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Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review

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Abstract

Hyperoxaluria results from either inherited disorders of glyoxylate metabolism leading to hepatic oxalate overproduction (primary hyperoxaluria), or increased intestinal oxalate absorption (secondary hyperoxaluria). Hyperoxaluria may lead to urinary supersaturation of calcium oxalate and crystal formation, causing urolithiasis and deposition of calcium oxalate crystals in the kidney parenchyma, a condition termed oxalate nephropathy. Considerable progress has been made in the understanding of pathophysiological mechanisms leading to hyperoxaluria and oxalate nephropathy, whose diagnosis is frequently delayed and prognosis too often poor. Fortunately, novel promising targeted therapeutic approaches are on the horizon in patients with primary hyperoxaluria. Patients with secondary hyperoxaluria frequently have long-standing hyperoxaluria-enabling conditions, a fact suggesting the role of triggers of acute kidney injury such as dehydration. Current standard of care in these patients includes management of the underlying cause, high fluid intake and use of calcium supplements. Overall, prompt recognition of hyperoxaluria and associated oxalate nephropathy is crucial, because optimal management may improve outcomes.

Index words: chronic kidney disease, kidney failure, urolithiasis, nephrolithiasis, oxalate, oxalosis, crystallopathies, fat malabsorption, steatorrhea, primary hyperoxaluria, lumasiran

Introduction

Hyperoxaluria results from either inherited disorders of glyoxylate metabolism leading to hepatic oxalate overproduction (primary hyperoxaluria), or increased intestinal oxalate absorption (secondary hyperoxaluria). Hyperoxaluria may lead to urinary supersaturation of calcium oxalate and crystal formation, contributing to urolithiasis and deposition of calcium oxalate crystals in the kidney parenchyma, leading to a condition termed oxalate nephropathy. We discuss the progress made in the understanding of intestinal and renal handling of oxalate and crystal-induced kidney damage and review the diagnosis and management of primary and secondary hyperoxaluria.

Oxalate metabolism and measurement

Oxalate, the ionized form of oxalic acid, originates from both hepatic production as part of normal metabolism, and absorption by the bowel from food (Figure 1). Hepatic synthesis of oxalate from glyoxylate contributes to 60-80% of plasma oxalate (1-2) (Figure 2). Dietary sources rich in oxalate include leafy vegetables, nuts, tea and fruits rich in vitamin C (3-4). Average daily oxalate intake is approximately 80-130 mg/day (5-6). Only 5 to 15% of dietary oxalate is normally absorbed because (i) oxalate bound to calcium in the gut is eliminated in the stools and (ii) oxalate is degraded by intestinal bacteria, such as *Oxalobacter formigenes* (1,7) (Figure 1).

Oxalate is absorbed in the gut via paracellular passive transport, but compelling evidence has also demonstrated active intestinal absorption and secretion via transcellular oxalate anion exchangers of the solute-linked carrier 26 (SCL26) family. The relative contribution of oxalate absorption involving paracellular and transcellular pathways and secretion determines the overall net oxalate movement across the intestine (8). SLC26A1 and SCL26A6 exchangers are expressed in the basolateral and apical membrane of enterocytes, respectively, allowing oxalate secretion into the intestinal lumen. SLC26A3 is an apical oxalate transporter mediating oxalate uptake (1,7). Studies suggest a remarkable adaptive capacity of the intestine to either actively absorb or secrete oxalate in response to local and systemic inputs integrated through the endocrine and autonomic nervous systems (8). Cholinergic regulation inhibits oxalate uptake through reduced expression of *SCL26A6* in human cell lines (8-10). A purinergic signaling system also regulates

oxalate transport across digestive epithelia (11-12). Lastly, in murine chronic kidney disease (CKD) models, Slc26a6-mediated enteric oxalate secretion is critical in decreasing the body burden of oxalate (13).

Plasma oxalate does not have any known function in the human body and is rapidly excreted by the kidney, via glomerular filtration and tubular secretion. Both mechanisms are critical in regulating plasma oxalate levels (14-15). SCL26A6 is also located at the apical membrane of the proximal tubule and actively transports oxalate into the urinary filtrate. SLC26A1 is localized to the basolateral membrane of the tubular cell and is thought to reduce urinary oxalate secretion (1,7).

Urinary oxalate excretion in healthy adults is influenced by dietary intake and levels exceeding 40-45 mg/24h (500 µmol/L) define hyperoxaluria (16). Oxaluria may also be quantified using the oxalate/creatinine ratio on a spot urine sample (17). Studies have shown a good correlation between spot level and 24h excretion, with no significant diurnal pattern of oxalate excretion (18-19). In individuals with stage 4 and 5 CKD, urinary oxalate excretion decreases and plasma oxalate starts to rise (20). Plasma oxalate levels are used to monitor primary hyperoxaluria patients with CKD and on dialysis, prior to transplantation (21-22). Plasma oxalate levels should be <30µmol/l at the end of each dialysis session as this is the cut-off value for oversaturation of plasma calcium oxalate (5). Accurate measurement of plasma oxalate concentration is however challenging. Prompt acidification or freezing of samples and storage at -80°C until acidification is required to prevent conversion of plasma ascorbate to oxalate (20). Moreover, plasma oxalate levels do not correlate well with eGFR and show significant intra-individual variation in patients with primary hyperoxaluria (21).

Primary Hyperoxaluria

Primary hyperoxaluria types 1, 2 and 3 are rare autosomal recessive inherited disorders of glyoxylate metabolism, caused by pathogenic variants in *AGXT, GRHPR* or *HOGA1*, respectively (Figure 2) (2,23). The inability to metabolize glyoxylate leads to excessive hepatic production of oxalate and subsequent accumulation in various organs, including the kidney (2,23). Massive urolithiasis and/or calcium oxalate deposition in the renal parenchyma impair kidney function and

oxalate elimination. When estimated glomerular filtration rate (eGFR) drops to ≤ 30-45 ml/min per 1.73m^2, plasma oxalate increases, and oxalate may deposit in bone, kidneys, skin, retina, the cardiovascular and the central nervous systems. This dramatic condition is referred to as systemic oxalosis (2, 22-23). Primary hyperoxaluria type 1 is the most common and severe form, generally leading to kidney failure during the first three decades of life. However, some patients are not diagnosed until adulthood and may only present occasional or recurrent urolithiasis. The Gly170Arg and Phe152Ile variants in *AGXT* are associated with adult-onset hyperoxaluria and with less severe prognosis, partly due to the response to pyridoxine (23). Primary hyperoxaluria types 2 and 3 are generally milder, although patients with type 2 may present CKD caused by recurrent urolithiasis (2,23).

Prompt diagnosis of primary hyperoxaluria is essential to prevent downstream complications. Unfortunately, up to 50% of patients have advanced CKD or kidney failure at diagnosis, and approximately 10% are diagnosed after disease recurrence on a kidney allograft (2). As a result, the possibility of primary hyperoxaluria should be systematically considered among children with kidney stones or nephrocalcinosis and in adults with recurrent calcium oxalate stones. Patients with primary hyperoxaluria usually have higher urinary oxalate concentration (> 100 mg/day, >1.0 mmol/1.73m^2 or 1000 µmol/L) than those with secondary hyperoxaluria (50-100 mg/d, 0.5-1.0 mmol/1.73m^2 or 500-1000 µmol/L) (2). In children, age-specific normal values for spot urinary oxalate-to-creatinine ratios are used (2, 17). Measures of plasma oxalate level may be helpful in patients with CKD stage 3b because they generally increase only when eGFR is below 30 ml/min per 1.73m^2 in patients with CKD from other etiologies. The definitive diagnosis of primary hyperoxaluria is achieved by molecular genetic testing (2,23).

Conservative therapeutic options in primary hyperoxaluria include massive fluid intake (tube or gastrostomy feeding in infants), calcium oxalate crystallization inhibitors, as well as vitamin B6 (pyridoxine) in primary hyperoxaluria type 1 (23). To date, liver transplantation is the only established ‘curative’ therapy to correct the metabolic defect contributing to endogenous oxalate formation (2, 22-23). Liver-kidney transplantation (simultaneously or sequentially) is the current standard of care in patients with primary hyperoxaluria type 1 and CKD. It should ideally

be performed prior to the development of systemic oxalosis and related complications (22-24). Indeed, outcome after kidney transplantation is improved by a substantial residual kidney function and by the absence of major systemic oxalate load (23). Oliguria should be avoided in the peri-transplant period; in this respect, minimizing the risk of acute tubular necrosis of the graft may impact the choice of donor. In patients with kidney failure awaiting transplantation, intensive hemodialysis strategies limit systemic oxalate accumulation (22-23).

New promising therapeutic agents are under investigation and are expected to dramatically influence management and outcome of patients with primary hyperoxaluria. Lumasiran is a RNA interference (RNAi)-based therapy, which blocks the synthesis of oxalate glycolate oxidase and reduces oxidation of glycolate to glyoxylate, the immediate precursor of oxalate (Figure 2). In the phase 3 Illuminate A study, patients with primary hyperoxaluria type 1 receiving Lumasiran showed a significant reduction in urinary oxalate excretion after 6 months of treatment in comparison with the placebo group (25). Two additional phase 3 trials testing the efficacy and safety of lumasiran are ongoing (Illuminate B, NCT03905694 and Illuminate C, NCT04152200) (22). The US Federal Drug Administration and European Medicine Agency have recently approved Lumasiran for the treatment of children and adults with primary hyperoxaluria type 1. Nedosiran, a RNAi therapy targeting lactate deshydrogenase and reducing conversion of glyoxylate to oxalate, is being tested in a phase 3 study (NCT04042402). If these emerging therapies are confirmed to be efficient and safe in patients on dialysis and kidney graft recipients, liver transplantation may perhaps no longer be required in the future. (22)

Secondary hyperoxaluria

Causes of secondary hyperoxaluria

Secondary hyperoxaluria results from (i) increased dietary oxalate or oxalate precursor intake, (ii) fat malabsorption, and (iii) decreased intestinal oxalate degradation due to alterations in gut microbiota (Figure 1, Box 1)). Hyperoxaluria has been associated with increased intake of nuts, tea, *Averrhoa carambola* (star fruit) and bilimbi, rhubarb, chaga mushroom, spinach, ‘green smoothies’ and ‘juicing’ (4). Ascorbic acid (vitamin C), ethylene glycol, naftidrofuryl oxalate (a

vasodilator) and methoxyflurane (an anesthetic agent) all are precursors of oxalate, and excessive intake or exposure may lead to hyperoxaluria (Figure 3). Fat malabsorption from various causes (pancreatic disorders, Roux-en-Y bypass surgery, short bowel disease, Crohn's disease, use of Orlistat) leads to steatorrhea, calcium binding by fatty acids in the intestinal lumen, increased intestinal absorption of free oxalate, and higher ileal and colonic permeability to oxalate. Secondary hyperoxaluria may also be multifactorial. For example, cystic fibrosis leads to hyperoxaluria *via* malabsorption due to exocrine pancreatic insufficiency, defects in oxalate exchangers and microbiota perturbations associated with frequent antibiotic use (26-27).

Obesity and the metabolic syndrome are also associated with calcium oxalate nephrolithiasis (28-29). Obese mice show local and systemic inflammation, which contributes to reduced active transcellular oxalate secretion into the bowel via anion exchanger SLC26A6 and enhanced gastrointestinal paracellular absorption of oxalate (29-31). Obesity-associated cholinergic activity also leads to slc26a6 inhibition (10). Increased dietary ingestion of oxalate and alterations in intestinal microbiota may furthermore contribute to obesity-associated hyperoxaluria (29, 31). Lastly, urinary excretion of oxalate is higher in individuals with diabetes mellitus (3). Plasma levels of glyoxylate, and glyoxal (a protein glycation product), potential precursors of oxalate, are higher in diabetic patients, possibly contributing to hyperoxaluria (3).

Secondary hyperoxaluria may lead to urinary supersaturation of calcium oxalate and crystal formation (16), contributing to urolithiasis and deposition of calcium oxalate crystals in the kidney parenchyma, a condition termed oxalate nephropathy (5) (Figure 1). In contrast to primary forms of the disease, characterized by a high systemic oxalate load, secondary hyperoxaluria only leads to extra-renal deposition of oxalate in very rare cases, such as in severe Crohn's disease (14).

Secondary hyperoxaluria and urolithiasis

Hyperoxaluria is the main risk factor for calcium oxalate urolithiasis (5). Supersaturation of calcium oxalate is ten times more dependent on a rise in urinary oxalate than on an equimolar rise of urinary calcium concentration (5). Urinary oxalate excretion correlates with the risk of developing a kidney stone event (32). In patients with malabsorption, fluid loss, low urinary pH

and citrate level also contribute to the pathogenesis of urolithiasis (27, 32). A meta-analysis of 12 observational studies showed a significantly higher risk of stone formation after Roux-en-Y gastric bypass surgery with a pooled relative risk of 1.79 (95%CI: 1.54-2.10) (33). Similarly, a recently published review reported a stone incidence ranging from 2 to 38% in patients with malabsorptive states other than after bariatric surgery (27).

The risk of calcium oxalate urolithiasis is also associated with intestinal microbiota composition. Healthy oxalate homeostasis in the gastrointestinal tract involves a collaborative effort between numerous bacterial species. Metagenomics studies reveal a network of bacterial taxa co-occuring with *Oxalobacter Formigenes* in fecal samples from healthy individuals, which are less represented in urinary stone formers (34). This would explain why the absence of *Oxalobacter Formigenes* is not causative of stone disease and why colonization with the bacteria failed to reduce urinary oxalate excretion in interventional studies (35). Similarly, children who are calcium oxalate stone formers have less oxalate degrading and butyrate forming bacterial taxa in the gut, leading to hyperoxaluria. Butyrate maintains the gut mucosal barrier and regulates intestinal SLC26 oxalate transporters (36).

Finally, *Slc26a1* gene deletion in mice causes a reduction in intestinal secretion of oxalate, leading to hyperoxalemia and hyperoxaluria (37). Human *SLC26A1* mutations may presumably lead to urolithiasis via similar mechanisms (1). Additionally, polymorphisms of *SLC26A6* in humans may explain accelerated lithogenesis in distinct populations (16, 38).

Secondary hyperoxaluria and oxalate nephropathy

Oxalate nephropathy is a severe condition, resulting from deposition of calcium oxalate crystals in the kidney tissue, leading to tubular-interstitial injury and fibrosis, acute kidney injury (AKI) and/or chronic kidney disease (CKD) (26, 39-41) (Figure 4). Most authors have used the following diagnostic criteria for oxalate nephropathy: (i) progressive kidney disease, (ii) oxalate crystal deposition with tubular injury and interstitial nephritis, and (iii) exclusion of other etiologies of kidney disease (apart from vascular and/or diabetes-associated nephropathy). A hyperoxaluria enabling-condition should ideally also be identified (26, 39-41) (Box 2).

The prevalence of oxalate nephropathy is unknown. We recently reported 22 cases (1%) of oxalate nephropathy out of 2265 consecutive native kidney biopsies performed during a 9-year period (40). Table 1 shows the clinical characteristics and outcomes of patients with oxalate nephropathy reported in four case series and 1 systematic review (26, 39-42). Upon presentation, most patients had hypertension, diabetes and/or a history of CKD. The latter may result from past subclinical deposition of oxalate crystals or represent a predisposing factor because of reduced excretion of oxalate (40).

Approximately two-thirds of the patients have malabsorption-associated hyperoxaluria (20, 32). We found that chronic pancreatitis and gastric bypass were the most common causes of oxalate nephropathy (48%) (32). Of note, Lumlertgul et al excluded patients with a short duration of exposure (<30d) to the hyperoxaluria-enabling conditions (i.e. vitamin C and oxalate rich foods) (20). Interestingly, hyperoxaluria-enabling conditions (i.e. malabsorptive states) may be long-standing; we reported the development of oxalate nephropathy a mean of 8 years after gastric bypass (N=5) and 1 and 8 years after orlistat initiation in 2 patients (40). This suggests that the combination of the hyperoxaluria-enabling condition with an additional factor or trigger may lead to crystal formation and kidney damage (40,43-44) (Figure 1). Factors such as acute dehydration, diuretic use, inflammation, antibiotic use or high dietary oxalate intake may increase the urinary oxalate concentration. Renin-angiotensin-aldosterone system (RAAS) blocker use is also highly prevalent in patients presenting with oxalate nephropathy and may favour oxalate crystal-associated kidney injury via the reduction of glomerular filtration fraction (39-41).

Clinical presentation of oxalate nephropathy varies from AKI, AKI on CKD to CKD. Patients present with kidney failure in most cases (mean serum creatinine 4.9 to 8.0 mg/dl). Moderate to profound hypocalcemia was reported in 9/12 patients with oxalate nephropathy associated with chronic pancreatitis and may evoke the diagnosis (41). Kidney biopsy shows variable degrees of acute tubular necrosis, interstitial nephritis and chronic damage. In addition, a substantial proportion of patients have glomerular changes (mostly glomerulosclerosis, associated or not with diabetes). The prognosis of oxalate nephropathy is variable, with approximately half of patients rapidly reaching kidney failure. The outcome may be more favorable in patients

presenting with oxalate nephropathy secondary to acute ingestion of high amounts of dietary oxalate (4).

Calcium oxalate crystals are most commonly found in proximal and distal tubules in the cortex. They are deposited within tubular lumens, tubular epithelial cells, and less frequently in the interstitium (45). Calcium oxalate crystals are strongly birefringent on polarized light, unlike calcium phosphate crystals (46) (Figure 4). Of note, scarce calcium oxalate crystals may be found in tubules in patients with other causes of kidney damage, especially in the setting of reduced eGFR (31, 39, 41-42). We thus recently suggested adding an oxalate crystal-to-glomerulus ratio of ≥0.25 in the definition of oxalate nephropathy. Indeed, we found this ratio to separate patients with oxalate nephropathy from those with other well-documented kidney diseases and scarce calcium oxalate crystals (40). Further studies are needed to validate this criterion distinguishing oxalate nephropathy from non-specific oxalate deposition. Lastly, the term 'nephrocalcinosis' is often used to refer to calcium salt deposits in kidney tissue; although it should probably be used for calcium phosphate and not for calcium oxalate deposition (47).

Studies have shown that different crystals such as calcium oxalate, uric acid and monoclonal light chains share cellular and molecular mechanisms leading to kidney damage, such as stimulation of the NLRP3 inflammasome, a multiprotein oligomer that triggers IL-1β-induced inflammation (48-51). In mice, *Nlrp3* deletion successfully protects from progressive renal failure secondary to ingestion of a diet high in soluble oxalate (51). NLPR3 inhibition in hyperoxaluric mice protects against nephrocalcinosis and CKD, via a shift in the phenotype of renal macrophages, promoting anti-inflammatory rather than proinflammatory and profibrotic responses. IL-1 inhibitor anakinra did not show such a protective effect, suggesting that NLPR3 contributes to nephrocalcinosis induced kidney fibrosis independently from IL-1 mediated tissue injury (52).

The dynamics of crystal deposition conditions the clinical presentation: (i) acute supersaturation, rapid crystal formation, direct and indirect kidney epithelial cytotoxicity and inflammation-driven cell necrosis lead to acute renal damage; whilst (ii) persistent mild supersaturation generating sub-acute crystal plug formation in distal tubules or collecting ducts

leads to chronic kidney disease (48). Crystal deposition is a potent driver of kidney fibrosis, leading to loss of kidney function (48-49).

Hyperoxaluria and progression of CKD

Given the potential nephrotoxicity of oxalate at high levels, Waikar et al hypothesized that a higher urinary oxalate, even within the normal range, would be associated with a higher risk of CKD progression. They tested this hypothesis in the Chronic Renal Insufficiency Cohort (CRIC) study, a prospective multicenter cohort study of risk factors for cardiovascular disease, progression of CKD and mortality in patients with mild to moderate CKD. Amongst 3123 participants, they showed that higher vs lower 24-h urinary oxalate excretion (at the 40th percentile) was independently associated with a 32% higher risk of CKD progression and 37% higher risk of kidney failure (53).

The association between hyperoxaluria and faster decline in estimated GFR was also shown in a small cohort of patients with chronic pancreatitis (54). Similarly, previous studies have suggested that calcium oxalate deposition in kidney graft biopsies may be associated with a negative impact on graft function beyond the early post-transplant period (55-56). Urinary oxalate excretion may thus be a potential risk factor for progression in common forms of CKD. Likewise, it was suggested that urinary oxalate may be a potential mediator of CKD development and progression in individuals with diabetes or obesity (3). Altogether, if these results are confirmed, the question of whether lowering urinary oxalate excretion could be beneficial in slowing CKD progression would need to be addressed.

Management of secondary hyperoxaluria and oxalate nephropathy

Treatment should be initiated rapidly, starting with high fluid intake (16,27,57) (Table 2). The goal is to obtain a daily urine output superior to 2-3 litres, in order to reduce urinary supersaturation in oxalate. Dietary measures to reduce intestinal oxalate absorption include a low-oxalate, low-fat and normal-calcium diet (27). Additionally, calcium supplements are given orally to reduce bioavailability of intestinal oxalate and its absorption (27, 58). Crystallization inhibitors such as citrate may also be used (59). Importantly, all studies performed with the above

interventions were performed on small numbers of subjects for a limited time period, often without control groups or randomization (60).

Therapeutic options currently tested include oral administration of intestinal degrading bacteria and/or enzymes. *Oxalobacter formigenes* administration has been shown to reduce urinary oxalate excretion in animal models with enteric hyperoxaluria (61). In humans, this strategy has only been tested in patients with primary hyperoxaluria (35). Oxalate decarboxylase, an oxalate-degrading enzyme, was shown to reduce urinary oxalate excretion amongst 16 subjects with both secondary hyperoxaluria and a kidney stone history, in a pilot phase III open-label study (62). Results will need to be confirmed in the phase III follow-up randomized controlled trial. A better understanding of the molecular mechanisms of crystal nephropathies may also lead to the development of targeted therapies (48). As previously mentioned, a NLRP3-specific inflammasome inhibitor attenuates crystal-induced kidney fibrosis in mice (63).

Diagnostic work-up is fundamental in order to treat the underlying cause of hyperoxaluria. Hyperoxaluria enabling conditions may be long-standing but pauci-symptomatic. We have shown for example that chronic pancreatitis may frequently be diagnosed only after oxalate nephropathy, even in kidney transplant recipients (40-41, 64). Morpho-constitutional analysis of kidney stones combining stereomicroscopy and Fourier-transform infrared spectroscopy may help in determining the cause of hyperoxaluria (65). Dietary hyperoxaluria may be difficult to identify because oxalate content is not provided by food manufacturers and food tables often report conflicting data on oxalate content (60). In patients with hyperoxaluria and/or oxalate nephropathy of unknown etiology, primary hyperoxaluria must not be overlooked (see section above) (66).

Treatment of the underlying cause of secondary hyperoxaluria includes withdrawal of oxalate rich foods or precursors, pancreatic enzyme therapy, intensification of Crohn's disease therapy and in some cases reversal of gastric bypass. Identification and management of the cause of secondary hyperoxaluria is also important to minimize risk of recurrence of oxalate nephropathy after kidney transplantation. Therapeutic considerations concerning patients with secondary hyperoxaluria on dialysis and during the per-transplantation period is beyond the scope

of this review. Lastly, further studies are needed to determine the clinical significance of hyperoxaluria in asymptomatic patients with hyperoxaluria-enabling conditions in order to identify those most likely to benefit from treatment in order to prevent renal complications.

Conclusions

Considerable progress has been made in the understanding of pathophysiological mechanisms leading to hyperoxaluria and associated kidney damage. Prompt recognition and management of primary and secondary hyperoxaluria is crucial. Fortunately, novel targeted therapeutic approaches are on the horizon in patients with primary hyperoxaluria.

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Box 1- Causes of secondary hyperoxaluria and oxalate nephropathy

Increased intestinal oxalate absorption
Chronic pancreatitis
Pancreatectomy
Use of Orlistat (lipase inhibitor)
Roux-en-Y gastric bypass
Small bowel resection
Crohn's disease
Celiac disease
Cystic fibrosis
Use of somatostatin analogue
Increased dietary oxalate or precursor intake
Rhubarb, Averrhoa carambola (star fruit), Averrhoa bilimbi, tea, nuts, 'juicing'
Vitamin C, ethylene glycol, methoxyflurane, naftidrofuryl oxalate
Decreased intestinal bacterial oxalate degradation
Antibiotic use
Others
Obesity, genetic variations in oxalate transporters? *

* data mostly obtained from murine models

Box 2 – Definition of oxalate nephropathy

1. Progressive kidney disease
2. Deposition of calcium oxalate crystals (birefringent on polarized light) within tubular epithelial cells, tubular lumens and less frequently in the interstitium, associated with tubular injury and interstitial nephritis
3. Exclusion of other causes of kidney disease (apart from non-specific microvascular lesions and/or diabetic associated glomerular lesions)
4. Ideally, a hyperoxaluria enabling-condition should be identified

Table 1 – Published cases series of secondary oxalate nephropathy

First Author	Nasr, 2008[a,39]	Cartery, 2011[a,41]	Lumlertgul, 2018[26]	Buysschaert, 2020[40]	Yang, 2020[42]
Included cases	OxN associated with gastric bypass	OxN associated with chronic pancreatitis	Review of case series OxN 1950-2018[b]	All-cause OxN	All-cause OxN
N	11	12	51 [c]	21[d]	25 [e]
Patient characteristics					
Age, yr	61	67	56	61	64
Male gender, no.	5 (45)	9 (75)	30 (59)	14 (67)	13 (52)
Diabetes, no.	9 (82)	9 (75)	NA	12 (57)	16 (64)
Hypertension, no.	11 (100)	8 (67)	NA	16 (76)	19 (76)
Prior CKD, no.	7 (64)	7 (58)	NA	13 (62)	NA
Last eGFR, ml/min/1,73m^2		57	NA	36	NA
RAS inhibitor use, no.	3 (30)	8 (67)	NA	8 (38)	NA
Diuretic use, no.	3 (30)	5 (42)	NA	9 (43)	NA
Kidney allograft, no.	0 (0)	1 (8)	3 (6)	0 (0)	3 (12)
Cause of oxalate nephropathy					
Malabsorptive state, no.	11 (100)	12 (100)	45 (88)[f]	15 (71)	10 (40)
Increased intake of oxalate or precursor, no.	-	-	10 (20)[f]	3 (14)	4 (16)
Duration of hyperoxaluria-predisposing condition, yr	2.8	10	NA	6.2	NA
Unknown cause	-	-	-	3 (14)	11 (44) [g]
Biological data at presentation					
Serum creatinine, mg/dl	6.5	6.6	4.9	8.0	6.3
Urinary oxalate, mg/24h[h]	NA	80	85	NA	NA
Urinary oxalate-to-creatinine ratio, mg/g[i]	NA	NA	NA	86	NA
Urinary protein, g/24h	1.4	0.3	NA	NA	NA
Urinary protein-to-creatinine ratio (g/g)	NA	NA	NA	1.4	0.05
Kidney biopsy data					
Number of glomeruli, no.	14	NA	NA	15	NA
Number of oxalate crystals, no.	43	NA	NA	28	NA
Glomerular abnormalities, no.	9 (82)	6 (50)	30 (59)	6 (29)	7 (28)
Outcome					
Follow-up duration, mo	19	18	13	29	3
Kidney failure, no.	8 (73)	3 (25)	30 (59)	11 (52)	6 (24)
Time to kidney failure, mo	0.8	3	NA	0.2	NA

Data are mean or n (%) unless otherwise noted; OxN, oxalate nephropathy; yr, years; mo, months; no., number; NA, not available (or too few numbers); [a] included in the systematic review by Lumlertgul et al; [b] patients with unknown causes of oxalate nephropathy and those with short duration of exposure (<30 days) to hyperoxaluria-enabling conditions were excluded; [c] quantitative data from 57 case reports of oxalate nephropathy not reported in Lumlertgul et al.; [d] 21/22 patients with available clinical data; [e] Patients with other causes of CKD such us lupus nephritis were

included; [f] some patients had 2 identified hyperoxaluria-enabling conditions; [g] no systematic gastrointestinal and/or genetic workup reported; [h] normal value ≤ 45 mg/day; [i] normal value <32mg/g.

Table 2 – Current and potential therapies of secondary hyperoxaluria

Treatment	Rationale	Supporting evidence
High fluid intake (urine output >2-3l/day)	Reduces urine calcium oxalate supersaturation.	Reduces stone formation (67-68).
Low-oxalate diet	Reduces bioavailability of intestinal oxalate.	Reduces urinary oxalate excretion in small sized studies; caveat: low oxalate diet compared to very high oxalate diet (60,69-70).
Low-fat diet	Reduces intestinal oxalate absorption (by increasing bioavailability of intestinal calcium).	Reduces urinary oxalate excretion in small studies (70-71).
Normal-calcium diet	Avoid low-calcium diets which lead to more free intestinal oxalate.	Reduces urinary oxalate excretion in small sized studies (69,72).
Calcium supplements	Reduce bioavailability of intestinal oxalate and its absorption.	Reduces urinary oxalate excretion but may lead to hypercalciuria (72-74). Calcium citrate may be more bioavailable than calcium carbonate (75).
Cholestyramine	Binds intestinal bile acids, reduces diarrhea and binds oxalate in vitro	Studies show contradicting results (70,73,76)
Oxalobacter formigenes administration	Increases intestinal oxalate degradation	Reduces urinary oxalate excretion in rat model (61,77) and plasma oxalate levels in dialysis patients with primary hyperoxaluria (phase II study) (35).
Oxalate decarboxylase	Degrades intestinal oxalate	Reduces urinary oxalate excretion in rat model (78) and in phase III pilot study in humans (62).
NLRP3-specific inflammasome inhibitor	Reduces crystal-induced kidney damage	Reduces calcium-oxalate crystal-induced kidney fibrosis in mouse model (63).

Figure 1 - Causes and consequences of secondary hyperoxaluria

Secondary hyperoxaluria results from increased dietary oxalate or oxalate precursor intake, fat malabsorption, and decreased intestinal oxalate degradation due to alterations in gut microbiota. Hyperoxaluria may lead to urinary supersaturation of calcium oxalate and crystal formation, contributing to nephrolithiasis, oxalate nephropathy and possibly CKD progression. Based on information in Sayer *et al* (1), Ermer *et al* (7), Hoppe *et al* (5) and Aronson *et al* (79).

Figure 2 – Glyoxylate metabolism in the hepatocyte and enzymatic deficiencies in primary hyperoxaluria.

Primary hyperoxaluria types 1 and 2, associated with peroxismal alanine-gmyoxylate aminotransferase (AGT) and cytosolic glyoxylate reducatse-hydroxypyruvate reducatse (GRHPR) deficiency respectively, result in accumulation of glyoxylate, which is converted to oxalate by lactate deshydrogenase (LDH). Primary hyperoxaluria 3 is caused by a defect in 4-hydroxy-2-oxoglutarate aldolase (HOGA) in the mithochondrion; mechanisms leading to increased oxalate levels are not well-defined. Glycolate oxidase (GO) catalyses the conversion of glycolate to glyoxylate and glyoxylate to oxalate. RNA interference (RNAi) based drugs targeting GO and LDH are potential therapies for patients with PH1.

Based on information in Cochat *et al* (23), Hoppe *et al* (2), and Devresse *et al* (18).

Figure 3 – Oxalate precursors and metabolic pathways

Figure 4 – Oxalate nephropathy

Renal biopsy showing intratubular translucent polyhedral or rhomboid crystals (black arrows) (A, hematoxylin and eosin stain, original magnification x20) on light microscopy, which are birefringent under polarized light (B, original magnification 5x). Biopsy also shows acute tubular injury and mild interstitial inflammation.