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Increased Rates of Supplement-Associated Oxalate Nephropathy During COVID-19 Pandemic

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Introduction: Causes of secondary oxalate nephropathy include enteric dysfunction and excessive intake of oxalate or oxalate precursors. During the COVID-19 pandemic, there has been a dramatic rise in sales of supplements and vitamin C, during which time we observed an apparent increase in the proportion of ingestion-associated oxalate nephropathy.

Methods: We retrospectively reviewed secondary oxalate nephropathy and compared pre-pandemic (2018–2019) and pandemic (2020–early 2022) time periods.

Results: We identified 35 patients with kidney biopsy proven (30 native, 5 allograft) oxalate nephropathy at a single academic institution. Supplement-associated oxalate nephropathy comprised a significantly higher proportion of cases during COVID-19 pandemic compared with the preceding 2 years (44% vs. 0%, $P = 0.002$), and was associated with use of vitamin C, dietary changes, and supplements. Oxalate nephropathy in the kidney allograft, in contrast, remained associated with enteric hyperoxaluria, antibiotic use, and dehydration. Many patients had diabetes mellitus (57%), hypertension (40%) and/or pre-existing chronic kidney disease (CKD, 49%). Of 9 patients in which the potentially causative ingestion was identified and removed, 8 experienced improvement in kidney function.

Conclusion: There was a shift toward supplements rather than enteric hyperoxaluria as a leading cause of secondary oxalate nephropathy during the COVID-19 pandemic. Kidney outcomes are better than those observed for enteric hyperoxaluria, if the offending agent is identified and removed.

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Oxalate nephropathy is characterized by deposition of calcium oxalate in tubules, usually accompanied by acute tubular injury (ATI) and sometimes acute or chronic interstitial inflammation.[1] Such deposition leads to impaired kidney function, and patients present with acute kidney injury (AKI) or AKI on CKD; a substantial proportion of patients require renal replacement therapy and may progress to end stage kidney disease.[2] Oxalate nephropathy is a result of supersaturation of urinary calcium oxalate and precipitation of insoluble calcium oxalate crystals;[3] those with hyperoxaluria, characterized by urinary concentrations exceeding 40 mg to 45 mg over 24 hours, are especially at an increased risk.[4] Hyperoxaluria is classified as either primary, caused by inherited hepatic enzyme deficiencies that increase oxalate synthesis; or secondary, which can be broadly divided into cases caused by enteric dysfunction, cases caused by ingestion, and cases of unknown cause.

Enteric dysfunction-associated oxalate nephropathy[3,5] is the result of a variety of conditions that all ultimately increase intestinal oxalate absorption. These conditions include intestinal fatty acid malabsorption, inflammation, altered permeability, and antibiotic use or other causes of dysbiosis of oxalate-degrading bacteria such as *Oxalobacter formigenes*.[1,6-8] In particular, intestinal fatty acid malabsorption, often due to gastric

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bypass or chronic pancreatitis[6,9], has been the most commonly reported cause of secondary oxalate nephropathy, comprising 75% of cases in a recent systematic review.[2]

Ingestion-associated oxalate nephropathy is predominantly due to increased dietary intake of foods or supplements rich in oxalate or oxalate precursors such as leafy green vegetables, rhubarb, starfruit, nuts, and soy products, particularly in the context of juicing diets.[6] Such excessive dietary consumption has been reported to account for approximately 20% of cases of secondary oxalate nephropathy.[5,6] In addition to foods, toxic ingestion of ethylene glycol (antifreeze), use of polyethylene glycol-based laxatives,[10] and intake of high doses of vitamin C for health benefits such as the treatment of SARS-CoV-2 sepsis[11] are also documented causes of secondary oxalate nephropathy. Finally, many cases of secondary oxalate nephropathy (14%[6] to 44%[12]) are of unknown etiology.

We recently observed an apparent increase in the incidence of ingestion-associated oxalate nephropathy, specifically with high-dose vitamin C and other food supplements or medications, rather than enteric dysfunction. This corresponded with a dramatic rise in sales of supplements and vitamin C during the COVID-19 pandemic,[13,14] and prompted us to review our experience with secondary oxalate nephropathy during 2020 through early 2022, and compare these with previous institutional cases and the published literature.

METHODS

After Oregon Health & Science University Institutional Review Board approval, we retrospectively searched our pathology database for cases of oxalate nephropathy in native and allograft kidney biopsies from 2018 to February 2022. Identified cases were those which demonstrated ATI and frequent deposition of calcium oxalate, in which oxalate was considered to be a potential or likely cause of, or contributor to, the ATI and kidney injury. Whether the oxalate deposition represented a metabolic abnormality causing ATI versus the consequence of tubular injury is not always known at time of biopsy, and the diagnosis of probable oxalate nephropathy was based on both the histology and clinical interpretation. Mild active interstitial inflammation was defined as areas of interstitial edema with associated mild inflammation, eosinophils, and/or focal tubulitis. For allograft kidney biopsies, we used the same inclusion criteria as for natives, and did not include those in which calcium oxalate deposits were present focally and not considered the likely driver of kidney injury.

Cases in which tubular oxalate deposition was present but considered uncertain or unlikely to be the main cause of kidney injury were excluded ($n = 8$), as were cases of primary hyperoxaluria ($n = 1$). Cases with concurrent non-diabetic glomerular disease were excluded except for 2 in which the clinicopathologic features were interpreted as combined injury both from the glomerular disease and oxalate nephropathy. One of these presented with AKI and had mesangial IgA deposits but no significant glomerular changes was observed by light microscopy. The other case had a history of high intake of vitamin C and oxalate-rich diet, hyperoxaluria, and had recurrent AKI prior to detection of a positive antineutrophil cytoplasmic antibody (ANCA) and nephrotic range proteinuria. This yielded 35 cases of suspected secondary oxalate nephropathy (30 native, 5 allograft), of 2608 native kidney biopsies, a native kidney biopsy incidence of 1.1% and allograft biopsy incidence of 0.32%. These were then divided into a 26-month period of the COVID-19 pandemic from January 2020 through February 2022, and compared against cases of secondary oxalate nephropathy from the preceding 24 months, 2018 and 2019. Because the primary focus was oxalate nephropathy associated with ingestion of supplements, follow up data was primarily sought for the 2020 to 2022 subgroup. Statistical analyses were performed in GraphPad Prism 8 (La Jolla, CA) using Mann-Whitney and Fisher's exact tests.

RESULTS

Shifting Etiology of Oxalate Nephropathy

In our overall cohort of secondary oxalate nephropathy, the median age was 70 years, 49% were male; many patients had diabetes mellitus (57%), hypertension (40%) and/or pre-existing CKD (49%) (Table 1). AKI was the most common reason for biopsy (in 94%). All kidney biopsies demonstrated ATI with scattered to frequent deposition of calcium oxalate (Figure 1a–c); 37% had associated mildly active interstitial inflammation with minimal tubulitis. Chronic injury in the form of arterionephrosclerosis (in 34%) or diabetic nephropathy (in 29%) was common.

Examining etiologies of secondary oxalate nephropathy by year, the 2020 to 2022 time period contained a significantly higher percentage of cases associated with increased dietary intake or supplements when compared with the cohort from the preceding 2 years (44% vs. 0%, $P = 0.002$) (Table 1 and Figure 2). Specifically, 8 of 16 in 2020 to 2022 were related to ingestion of foods, supplements, herbals, or medications, described in detail below. One of these 8 patients also had had gastric bypass surgery over 40

Table 1. Comparison of demographics and etiologies of secondary oxalate nephropathy from 2017 to 2022, with analysis of time-based cohorts before (2018–2019) and during (2020–2022) the COVID-19 pandemic

Variable	2018–2022 Overall	2020–2022 Subgroup	2018–2019 Subgroup	*P* value
Total patients	35	16	19	0.57
Native/allograft	30/5	14/2	16/3	>0.99
Median age (range)	70 (41–94)	67 (44–85)	70 (41–94)	0.72
Male/Female	17/18 (50%)	9/7	8/11	0.51
Diabetes	20 (57%)	9 (56%)	11 (58%)	>0.99
Hypertension	14 (40%)	7 (44%)	7 (37%)	0.74
Prior nephrolithiasis	3 (8%)	2 (13%)	1 (5%)	0.58
AKI as reason for biopsy	33 (94%)	16 (100%)	17 (89%)[e]	0.49
Prior CKD	17 (49%)	9 (56%)	8 (42%)	0.51
Nephrotic proteinuria	1 (3%)[a]	1[a]	0	0.46
Potential etiologies for or contributors to secondary oxalate nephropathy				
Supplements and foods	7 (20%)	7 (44%)[c]	0	0.002
Enteric dysfunction	10 (29%)	2 (13%)[b]	8 (42%)[d]	0.053
Polyethylene glycol	2 (6%)	1 (6%)[b]	1 (5%)	>0.99
Recent antibiotics	5 (14%)	1 (6%)[c]	4 (21%)[d]	0.35
Dehydration[f]	5 (14%)	2 (13%)	3 (16%)	>0.99
Unknown etiology	8 (23%)	4 (25%)	4 (21%)	>0.99
Concurrent biopsy findings				
Mild active interstitial inflammation	13 (37%)	7 (44%)	6 (32%)	0.50
Diabetic nephropathy	10 (29%)	4 (25%)	6 (32%)	0.72
Arterionephrosclerosis	12 (34%)	5 (31%)	7 (37%)	>0.99
Other	2 (6%)[a]	ANCA GN,[a] IgAN[a]	0	0.20

AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease; GN, glomerulonephritis; IgAN, IgA nephropathy.
[a]Cases with concurrent nondiabetic glomerular disease were excluded except for 2 in which the clinicopathologic features were interpreted as combined injury both from the glomerular disease and oxalate nephropathy.
[b]One patient with had polyethylene glycol use and gastric bypass >40 years prior, and is included in both groups in this table.
[c]One patient had high dose vitamin C and recent antibiotic use, and is included in both groups in this table.
[d]One patient had gastric bypass and recent antibiotic use, and is included in both groups in this table.
[e]Remaining 2 patients biopsied for quickly progressive CKD.
[f]Dehydration presenting as AKI with recent diarrhea and/or vomiting, in the absence of other known causes of oxalate nephropathy.

years ago, but the remaining were without history of enteric dysfunction. Only one patient had oxalate nephropathy associated with gastric bypass surgery.

In contrast, and concordant with prior studies, there was a trend toward oxalate nephropathy secondary to enteric dysfunction in the earlier cohort (42% vs. 13%, $P = 0.053$). Specifically, 8 of 19 during 2018 to 2019 were associated with gastric bypass surgery ($n = 3$), chronic pancreatitis ($n = 4$), or active inflammatory bowel disease ($n = 1$). There were no other significant differences between the 2020 to 2022 and the 2018 to 2019 cohorts (Table 1). Evaluation of the overall cohort was somewhat limited by the proportion of secondary oxalate nephropathy of unknown etiology (23%), which is commensurate with that observed in other studies.[12] Notably, the proportion of cases of unknown etiology was similarly distributed between the 2020 to 2022 and 2018 to 2019 cohorts, suggesting that the apparent increase in supplement-associated oxalate nephropathy was not due simply to changes in patient history-taking or reporting.

Patients with oxalate nephropathy were managed with supportive care. Immunosuppression was generally not used for patients with concurrent interstitial inflammation. In the 9 cases of ingestion-associated oxalate nephropathy (Table 2), the offending substance was discontinued shortly after biopsy whenever possible (in all but 1 patient in which this could not be confirmed). At a median follow up time of 10 months (range 2–36 months), 8 of 9 patients with ingestion-associated oxalate nephropathy experienced improvement in, but not normalization of, kidney function, and one remained dialysis-dependent (Table 2 and detailed below).

Oxalate Nephropathy Associated With Ingestion of Mushrooms

Two patients had oxalate nephropathy associated with heavy ingestion of mushrooms or mushroom extracts (Table 2). The first (case #1) is a 55-year-old woman with a history of recurrent urinary tract infection with pyelonephritis, nephrolithiasis, and CKD who presented with AKI with a peak serum creatinine (Cr) of 2.9 mg/dl, without significant proteinuria or hematuria. She had been empirically treated with steroids for 5 days, which was stopped after biopsy. Kidney biopsy showed oxalate nephropathy and arterionephrosclerosis. Further testing revealed an elevated plasma oxalate level of 10.4 umol/l (normal ≤2.0), and hyperoxaluria random urine panel showed elevated

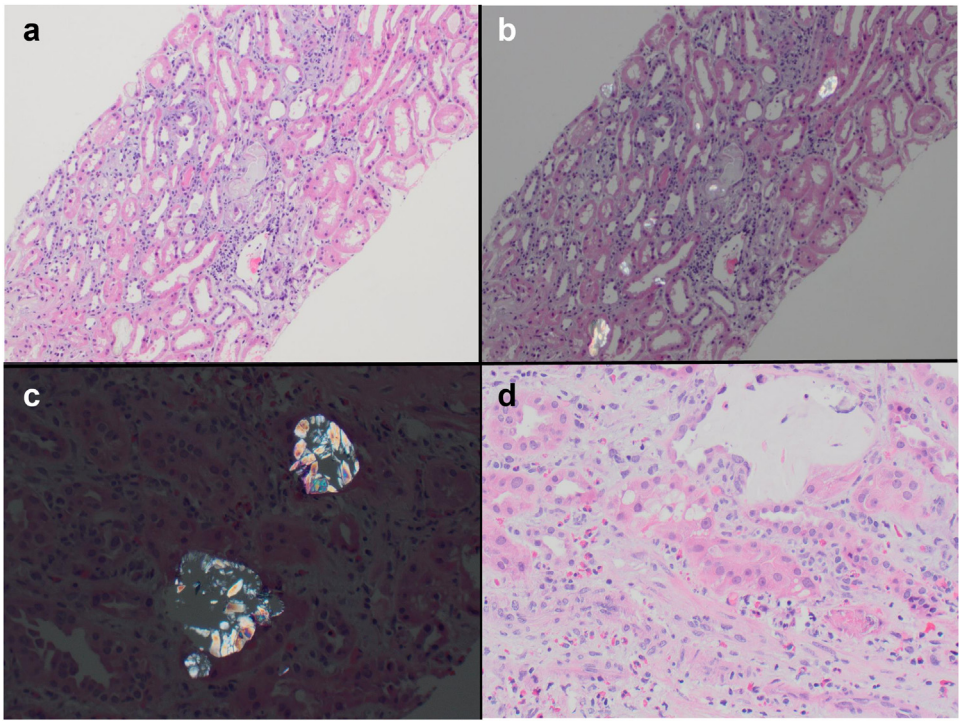

Figure 1. Oxalate nephropathy with (a) acute tubular injury with widespread attenuation of tubular epithelial cytoplasm and associated crystalline deposits which are (b) birefringent under polarized light (both 100×) and (c) have a characteristic "fan-shaped" appearance (200×). (d). Some cases had associated active tubulointerstitial inflammation, including with eosinophils (200×).

oxalate level of 84 mg/g Cr (normal <75); genetic testing for primary hyperoxaluria was negative. The patient reported ingestion of liquid mushroom extracts for at least 2 months, including extracts of: *Ganoderma* (Linghzi), *Lentinula edodes*, *Hericium erinaceus*, *Trametes versicolor*, and *Cordycipitaceae*. She was treated with hydration and discontinuation of supplements, and Cr improved to 1.68 mg/dl at 11 months follow up.

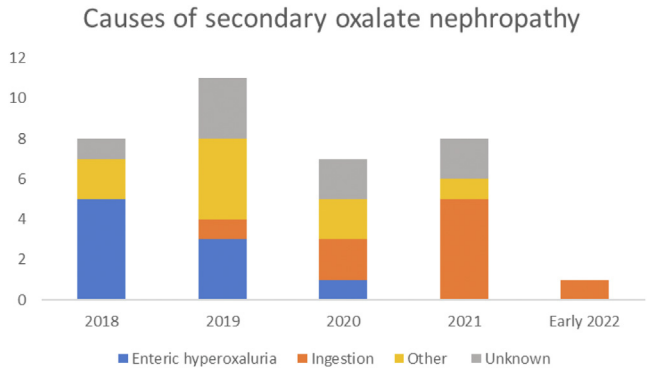

Figure 2. Number of cases with causes of or contributors to development of secondary oxalate nephropathy by year, where enteric hyperoxaluria includes gastric bypass, pancreatitis, and active inflammatory bowel disease; ingestion includes vitamin C and other supplements, foods, and polyethylene glycol; other includes cases associated with antibiotics (potentially leading to enteric dysbiosis), dehydration, or known nephrolithiasis in the absence of other identified precipitating factors.

The second (case #2) is a 62-year-old man with a history of obesity, diabetes with retinopathy, and granulomatosis with polyangiitis without kidney involvement who presented with leg swelling suspicious for cellulitis and AKI (Cr of 12 from a baseline of 1.7 mg/dl) and ~1 gram of proteinuria. He described frequent consumption of mushrooms in meals, ~6 g/d (mushroom varieties not known). Kidney biopsy demonstrated oxalate nephropathy, as well as mild acute and chronic interstitial inflammation and a background of diabetic nephropathy. The patient remained dialysis-dependent at 10 months.

Oxalate nephropathy associated with ingestion of high-dose vitamin C and supplements

Five cases (#3–7) of oxalate nephropathy were associated with high-dose vitamin C ($n = 3$), "supplements" not further described ($n = 1$) or "high-oxalate diet" ($n = 1$) (Table 2). Of the 3 cases associated with high-dose vitamin C, 1 patient (case #3) is a 76-year-old man with a history of diabetes and hypertension who presented with 2 days of dyspnea on exertion found to have AKI with a Cr of 12.2 mg/dl. Kidney biopsy demonstrated oxalate nephropathy and mild acute interstitial nephritis with eosinophils (Figure 1d). He reported taking high-dose (2 g/d) vitamin C for months, and had no other known recent exposure nor nephrotoxic medications. He was treated with supportive

Table 2. Clinicopathologic features of ingestion-associated secondary oxalate nephropathy

Case	Age sex	Condition or exposure likely contributing to oxalate nephropathy	Comorbid conditions	Reason for biopsy	Summary biopsy findings	Intervention	Outcome
1	55 F	Ingestion of mushroom extracts	recurrent UTI, nephrolithiasis	AKI	Oxalate nephropathy; Arterionephrosclerosis; 15% GS/40% IFTA	Stopped mushrooms, hydration	Cr 3.0 → 1.7 mg/dl at 11 mo
2	62 M	Ingestion of ∼6 g of mushrooms/d	Obesity, DM with retinopathy, GPA without kidney involvement	AKI	Oxalate nephropathy; Mild acute and chronic interstitial inflammation; Diabetic nephropathy; 50% GS/35% IFTA	Unknown	Cr 12.0 mg/dl → dialysis dependent at 10 mo
3	76 M	Ingestion of high dose vitamin C	DM, HTN	AKI	Oxalate nephropathy; Mild acute interstitial inflammation; 8% GS/10% IFTA	Stopped vitamin C, hydration	Cr 12.2 → 1.3 mg/dl at 3 mo
4	72 F	Ingestion of high dose vitamin C, high oxalate diet	UTI with recent antibiotic use, DM, new positive ANCA	AKI, proteinuria (5g)	Focally crescentic ANCA GN; Oxalate nephropathy; 27% GS/25% IFTA	Stopped vitamin C, Rituximab and steroids for GN	Cr 4.0 → 1.6 mg/dl at 4 mo
5	85 M	Ingestion of high dose vitamin C, "herbals"	DM, HTN	AKI	Oxalate nephropathy; Mild acute and chronic interstitial inflammation; Diabetic nephropathy; 7% GS/20% IFTA	Stopped vitamin C, dialysis	Cr 7.4 → 3.5 mg/dl at 4 mo
6	61 F	"Supplements"	DM, HTN	AKI	Oxalate nephropathy; Mild acute and chronic interstitial inflammation; Diabetic nephropathy; 35% GS/30% IFTA	Stopped supplements	Cr 4.7 → 2.1 mg/dl at 6 mo
7	74 M	"High-oxalate diet"	HTN	AKI	Oxalate nephropathy; Arterionephrosclerosis; 40% GS/40% IFTA	Altered diet	Cr 6.0 → 2.4 mg/dl at 17 mo
8	70 F	Ingestion of polyethylene glycol	Gastric bypass surgery >40 years prior	Progressive CKD	Oxalate nephropathy; Mild acute and chronic interstitial inflammation; 14% GS/40% IFTA	Avoidance of PEG; low oxalate diet	Cr 4.9 → 1.7 mg/dl at 2 yr
9	76 F	Ingestion of polyethylene glycol	DM	Progressive CKD	Oxalate nephropathy; 20% GS/20% IFTA	Avoidance of PEG	Cr 2.9 → 1.2 mg/dl at 3 yr

AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic antibody; CKD, chronic kidney disease; Cr, serum creatinine; DM, diabetes mellitus; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; GS, global glomerulosclerosis; HTN, hypertension; IFTA, interstitial fibrosis and tubular atrophy; mo, months; PEG, polyethylene glycol; UTI, urinary tract infection; yr, years.
Serum creatinine, provided as mg/dl. Cases #1–8 are from 2020 to 2022 cohort; case #9 is from 2018 to 2019 cohort.

Table 3. Secondary oxalate nephropathy in kidney transplant patients

Case	Age sex	Condition or exposure likely contributing to oxalate nephropathy	Reason for ESKD	Biopsy timing post-transplant	Reason for biopsy	Summary biopsy findings	Intervention	Outcome
10	64 M	Gastric bypass	Oxalate nephropathy	5 wk	Dialysis dependence after transplant	Oxalate nephropathy; 0% GS/15% IFTA	Dialysis	Allograft failed
11	41 M	Chronic pancreatitis	Hepatorenal syndrome	2.5 yr	AKI	Oxalate nephropathy; 33% GS/40% IFTA	Low oxalate diet, calcium supplementation	Graft functioning at 6 yr
12	52 F	Recurrent UTI, antibiotic use, nephrolithiasis	Unknown	>20 yr	AKI	Oxalate nephropathy; 20% GS/20% IFTA	Dialysis	Allograft failed
13	76 M	Recurrent UTI, antibiotic use, diarrhea, volume depletion	Diabetic nephropathy	4.5 yr	Worsening renal function	Oxalate nephropathy; Early diabetic glomerulopathy; 4% GS/5% IFTA	Unknown	Graft functioning at 7.5 yr
14	67 M	Unknown	Diabetic nephropathy	3 yr	AKI	Oxalate nephropathy; 20% GS/20% IFTA	Dialysis	Allograft failed

AKI, acute kidney injury; ESKD, end stage kidney disease; F, female; GS, global glomerulosclerosis; IFTA, tubular atrophy and interstitial fibrosis; M, male; UTI, urinary tract infection; wk, weeks; yr, years.
Cases #10 and 14 are from 2020 to 2022 cohort. Cases #11-13 are from 2018 to 2019 cohort.

care, vitamin C supplements were held, and his Cr improved to 1.3 mg/dl at 3 months of follow up.

Patient #4 is a 72-year-old woman with diabetes, schizophrenia, high-dose vitamin C use and frequent spinach intake who experienced a prior episode of AKI (Cr 6.3 from baseline of 0.7 mg/dl) in the setting of trimethoprim-sulfamethoxazole use 3 months prior, which had partially resolved (Cr 3.7 mg/dl). When Cr rose again (to 4.0 mg/dl), additional workup revealed a urine protein to creatinine ratio of ~5 g/g and a new positive c-ANCA. Kidney biopsy demonstrated an ANCA-associated pauci-immune complex focally crescentic GN as well as frequent tubular deposition of calcium oxalate. Twenty-four hour urine oxalate level was elevated (47 mg/day; normal 13–40 mg/day). She was treated with rituximab, steroids, and cessation of vitamin C supplements, and Cr improved to 1.6 mg/dl at 4 months.

Patient #5 is an 85-year-old man with a history of diabetes who was found to have AKI (Cr 7.4 mg/dl from baseline of 1.1). He also reported taking high-dose vitamin C, various unknown herbals and supplements, and ivermectin for COVID-19 prophylaxis. Kidney biopsy demonstrated oxalate nephropathy, mild chronic and active interstitial inflammation, and a background of nodular diabetic nephropathy. He was treated with dialysis and discontinuation of vitamin C, and creatinine improved to 3.5 mg/dl off dialysis at 4 months follow up.

Oxalate nephropathy associated with polyethylene glycol

One patient (case #8) had a history of gastric bypass surgery >40 years ago and presented with progressively worsening CKD with Cr which rose from 1.6 to 4.9 mg/dl over 6 months. This began after receipt of polyethylene glycol prep for a colonoscopy; she experienced no other changes in her medications or health during that time period, and did not report taking any supplements. Kidney biopsy demonstrated oxalate nephropathy and mild chronic and active interstitial inflammation. Twenty-four hour urine oxalate was elevated (62.4 mg/day). She was treated with a low oxalate diet and avoidance of polyethylene glycol, and renal function improved to 1.7 mg/dl at 2 years of follow up. The second patient with oxalate nephropathy associated with polyethylene glycol use (case #9) is a 76-year-old woman with a history of diabetes and worsening CKD with Cr which rose to 2.9 mg/dl from 1.1 mg/dl over an 8-month period, in the setting of polyethylene glycol use for constipation. Polyethylene glycol was discontinued after biopsy, and kidney function improved to 1.2 mg/dl at 3 years follow-up.

Allograft kidney biopsies with oxalate nephropathy

Five cases of secondary oxalate nephropathy were seen in kidney transplant patients at a median time of 3 years post-transplant (range 5 weeks to >20 years), 4 of which occurred >2 years post-transplant (Table 3). Two were due to enteric dysfunction, including one patient (case #10) with end stage kidney disease (ESKD) due to oxalate nephropathy after gastric bypass surgery, who was biopsied 5 weeks post-transplant due to delayed graft function with continued dialysis dependence. Kidney biopsy demonstrated oxalate nephropathy and no evidence of rejection. Plasma oxalate level was elevated at 24 umol/l, and the patient remained dialysis dependent after 2 years of follow up. The second allograft with enteric dysfunction-associated oxalate nephropathy (case #11) was a 41-year-old man with ESKD due to hepatorenal syndrome secondary to α1 antitrypsin deficiency with associated cirrhosis and chronic pancreatitis who underwent combined liver-kidney transplant. A kidney biopsy performed for AKI at 2.5 years post-transplant demonstrated oxalate nephropathy, which was treated with a low-oxalate diet and calcium supplementation, and the graft remained functional at 6 years. Two kidney transplant patients (cases #12 and 13) had oxalate nephropathy in the setting of recurrent urinary tract infection and antibiotic use, one of whom also had diarrhea and volume depletion, and the other of whom had a history of nephrolithiasis. The fifth patient had oxalate nephropathy of unknown etiology. At a median follow-up time of 6 years, 3 patients experienced kidney allograft failure and 2 had functioning allografts.

DISCUSSION

The primary findings of this single-institution observational study are that during the COVID-19 pandemic, the rate of supplement-associated secondary oxalate nephropathy (44%) increased significantly above our comparative internal historic cohort as well as the published range of approximately 8% to 20%.[1,5,6] Ingestion-associated oxalate nephropathy had substantially better kidney outcomes than enteric dysfunction associated oxalate nephropathy, with 89% experiencing improvement in renal function. In addition to identifying high vitamin C intake,[1,15,16] a well-known cause of oxalate nephropathy, our series also adds to the limited data on the following more obscure causes of secondary oxalate nephropathy: mushrooms or mushroom extracts, polyethylene glycol, and those occurring in the renal allograft. Because there are often unreliable findings to clinically diagnose oxalate nephropathy, awareness of supplement use and consideration for biopsy in patients with unexplained kidney disease may prove valuable in identifying those with reversible kidney dysfunction.

Causes for the rise in ingestion-associated secondary oxalate nephropathy are likely multifactorial. Increased intake of health and wellness products, some of which are unregulated, may be a strong contributing factor because there have been dramatic increases in sales of dietary supplements during the COVID-19 pandemic.[13,14] The associated comparative decrease in secondary oxalate nephropathy due to enteric dysfunction may reflect changes in restrictive weight loss surgery; surgeries in which the small bowel is not bypassed, i.e., sleeve gastrectomy, are increasingly popular and are not associated with the same increased risk of oxalate stone formation.[1,17]

Mushrooms are rich in oxalates, most of which are thought to be insoluble and not bioavailable.[18] Though species type can account for varying amounts of oxalate, differing methods in processing, such as drying, suspension in alcohol or water, may lead to varying amounts of soluble oxalate.[19,20] In Korea, there have been several reports of Chaga mushroom-induced oxalate nephropathy.[20] In greater Asia, Chaga mushroom is used as a traditional remedy for cancer and gastritis, amongst other diseases.[21] Although both of our cases appear associated with heavy mushroom ingestion, including concentrated extracts, use of other unreported supplements or high-oxalate foods is possible, and we are unable to establish causality between ingested mushroom species or dosage and development of oxalate nephropathy.

Polyethylene glycol is hypothesized to contribute to the development of oxalate nephropathy via depolymerization and conversion into oxalate substrates.[10,22-25] Importantly, polyethylene glycol has been shown to be safe in most patients with CKD,[26] and although both patients in our series improved with removal of this agent, there are a wide variety of patient-specific and potentially confounding factors that may contribute to these observations. As with other associations, a direct connection with polyethylene glycol use is difficult to confirm. A clinical trial aims to further investigate the association of polyethylene glycol and hyperoxaluria.[27]

Oxalate nephropathy affecting allograft kidneys has been reported in patients with enteric hyperoxaluria due to gastric bypass[28-30] and pancreatic insufficiency,[31] similar to our findings. The apparent temporal increase in ingestion-associated oxalate nephropathy was not observed in our small cohort of kidney transplant patients. Other associations with oxalate nephropathy in our kidney transplant patients were antibiotic use and dehydration, which are also associated with oxalate nephropathy in native kidneys.[1,7,8]

Oxalate deposits have been reported in up to 17% of allograft kidney biopsies in 1 series, usually within 3 months post-transplant.[32] The cases in our series are distinct from these because all but one occurred more than 2 years post-transplant; we did not evaluate specifically all transplant biopsies for the presence of focal oxalate deposits.

Our conclusions are tempered by the rate of secondary oxalate nephropathy for which a single driver could not be pinpointed (23%), a published challenge in this entity.[12] These were likely multifactorial; diabetes and obesity are both associated with higher urinary oxalate excretion,[33] and 57% of our patients were diabetic. Some patients had more than one exposure or risk factor for oxalate nephropathy. In others, the only identified risk factor was recent antibiotic use or dehydration, which do not independently cause oxalate nephropathy in most individuals but can precipitate stone formation in some. Determining exact duration and dose of certain supplements in diverse patient groups with oxalate nephropathy may inform safety profiles. Although our rate of oxalate nephropathy in native kidney biopsies (1.1%) is similar to the published literature,[6] this may be an underestimation due to reduced access to certain health care[34] and reported lower rates of kidney biopsies during the COVID-19 pandemic.[35] Further, we used only kidney biopsy cases in which oxalate was strongly suspected to be the driver of ATI. Patients with ATI and only scattered calcium oxalate deposits were excluded, some of which may have been better considered as milder forms of oxalate nephropathy, adding to the potential for underestimation of disease burden. Our findings are limited to a single institution, and larger multi-institutional studies could determine the extent of these trends.

In summary, our recent increase in supplement-associated oxalate nephropathy correlates with the rise in supplement sales during the COVID-19 pandemic. The high rate of improvement in kidney function and low rate of progression to ESKD with identification and removal of the offending agent in our series provides additional impetus to consider biopsy in patients with unexplained kidney dysfunction, and for vigilance in history-taking, accounting for patient comorbidities, vitamins, supplements, and diet.

DISCLOSURE

All the authors declared no competing interests.

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