Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review

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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.

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 (Fig 1). Hepatic synthesis of oxalate from glyoxylate contributes to 60%-80% of plasma oxalate. Dietary sources rich in oxalate include leafy vegetables, nuts, tea, and fruits rich in vitamin C. Average daily oxalate intake is approximately 80-130 mg. Only 5% to 15% of dietary oxalate is normally absorbed because oxalate bound to calcium in the gut is eliminated in the stools and oxalate is degraded by intestinal bacteria, such as Oxalobacter formigenes. Oxalate is absorbed in the gut via paracellular passive transport, but there is also strong evidence of 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. SLC26A1 and SLC26A6 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. 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. Cholinergic regulation inhibits oxalate uptake through reduced expression of SCL26A6 in human cell lines. A purinergic signaling system also regulates oxalate transport across digestive epithelia. In murine chronic kidney disease (CKD) models, Slc26a6-mediated enteric oxalate secretion is critical in lowering the body burden of oxalate.

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. 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.

Urinary oxalate excretion in healthy adults is influenced by dietary intake, and levels exceeding 40-45 mg/d (500 μmol/d) define hyperoxaluria. Oxaluria may also be quantified using the oxalate to creatinine ratio on a spot urine sample. Studies have shown a good correlation between spot level and 24-hour excretion, with no significant diurnal pattern of oxalate excretion. In individuals with stages 4 and 5 CKD, urinary oxalate excretion decreases and plasma oxalate starts to rise. Plasma oxalate levels are used to monitor primary hyperoxaluria patients with CKD and on dialysis before transplantation. Plasma oxalate levels should be <30 μmol/L at the end of each dialysis session because this is the...
threshold value for oversaturation of plasma calcium oxalate.\textsuperscript{5}

However, accurate measurement of plasma oxalate concentration is challenging. Prompt acidification or freezing of samples and storage at $-80^\circ$C until acidification is required to prevent conversion of plasma ascorbate to oxalate.\textsuperscript{20} Moreover, plasma oxalate levels do not correlate well with estimated glomerular filtration rate (eGFR) and show significant intraindividual variation in patients with primary hyperoxaluria.\textsuperscript{21}

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,\textsuperscript{1} Ermer et al,\textsuperscript{7} Hoppe et al,\textsuperscript{5} and Aronson et al.\textsuperscript{79} Abbreviations: CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system.

Figure 2. Glyoxylate metabolism in the hepatocyte and enzymatic deficiencies in primary hyperoxaluria. Primary hyperoxaluria types 1 and 2, associated with peroxisomal AGT and cytosolic GRHPR deficiency respectively, result in accumulation of glyoxylate, which is converted to oxalate by LDH. Primary hyperoxaluria 3 is caused by a defect in HOGA in mitochondria; mechanisms leading to increased oxalate levels are not well-defined. 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. Abbreviations: AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GRHPR, glyoxylate reductase–hydroxypyruvate reductase; HOGA, 4-hydroxy-2-oxoglutarate aldolase; LDH, lactate dehydrogenase. Based on information in Cochat and Rumsby,\textsuperscript{23} Hoppe,\textsuperscript{2} and Devresse et al.\textsuperscript{22}
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 (Fig 2). The inability to metabolize glyoxylate leads to excessive hepatic production of oxalate and subsequent accumulation in various organs, including the kidney. Massive urolithiasis and/or calcium oxalate deposition in the renal parenchyma impairs kidney function and oxalate elimination. When the eGFR drops to ≤30-45 mL/min/1.73 m², plasma oxalate increases, and oxalate may deposit in bone, kidneys, skin, retina, and the cardiovascular and central nervous systems. This dramatic condition is referred to as systemic oxalosis.

Primary hyperoxaluria type 1 is the most common and severe form, generally leading to kidney failure during the first 3 decades of life. However, in some patients the condition is not diagnosed until adulthood with occasional or recurrent urolithiasis as the only clinical manifestations. The Gly170Arg and Phe152Ile variants in AGXT (a glycine to arginine substitution at amino acid 170 and a phenylalanine to isoleucine substitution at amino acid 152, respectively) are associated with adult-onset hyperoxaluria and with a less severe prognosis, partly due to the response to pyridoxine. Primary hyperoxaluria types 2 and 3 are generally milder, although patients with type 2 may present with CKD caused by recurrent urolithiasis.

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. 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 a higher urinary oxalate excretion (>100 mg/d, >1.0 mmol/1.73 m²/d, or 1,000 μmol/d) than those with secondary hyperoxaluria (50-100 mg/d, 0.5-1.0 mmol/1.73 m²/d, or 500-1,000 μmol/d). In children, age-specific reference ranges for spot urinary oxalate to creatinine ratios are used.

Measurements of plasma oxalate level may be helpful in patients with CKD stage 3b because they generally increase only when the eGFR is below 30 mL/min/1.73 m² in patients with CKD from other etiologies. The definitive diagnosis of primary hyperoxaluria is achieved by molecular genetic testing.

The conservative therapeutic options in primary hyperoxaluria include massive fluid intake (tube or gastrostomy feeding in infants), calcium oxalate crystallization inhibitors, and vitamin B₆ (pyridoxine) in primary hyperoxaluria type 1. To date, liver transplantation is the only established “curative” therapy to correct the metabolic defect contributing to excessive endogenous oxalate formation. 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 before the development of systemic oxalosis and related complications.

Indeed, outcomes after kidney transplantation are improved by a substantial residual kidney function and by the absence of major systemic oxalate load. Oliguria should be avoided in the peritransplant 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.

New promising therapeutic agents are under investigation and are expected to dramatically influence the management and outcomes of patients with primary hyperoxaluria. Lumasiran is a RNA interference (RNAi)-based therapy that blocks the synthesis of oxalate glycolate oxidase and reduces oxidation of glycolate to glyoxylate, the immediate precursor of oxalate (Fig 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. Two additional phase 3 trials testing the efficacy and safety of lumasiran are ongoing: ILLUMINATE-B and ILLUMINATE-C. The US Food and Drug Administration and European Medicines Agency have recently approved lumasiran for the treatment of children and adults with primary hyperoxaluria type 1. Nedosiran, a RNAi therapy targeting lactate dehydrogenase and reducing conversion of glyoxylate to oxalate, is being tested in a phase 3 study. If these emerging therapies are confirmed to be efficient and safe in patients on dialysis and in kidney graft recipients, liver transplantation may perhaps no longer be required in the future.

Secondary Hyperoxaluria

Causes of Secondary Hyperoxaluria

Secondary hyperoxaluria results from (1) increased dietary oxalate or oxalate precursor intake, (2) fat malabsorption, and (3) decreased intestinal oxalate degradation due to alterations in gut microbiota (Fig 1; Box 1). Hyperoxaluria has been associated with increased intake of nuts, tea, Averrhoa carambola (star fruit) and bilimbi, rhubarb, chaga mushroom, spinach, and “green smoothies” and “juicing.” 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 (Fig 3). Fat malabsorption from various causes (pancreatic disorders, Roux-en-Y bypass surgery, short bowel disease, Crohn disease, use of orlistat) leads to steatorrhea, calcium
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.

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. Increased dietary ingestion of oxalate and alterations in intestinal microbiota may further contribute to obesity-associated hyperoxaluria. Moreover, urinary excretion of oxalate is higher in individuals with diabetes mellitus. Plasma levels of glyoxylate and glyoxal (a protein glycation product), potential precursors of oxalate, are higher in diabetic patients, possibly contributing to hyperoxaluria.

Secondary 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, a condition termed oxalate nephropathy (Fig 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 disease.

Secondary Hyperoxaluria and Urolithiasis

Hyperoxaluria is the main risk factor for calcium oxalate urolithiasis. Supersaturation of calcium oxalate is 10 times more dependent on a rise in urinary oxalate than on an equimolar rise of urinary calcium concentration. Urinary oxalate excretion correlates with the risk of developing a kidney stone event. In patients with malabsorption, fluid loss and a low urinary pH and citrate level also contribute to the pathogenesis of urolithiasis. 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). Similarly, a recently published review reported a stone incidence ranging from 2% to 38% in patients with malabsorptive states other than after bariatric surgery.

The risk of calcium oxalate urolithiasis is also associated with intestinal microbiota composition. Healthy oxalate homoeostasis in the gastrointestinal tract involves a collaborative effort between numerous bacterial species. In fecal samples from healthy individuals, metagenomics studies reveal a network of bacterial taxa co-occurring with Oxalobacter formigenes, which are less represented in urinary stone formers. This would explain why the absence of O formigenes is not causative of stone disease and why colonization with the bacteria failed to reduce urinary oxalate excretion in interventional studies. Similarly, children who are calcium oxalate stone formers have fewer 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.

In mice, Slc26a1 gene deletion causes a reduction in intestinal secretion of oxalate, leading to hyperoxalemia and hyperoxaluria. Human Slc26a1 mutations may presumably lead to urolithiasis via similar mechanisms. Additionally, polymorphisms of Slc26a6 in humans may explain accelerated lithogenesis in distinct populations.
Secondary Hyperoxaluria and Oxalate Nephropathy

Oxalate nephropathy is a severe condition resulting from deposition of calcium oxalate crystals in kidney tissue, which causes tubular-interstitial injury and fibrosis, acute kidney injury (AKI), and/or CKD. Most investigators have used the following diagnostic criteria for oxalate nephropathy: (1) progressive kidney disease, (2) oxalate crystal deposition with tubular injury and interstitial nephritis, and (3) exclusion of other etiologies of kidney disease (aside from vascular and/or diabetes-associated nephropathy). A hyperoxaluria-enabling condition should ideally also be identified.

The prevalence of oxalate nephropathy is unknown. We recently reported 22 cases (1%) of oxalate nephropathy out of 2,265 consecutive native kidney biopsies performed during a 9-year period. Table 1 shows the clinical characteristics and outcomes of patients with oxalate nephropathy reported in 4 case series and 1 systematic review. 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.

Approximately two-thirds of the patients have malabsorption-associated hyperoxaluria. We found that chronic pancreatitis and gastric bypass were the most common causes of oxalate nephropathy (48%). Of note, Lumertgul et al excluded patients with a short duration of exposure (<30 days) to the hyperoxaluria-enabling conditions (ie, vitamin C and oxalate-rich foods). Interestingly, hyperoxaluria-enabling conditions (ie, malabsorptive states) may be long standing; we reported the development of oxalate nephropathy a mean of 8 years after gastric bypass in 5 patients and 1 and 8 years after orlistat initiation in 2 patients. This suggests that the combination of the hyperoxaluria-enabling condition with an additional factor or trigger may lead to crystal formation and kidney damage. 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 favor oxalate crystal-associated kidney injury via the reduction of glomerular filtration fraction.

Clinical presentation of oxalate nephropathy varies across the spectrum of AKI, AKI on CKD, and CKD. Patients present with kidney failure in most cases (mean serum creatinine level of 4.9–8.0 mg/dL). Moderate to profound hypocalcemia was reported in 9 of 12 patients with oxalate nephropathy associated with chronic pancreatitis and may evoke the diagnosis. 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.
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 crystals46 (Fig 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 that this ratio separates patients with oxalate nephropathy from those with other well-documented kidney diseases and scarce calcium oxalate crystals.46 Further studies are needed to validate this criterion for distinguishing oxalate nephropathy from nonspecific oxalate deposition. It is also worth noting that although the term “nephrocalcinosis” is often used to refer to calcium salt deposits in kidney tissue, 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 interleukin-1β (IL-1β)-induced inflammation.48,51 In mice, Nlrp3 deletion successfully protects from progressive kidney failure secondary to ingestion of a diet high in soluble oxalate.51 Nlrp3 inhibition in hyperoxaluric mice protects against calcium oxalate deposition and CKD via a shift in the phenotype of renal macrophages, promoting anti-inflammatory rather than proinflammatory and profibrotic responses. The IL-1 inhibitor anakinra did not show such a protective effect, suggesting that Nlrp3 contributes to calcium oxalate deposition-induced kidney fibrosis independently from IL-1-mediated tissue injury.48

The characteristics of crystal deposition condition the clinical presentation. Acute supersaturation, rapid crystal formation, direct and indirect kidney epithelial cytotoxicity, and inflammation-driven cell necrosis lead to acute kidney damage. By contrast, ongoing mild supersaturation generating subacute crystal plug formation in distal tubules or collecting ducts leads to CKD.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 al35 hypothesized that a higher urinary oxalate, even within the reference 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. Among 3,123 participants, they showed that higher versus lower 24-hour 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 eGFR 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 lesser graft function beyond the early posttransplant period.55,56 Urinary oxalate excretion may thus be a potential risk factor for progression in common forms of CKD. Likewise, it has been suggested that urinary oxalate may be a potential mediator of CKD development and progression in individuals with diabetes or obesity.1 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 intake16,27,57 (Table 2). The goal is to obtain a daily urine output in excess of 2-3 liters in order to reduce urinary supersaturation with 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 the bioavailability of intestinal oxalate and its absorption.27,58 Crystallization inhibitors such as citrate may also be used.59 Importantly, all studies performed with these interventions were performed on small numbers of individuals for a limited periods of time, often without control groups or randomization.60

The therapeutic options currently being tested include oral administration of intestinal bacteria and/or enzymes capable of degrading oxalate. O 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 in a pilot phase 3 open-

**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 nonspecific microvascular lesions and/or diabetes-associated glomerular lesions). |
| 4. Ideally, a hyperoxaluria enabling-condition should be identified. |
label study to reduce urinary oxalate excretion among 16 patients with both secondary hyperoxaluria and a history of kidney stones.62 The results will need to be confirmed in the phase 3 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

A diagnostic workup is fundamental to treating the underlying cause of hyperoxaluria. Hyperoxaluria-enabling conditions may be long standing but paucisymptomatic. We have shown, for example, that chronic pancreatitis may frequently be diagnosed only after oxalate nephropathy, even in kidney transplant recipients.40,41,64 Morphoconstitutional analysis of kidney stones, combining stereomicroscopy and Fourier-transform infrared spectroscopy, may help in determining the cause of hyperoxaluria.65

Table 1. Published Cases Series of Secondary Oxalate Nephropathy

<table>
<thead>
<tr>
<th>Nasr et al, 2008a,39</th>
<th>Carter et al, 201141</th>
<th>Lumlertgul et al, 201826</th>
<th>Buyschaert et al, 202040</th>
<th>Yang et al, 202042</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included cases</td>
<td>OxN associated with gastric bypass</td>
<td>OxN associated with chronic pancreatitis</td>
<td>Review of OxN case series, 1950-2018b</td>
<td>All-cause OxN</td>
</tr>
<tr>
<td>No. of patients</td>
<td>11</td>
<td>12</td>
<td>51c</td>
<td>21d</td>
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</table>

**Patient characteristics**

<table>
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<tr>
<th>Age, y</th>
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<th>67</th>
<th>56</th>
<th>61</th>
<th>64</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>5 (45%)</td>
<td>9 (75%)</td>
<td>30 (59%)</td>
<td>14 (67%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (82%)</td>
<td>9 (75%)</td>
<td>NA</td>
<td>12 (57%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (100%)</td>
<td>8 (67%)</td>
<td>NA</td>
<td>16 (76%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Prior CKD</td>
<td>7 (64%)</td>
<td>7 (58%)</td>
<td>NA</td>
<td>13 (62%)</td>
<td>NA</td>
</tr>
<tr>
<td>Last eGFR, mL/min/1.73 m²</td>
<td>57</td>
<td>NA</td>
<td>36</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RAAS inhibitor use</td>
<td>3 (30%)</td>
<td>8 (67%)</td>
<td>NA</td>
<td>8 (38%)</td>
<td>NA</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>3 (30%)</td>
<td>5 (42%)</td>
<td>NA</td>
<td>9 (43%)</td>
<td>NA</td>
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<tr>
<td>Kidney allograft</td>
<td>0 (0)</td>
<td>1 (8%)</td>
<td>3 (6%)</td>
<td>0 (0)</td>
<td>3 (12%)</td>
</tr>
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**Cause of OxN**

<table>
<thead>
<tr>
<th>Malabsorptive state</th>
<th>11 (100%)</th>
<th>12 (100%)</th>
<th>45 (88%)</th>
<th>15 (71%)</th>
<th>10 (40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased intake of oxalate or precursor</td>
<td>—</td>
<td>—</td>
<td>10 (20%)</td>
<td>3 (14%)</td>
<td>4 (16%)</td>
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<tr>
<td>Unknown cause</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3 (14%)</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Duration of hyperoxaluria-predisposing condition, y</td>
<td>2.8</td>
<td>10</td>
<td>NA</td>
<td>6.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Biological data at presentation**

| Serum creatinine, mg/dL | 6.5          | 6.6                     | 4.9                      | 8.0                  | 6.3                  |
| Urinary oxalate, mg/24 h | NA          | 80                      | 85                       | NA                   | NA                   |
| Urinary oxalate-creatinine ratio, mg/g | NA          | NA                      | NA                       | 86                   | NA                   |
| Urinary protein, g/d | 1.4         | 0.3                     | NA                       | NA                   | NA                   |
| UPCR (g/g) | NA          | NA                      | NA                       | 1.4                  | 0.05                 |

**Kidney biopsy data**

| No. of glomeruli    | 14                 | NA                      | NA                       | 15                   | NA                   |
| No. of oxalate crystals | 43               | NA                      | NA                       | 28                   | NA                   |
| No. of glomerular abnormalities | 9 (82%)         | 6 (50%)                 | 30 (59%)                | 6 (29%)              | 7 (28%)              |

**Outcome**

| Follow-up duration, mo | 19                  | 18                      | 13                       | 29                   | 3                    |
| Kidney failure        | 8 (73%)             | 3 (25%)                 | 30 (59%)                | 11 (52%)             | 6 (24%)              |
| Time to kidney failure, mo | 0.8               | 3                       | NA                      | 0.2                  | NA                   |

Values for categorical variables are given as n (%) or count; for continuous values as mean. Abbreviations: NA, not available (or too few numbers); OxN, oxalate nephropathy; RAAS, renin-angiotensin-aldosterone system; UPCR, urinary protein-creatinine ratio.

*included in the systematic review by Lumlertgul et al.26

*Patients with unknown causes of oxalate nephropathy and those with short duration of exposure (<30 days) to hyperoxaluria-enabling conditions were excluded.

*Quantitative data from 57 case reports of oxalate nephropathy not reported in Lumlertgul et al.26

*Twenty-one of 22 patients with available clinical data.

*Patients with other causes of CKD such as lupus nephritis were included.

*Suggestive but not definitive evidence of oxalate nephropathy.

*Some patients had 2 identified hyperoxaluria-enabling conditions.

*No systematic gastrointestinal and/or genetic workup reported.

*Normal value ≤ 45 mg/d.

*Normal value < 32 mg/g.
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. In patients with hyperoxaluria and/or oxalate nephropathy of unknown etiology, primary hyperoxaluria must not be overlooked (see the previous section).

Treatment of the underlying cause of secondary hyperoxaluria includes withdrawal of oxalate-rich foods or precursors, pancreatic enzyme therapy, intensification of Crohn disease therapy, and in some cases reversal of gastric bypass. Identification and management of the cause of secondary hyperoxaluria is also important to minimize the risk of recurrence of oxalate nephropathy after kidney transplantation. Therapeutic considerations concerning patients with secondary hyperoxaluria on dialysis and during the peritransplantation period are beyond the scope of this review. In addition, further studies are needed to determine the clinical significance of hyperoxaluria in asymptomatic patients with hyperoxaluria-enabling conditions in order to determine the subset with the greatest likelihood of deriving benefit from treatment aimed at preventing 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 for patients with primary hyperoxaluria.

### Table 2. Current and Potential Therapies of Secondary Hyperoxaluria

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rationale</th>
<th>Supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fluid intake (urine output &gt;2-3 L/d)</td>
<td>Reduces urine calcium oxalate supersaturation.</td>
<td>Reduces stone formation,60,68</td>
</tr>
<tr>
<td>Low-oxalate diet</td>
<td>Reduces bioavailability of intestinal oxalate.</td>
<td>Reduces urinary oxalate excretion in small-sized studies; caveat: comparisons were based on a low-oxalate diet compared to a very-high-oxalate diet.50,66,70</td>
</tr>
<tr>
<td>Low-fat diet</td>
<td>Reduces intestinal oxalate absorption (by increasing bioavailability of intestinal calcium).</td>
<td>Reduces urinary oxalate excretion in small studies.69,71</td>
</tr>
<tr>
<td>Normal-calcium diet</td>
<td>Avoid low-calcium diets, which lead to more free intestinal oxalate.</td>
<td>Reduces urinary oxalate excretion in small-sized studies.69,72</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>Reduce bioavailability of intestinal oxalate and its absorption.</td>
<td>Reduces urinary oxalate excretion but may lead to hypercalciuria.72-74 Calcium citrate may be more bioavailable than calcium carbonate.61</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Binds intestinal bile acids, reduces diarrhea, and binds oxalate in vitro.</td>
<td>Studies show contradicting results.70,73,76</td>
</tr>
<tr>
<td>Oxalobacter formigenes administration</td>
<td>Increases intestinal oxalate degradation.</td>
<td>Reduces urinary oxalate excretion in rat model61,77 and plasma oxalate levels in dialysis patients with primary hyperoxaluria (phase 2 study).59</td>
</tr>
<tr>
<td>Oxalate decarboxylase</td>
<td>Degrades intestinal oxalate.</td>
<td>Reduces urinary oxalate excretion in rat model78 and in phase 3 pilot study in humans.93</td>
</tr>
<tr>
<td>NLRP3-specific inflammasome inhibitor</td>
<td>Reduces crystal-induced kidney damage.</td>
<td>Reduces calcium-oxalate crystal-induced kidney fibrosis in mouse model.63</td>
</tr>
</tbody>
</table>

### Article Information

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**References**


37. Clark JS, Vandorpe DH, Chernova MN, et al. Species differences in Ca2+ affinity and in electrogenicity of SLC26A6-mediated oxalate/Cl− exchange correlate with the distinct


