Oxalate Nephropathy Due to High Oxalate Vegan Diet

Sandra M. Herrmann, MD
Assistant Professor of Medicine
Division of Nephrology and Hypertension
Mayo Clinic, Rochester, MN
Email: herrmann.sandra@mayo.edu

Lourdes Gonzalez Suarez, MD, PhD
Nephrology Fellow
Division of Nephrology and Hypertension
Mayo Clinic, Rochester, MN
Email: gonzalez.lourdes@mayo.edu

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Abstract
Oxalate nephropathy is associated with progressive renal injury due to intratubular precipitation of calcium oxalate leading to renal failure. It can be caused by primary or secondary hyperoxaluria. Secondary hyperoxaluria can occur with excessive intake of oxalate (or substances that metabolize to oxalate), increased oxalate absorption or decreased oxalate excretion. The following article is a case study presentation of a patient with chronic kidney disease secondary to oxalate nephropathy after excessive consumption of high oxalate foods.

The case reviewed in this article is that of a 52 year old male with worsening kidney function over a period of one year. His creatinine increased progressively and kidney biopsy results showed significant amounts of oxalate crystals. Serum and urine oxalate levels were elevated at 19.9(<1.8) µmol/L and 132(9.7-40.5) mg/24hr, respectively. Genetic testing for primary hyperoxaluria was negative. The patient’s only identified risk factor for oxalate nephropathy was a vegan diet with excessive dietary intake of foods containing high oxalate levels.

Intake of oxalate rich foods may potentially precipitate acute renal failure, especially in patients with mild to moderate chronic kidney disease. In our case study, the patient’s only risk factor for hyperoxaluria was high dietary oxalate intake. Awareness of high oxalate content foods may help prevent kidney damage associated with oxalate nephropathy.

Introduction
Oxalate is the salt-forming ion of oxalic acid, which is an end-product of plant and animal metabolism (Figure 1). This ion binds easily to calcium, and forms a nearly insoluble salt that tends to crystallize (1,2). Oxalate molecules are filtered by the kidneys through the glomerulus. When there is an increased content of urinary oxalate beyond dissolution, the complex formed with calcium supersaturates the urine causing precipitation. Acute oxalate nephropathy is caused by deposits of oxalate crystals in the tubules and...
results in inflammation, interstitial fibrosis, and progressive renal injury. However, in patients with decreased kidney function who present with impaired renal clearance, serum oxalate levels may increase leading to tissue crystal formation in uremic patients (3). Autopsies in patients with end stage kidney disease have shown a correlation between serum oxalate levels and severity of crystal deposition in the heart and kidneys (4). The incidence and severity of this type of secondary oxalosis was found to be related to the duration of renal failure.

About 75% of all kidney stones are primarily composed of calcium oxalate. The pathogenesis of stone formation consists of crystal nucleus formation, followed by growth and aggregation (5). Once a calcium oxalate crystal has formed, it starts to grow by further deposition of crystal components. If urinary oxalate concentration remains elevated, this may lead to stone formation (6). This mechanism has been confirmed by in vitro studies performed by Lieske et al. showing intracellular crystal engulfment as a possible pathway of stone formation (7). There are several promotors of stone formation (Table 1), such as low urine volume and pH, as well as high sodium, calcium and oxalate content in urine. In contrast, several substances have been shown to inhibit stone formation, including citrate and magnesium (5).

**Etiology of Hyperoxaluria**

Several etiologies for hyperoxaluria have been identified, including endogenous and exogenous causes such as intrinsic overproduction, increased ingestion and/or absorption of oxalate or its metabolites (i.e. oxalic acid, ascorbic acid, glycolic acid). Increased oxalate excretion after renal transplantation in patients with primary hyperoxaluria has also been described (8). In some patients the cause of hyperoxaluria could be multi-factorial (9).

**Primary Hyperoxaluria**

Genetic disorders causing endogenous overproduction of oxalate are referred to as primary hyperoxaluria (PH). This group of rare autosomal recessive inherited diseases has been associated with increased urinary excretion of oxalate. In type I PH, defective hepatic enzyme activity of alanine glyoxalate aminotransferase (AGT) may lead to high content of calcium oxalate in blood deposits in the heart, bone marrow and kidney. Urinary oxalate concentration may be as high as 300 mg/24 hrs. Molecular analysis showing mutations of the AGXT gene (PH, type I), GRHPR gene (PH, type II) or HOGA1 gene (PH, type III) may confirm diagnosis in some patients (10, 11).

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**Figure 1.** Oxalate is the salt-forming ion of oxalic acid, an end product of the metabolism of plants and animals, and some organic compounds (i.e. ethylene glycol).

**Table 1. Risk factors for stone formation**

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Low urine volume</td>
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<tr>
<td>Low fluid intake</td>
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<tr>
<td>High oxalate intake</td>
</tr>
<tr>
<td>High sodium intake</td>
</tr>
<tr>
<td>High protein intake</td>
</tr>
<tr>
<td>High vitamin C intake</td>
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<tr>
<td>High urinary calcium</td>
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<tr>
<td>Low urinary citrate</td>
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<tr>
<td>Urine pH</td>
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<tr>
<td>Family history of kidney stones</td>
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<tr>
<td>Frequent urinary tract infections</td>
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<tr>
<td>Anatomic abnormalities such as</td>
</tr>
<tr>
<td>• horseshoe kidney, medullary sponge kidney</td>
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<tr>
<td>Malabsorption conditions such as</td>
</tr>
<tr>
<td>• Crohn’s disease, gastric bypass surgery</td>
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</table>

*References: 5,6,13,14,33,35*
Secondary Causes of Hyperoxaluria

In general, the human body is able to excrete excess intake of oxalate from our diets. However, when there is malabsorption associated with bowel disease such as Crohn’s disease, celiac disease, short bowel syndrome or gastric bypass surgery, there is an increased absorption of colonic oxalate (12). Because of fat malabsorption, a high content of lipids can remain in the gut. Lipids bind available calcium, thereby decreasing calcium’s availability to generate calcium oxalate complexes, and resulting in excessive oxalate absorption (13). Orlistat, a lipase inhibitor used in weight reduction therapy, has also been shown to increase urinary oxalate, increasing the risk of kidney stones and nephrocalcinosis (14).

Ethylene glycol ingestion has been associated with oxalate nephropathy (15). Ethylene glycol is an odorless and sweet-tasting alcohol found in antifreeze. Upon intentional or unintentional ingestion, this toxin degrades to oxalic acid and precipitates in the kidneys, causing acute tubular damage. Severe kidney injury can cause irreversible damage that may be life-threatening, requiring treatment with dialysis (16).

Multiple factors were found to play a role in calcium oxalate crystal formation in the kidneys of transplanted patients, including malabsorption and modification of intestinal flora due to antibiotic use. During the first few weeks after kidney transplantation, the allograft is able to excrete accumulated oxalate in a short period of time, promoting deposition and allograft damage. Calcium oxalate deposits may be seen in kidney allograft biopsies within 3 weeks after transplant. This phenomenon is associated with poor allograft survival (17). In one retrospective study of 65 patients with biopsy-proven renal calcium oxalate crystals, 17% of the cases had a history of kidney transplantation as a single risk factor, and 12% had a second risk factor, primarily a high oxalate diet (9). Oxalate nephropathy following non-renal solid organ transplantation (i.e. lung, lung-liver) has also been described (18).

Dietary Hyperoxaluria

Excessive dietary intake of oxalate may lead to urinary hyperoxaluria. Oxalate rich diets contribute to a urinary oxalate excretion ranging from 24 to 42 mg/day for a 2,500 calorie diet. Furthermore, if the diet is low in calcium, oxalate levels in the urine may increase to 53 mg/day (19).

Natural sources of oxalate in our diet are varied. These include almonds, peanuts, soybeans and other legumes, some leafy greens such as spinach and rhubarb, chocolate, and tofu, among others (20-24,29) (Table 2). Star fruit has also been identified as a source of high oxalate content (25). Fang et al. showed that rats fed with star fruit juice developed acute kidney injury and their renal biopsies showed typical changes of oxalate nephropathy (26). Cases associated with black iced tea and oxalate-rich fruit and vegetable juicing as causes of oxalate nephropathy have been reported (9,27). Nuts have been associated with acute oxalate nephropathy (28). Of the tree nuts, almonds have been found to have the highest content of oxalate (Table 3) (20). Although high dietary oxalate alone has not been proven to lead to hyperoxaluria, the increased intestinal absorption of dietary oxalate has been associated with a higher risk of stone formation (19).

Oxalate is also the end product of vitamin C metabolism. A significant increase in urinary oxalate content ranging from 48 to 79% has been reported in calcium-stone formers after supplementation with 1-2 g of vitamin C (29,30). The use of over-the-counter vitamin C supplementation may lead to potentially toxic consequences causing irreversible kidney damage, even in previously healthy individuals (31).

Table 3. Oxalate content in nuts*

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Oxalate (mg/ per 100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almonds</td>
<td>469</td>
</tr>
<tr>
<td>Soy nuts</td>
<td>392</td>
</tr>
<tr>
<td>Cashews</td>
<td>262</td>
</tr>
<tr>
<td>Hazelnuts</td>
<td>222</td>
</tr>
<tr>
<td>Pine nuts</td>
<td>198</td>
</tr>
<tr>
<td>Peanuts</td>
<td>140</td>
</tr>
<tr>
<td>Walnuts</td>
<td>74</td>
</tr>
<tr>
<td>Pecans</td>
<td>64</td>
</tr>
<tr>
<td>Pistachio</td>
<td>49</td>
</tr>
<tr>
<td>Macadamia nuts</td>
<td>42</td>
</tr>
</tbody>
</table>

*References: 21, 22

Case Study

A 52 year-old male was referred to our nephrology clinic for evaluation of progressively worsening chronic kidney disease (CKD). His past medical history was remarkable for migraine headaches treated prophylactically with verapamil and, as needed, use of NSAIDs. The patient was not taking any other medications or over-the-counter supplements. There was no family history of kidney disease and no previous personal history of kidney stones, gastric surgeries, diarrhea, or other urinary tract symptoms. His creatinine increased from a baseline of 1.2 mg/dL to 1.4 mg/dL during a period of 4 years, and his CKD was thought to be caused by chronic NSAID use in the setting of unremarkable urinalysis (Table 4). Therefore, NSAIDs were discontinued.
serum oxalate level and it was elevated at 19.9 µmol/L (normal <1.8 µmol/L). A 24hr urine oxalate was also elevated at 132.9 mg (normal 9.7-40.5 mg/24 hours). His 24 hour proteinuria was 77 mg/dL (Table 6). Genetic testing for the three forms of primary hyperoxaluria (PH) was negative. The patient's only risk factor for oxalate nephropathy was a vegan diet with intake of high oxalate foods (Table 7). His daily breakfast was rich in oxalate containing oatmeal with chia and flax seeds and raisins or prunes. For lunch, he usually had vegetables, including a spinach salad with dry beans, sesame seed and hummus. Dinner often consisted of a salad with beets and tofu. He was not taking any calcium supplements, and his dairy intake consisted of one glass of low-fat milk per day. His daily fluid intake was about 1.5 to 2L of water. His diet was also rich in a variety of berries, almonds, and dark chocolate. His almond consumption was approximately 3 ounces (85 mg) per day, with an estimated oxalate content of 398 mg per day. In the absence of other known risk factors, the diagnosis of oxalate nephropathy due to high oxalate dietary intake was made. He was referred to a renal dietitian nutritionist who educated him about the average oxalate content of his current diet and recommended portion sizes for high oxalate content foods. He was also advised to increase his fluid intake to 3L per day, and to take calcium citrate with meals. Two months after these changes were made his kidney function improved, shown by a creatinine decrease from 2.5 mg/dL to 2.1 mg/dL.

However, despite discontinuation of NSAIDs, his creatinine continued to worsen from 1.4 mg/dL to 2.1 mg/dL over a period of 11 months. Upon presentation to our clinic, his physical exam was unremarkable; his body mass index was 23. His creatinine was further elevated to 2.5 mg/dL and blood urea nitrogen was 41 mg/dL. Laboratory investigation showed anemia with a hemoglobin of 11.5 g/dL, a white blood cell count of 5.5 x10^9/L, and normal platelets. His iron stores were slightly elevated: iron level 158 mcg/dL (normal 60-150 mcg/dL), ferritin 383 mcg/L (normal 40-200 mcg/L), transferrin saturation 59% (normal 20-50%); he had recently received IV iron supplementation for anemia. Serum electrolytes, calcium, phosphorus, and bicarbonate were within normal limits; only uric acid was mildly elevated at 8.2 mg/dL. Rheumatological work-up, including extractable nuclear antibodies panel, vasculitis and a hepatitis panel were all negative. C3-C4 complements were normal. No monoclonal protein was identified. A repeated urine sediment was again unremarkable and the renal ultrasound showed normal sized kidneys with increased parenchymal echogenicity, but no hydropsyrosis or other structural abnormalities. The renal artery doppler was normal. Due to the unexplained cause of his renal dysfunction, a kidney biopsy was performed. The biopsy showed a significant amount of intratubular polarizable oxalate crystals (Figure 2) with associated interstitial fibrosis. The results prompted evaluation of serum oxalate level and it was elevated at 19.9 µmol/L (normal <1.8µmol/L). A 24hr urine oxalate was also elevated at 132.9 mg (normal 9.7-40.5 mg/24 hours). His 24 hour proteinuria was 77 mg/dL (Table 6). Genetic testing for the three forms of primary hyperoxaluria (PH) was negative. The patient’s only risk factor for oxalate nephropathy was a vegan diet with intake of high oxalate foods (Table 7). His daily breakfast was rich in oxalate containing oatmeal with chia and flax seeds and raisins or prunes. For lunch, he usually had vegetables, including a spinach salad with dry beans, sesame seed and hummus. Dinner often consisted of a salad with beets and tofu. He was not taking any calcium supplements, and his daily intake consisted of one glass of low-fat milk per day. His daily fluid intake was about 1.5 to 2L of water. His diet was also rich in a variety of berries, almonds, and dark chocolate. His almond consumption was approximately 3 ounces (85 mg) per day, with an estimated oxalate content of 398 mg per day. In the absence of other known risk factors, the diagnosis of oxalate nephropathy due to high oxalate dietary intake was made. He was referred to a renal dietitian nutritionist who educated him about the average oxalate content of his current diet and recommended portion sizes for high oxalate content foods. He was also advised to increase his fluid intake to 3L per day, and to take calcium citrate with meals. Two months after these changes were made his kidney function improved, shown by a creatinine decrease from 2.5 mg/dL to 2.1 mg/dL.
large oxalate intake of about 750 mg per day (36). Probiotics containing anaerobic bacteria, such as Lactobacillus acidophilus, have shown to prevent intestinal oxalate absorption and therefore decrease oxalate urinary excretion (37,38).

Additional therapies have been studied to treat secondary hyperoxaluria, but have not yet been implemented as part of standard management. ALLN-177 is an oral formulation of a recombinant form of a microbial enzyme that degrades dietary oxalate in the gut. It has been shown to decrease urinary oxalate excretion in healthy volunteers; however more trials to determine its safety are required before its accepted use (39).

Conclusion
We presented a case of oxalate nephropathy associated with high oxalate consumption in a patient with an oxalate rich vegetarian diet. Our patient had no other risk factors for hyperoxaluria. Identification of calcium oxalate crystals in a kidney biopsy should prompt further detailed dietary history. Intake of oxalate rich foods may potentially precipitate acute renal failure, especially in patients with mild to moderate CKD. A referral to a dietitian can help assess dietary risk factors for oxalate nephropathy. Decreased consumption of these foods may help prevent kidney damage associated with oxalate nephropathy.

Conflict of Interest
The authors do not have any financial or non-financial potential conflicts of interest.

References

Hyperoxaluria Management
High fluid intake of more than 2L per day and urine alkalinization have been the main therapy to prevent stone formation (32). Vitamin B6 (pyridoxine) has been recommended as part of the management for PH type I, with the purpose to decrease urine oxalate excretion (33).

For patients with secondary hyperoxaluria, diet plays a major role in reducing the risk of oxalate nephropathy. Avoiding oxalate rich foods helps to reduce hyperoxaluria. In individuals at higher risk, especially those following a strict vegan diet or with known risk factors for kidney disease (i.e. history of kidney stones, diabetes), other measures, such as diet changes, may be beneficial.

Individuals who follow a DASH-style diet, consisting of a high content of fruits and vegetables, moderate intake of low-fat dairy products, and low content of animal protein, may tend to have a higher oxalate intake when compared to other types of diets. Although this may increase the urinary oxalate, and therefore increase the risk for calcium oxalate stone formation, high intake of fruits and vegetables may also help increase urinary citrate, known to be an important inhibitor of calcium stones (32,34). Furthermore, a direct comparison done between the DASH and low-oxalate diets showed a decrease of calcium oxalate supersaturation in those following a DASH diet, associated with higher urinary pH and increased urinary magnesium and citrate excretion (35). Unfortunately our patient had a low urinary citrate despite the daily consumption of fruits and vegetables in his diet.

Ingestion of the recommended dietary allowance of calcium in the diet (i.e. 1000 mg of calcium per day) has been shown to decrease the risk of stone formation in those who have a large oxalate intake of about 750 mg per day (36). Probiotics containing anaerobic bacteria, such as Lactobacillus acidophilus, have shown to prevent intestinal oxalate absorption and therefore decrease oxalate urinary excretion (37,38).

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