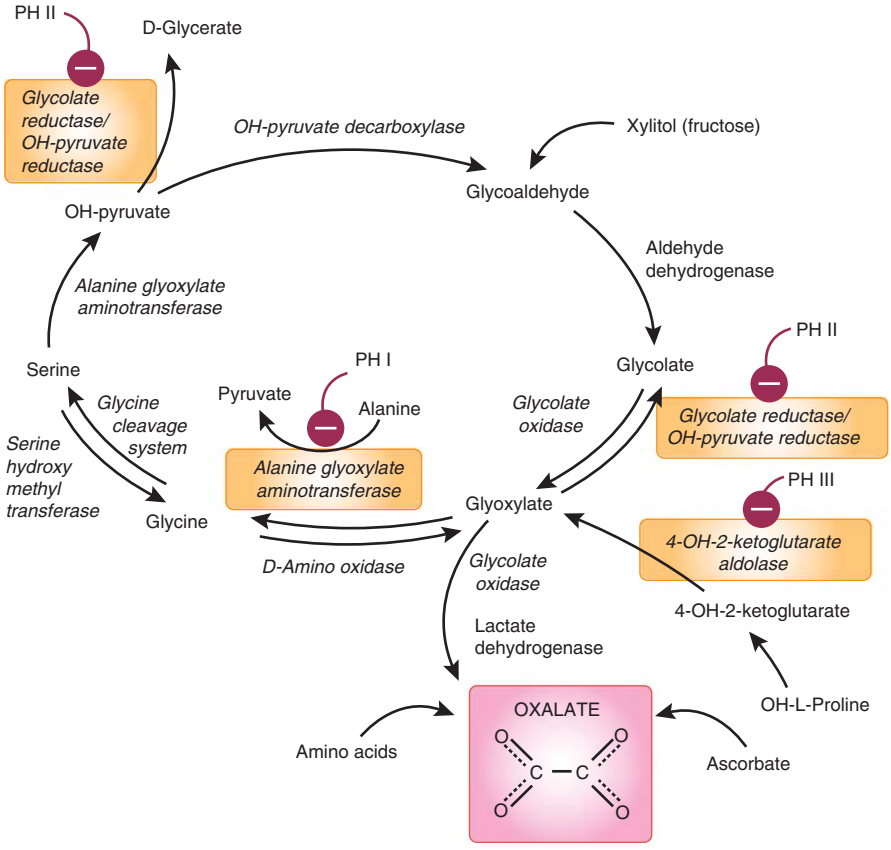

Figure 1 | Overview of endogenous oxalate synthesis pathways. PH I–III, primary hyperoxaluria types I–III.