Secondary Oxalosis: A Cause of Delayed Recovery of Renal Function in the Setting of Acute Renal Failure\(^1,2\)

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ABSTRACT

Oxalosis, or calcium oxalate deposition in the tissues, may develop in patients with inherited disorders of oxalate metabolism or can occur secondary to other diseases. In this study, a case of renal oxalosis probably secondary to excessive parenteral vitamin C administration in a patient with acute post-traumatic oliguric renal failure is reported. Oxalate deposits may have contributed to further worsening and delayed recovery of renal function. The elimination of the source of excess vitamin C and its presumed effect on oxalate production, together with enhanced removal of oxalate during aggressive dialysis, resulted in prompt recovery of renal function. Secondary oxalosis represents a possible cause of delayed recovery of renal function in patients with acute renal failure who are receiving vitamin C supplementation if excess dosage of that supplementation is given. Vitamin C supplementation, if utilized, should be carefully monitored in patients receiving artificial renal replacement therapy.

Key Words: Oxalosis, acute renal failure, acute tubular necrosis, vitamin C, oxalic acid

Primary oxalosis or hyperoxaluria is a multiorgan disease that results from calcium oxalate deposition in multiple tissues. Primary hyperoxaluria is inherited as an autosomal recessive trait and is characterized by the deficiency of the enzyme glyoxylate aminotransferase as in Type I primary hyperoxaluria.
(1), and the enzyme d-glyceric dehydrogenase as in Type II (2). Renal oxalate deposits are found primarily in the proximal tubules, and the natural history of this disease is the development of renal failure secondary to massive oxalate deposition in the kidneys (3–5). Renal transplantation is often complicated by recurrence of the disease (6–9), and a combined kidney and liver transplantation has been suggested by many to be the procedure of choice for primary hyperoxaluria Type I (10–12).

In contrast, secondary oxalosis is the result of excessive oxalate accumulation because of increased ingestion, increased production, or decreased excretion. The kidney is the primary organ for oxalate excretion, and in renal failure, oxalate deposition in the kidney and other organs may occur. The significance of oxalate deposits in a number of tissues has been debated. However, it is suggested that increased oxalate load may result in renal insufficiency.

CASE REPORT

A 58-yr-old white male patient with no significant past medical history was admitted to the University of Colorado hospital for burn injury. On admission to the burn unit, the patient was in circulatory shock and respiratory distress with a blood pressure measurement of 80/40 and a heart rate of 130/min. His weight was 70 kg. He had third-degree burns covering 40% of the total body surface area. His cardiovascular exam was remarkable for tachycardia, and on pulmonary exam, he had diminished breath sounds bilaterally. On abdominal exam, there was no organomegaly, and bowel sounds were diminished. Perioperative cyanosis was noted in the extremities. Urinalysis revealed a pH of 5.0, and a negative dipstick test for protein and blood. Microscopy revealed granular brown casts and many tubular epithelial cells, findings consistent with acute tubular necrosis. His serum creatinine concentration was 1.4 mg/dL and BUN was 56 mg/dL. His hematocrit value was 50% and white blood cell count was 18,000/mm³. Liver function tests were within normal limits. The patient required intubation and mechanical ventilation. He received amikacin for a short period of time after his admission. Shortly after admission, he developed anuria, and was placed on continuous arteriovenous hemofiltration and dialysis, followed by intermittent hemodialysis once he became hemodynamically stable. Cellulosic hollow-fiber dialyzers were used with blood flow rate of up to 400 mL/min and dialysate flow rate of 600 mL/min. Dialysis was continued on a daily to every-other-day basis, with an average dialysis time of 16 h/wk. He remained hemodynamically stable during most of the sessions. Total parenteral nutrition was started on the second hospital day. Beside the usual glucose, amino acids, lipids, and trace element solution, daily vitamin supplementation including 1 g of vitamin C was also administered intravenously. Recurrent episodes of sepsis complicated by paralytic ileus precluded sufficient enteral alimentation, requiring that continuous parenteral nutrition with the above solution be continued for over 2 months. During this time period, the patient continued to be anuric and dialysis-dependent, with no signs of recovery of renal function. Renal ultrasound revealed normal-sized kidneys and renal technetium diethylene-triamine-pentaacetic acid scan revealed decreased RBF to both kidneys. Seven weeks after the initiation of dialysis, a percutaneous biopsy of the right kidney was performed. Light microscopy revealed mild ischemic wrinkling of the basement membrane in most of the glomeruli. The arteries revealed age-consistent intimal fibrosis with occasional vacuolization of smooth muscle cells. There was marked interstitial edema, and mild interstitial fibrosis. The tubules showed varying degrees of dilation with occasional sloughing of the epithelium. However, there was extensive calcium oxalate deposition seen in the interstitium and within the tubules (Figure 1). The presence of oxalate was highly prominent under polarized microscopy. One day after renal biopsy, vitamin C supplementation was reduced from 1 to 0.2 g/24 h. At the same time, aggressive daily dialysis for up to 6 h each day was begun using a blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min. Within 1 wk, there was an increase in urinary flow, with a corresponding decrease in serum creatinine concentration (Figure 2). Approximately 2 wk after the renal biopsy, dialysis was no longer required. During the recovery phase, urinary microscopy revealed numerous oxalate crystals and, 4 days before discharge, a 24-h urinary oxalate measurement was 88 mg (normal values for men, 7 to 44 mg/24 h). At the time the patient was discharged from the hospital, his serum creatinine concentration was 2.2 mg/dL. On further outpatient follow-up, his creatinine concentration was 1.4 mg/dL. Repeat urinary collection for oxalate determination was not performed because of difficulty in follow-up because of geographical distance. However, 1 yr after discharge, the patient died of a myocardial infarction and an autopsy was performed. No evidence of oxalate deposits was found in any of the internal organs, which suggests that primary hyperoxaluria was not the underlying cause of the renal insufficiency or oxalate deposits that were found during renal biopsy 1 yr earlier. Renal histology showed occasional sclerosed glomeruli consistent with age. The remainder of the glomeruli were unremarkable, with only a mild increase in fibrosis in the interstitium (Figure 3).

DISCUSSION

Our patient had acute tubular necrosis secondary to severe volume loss from his burn injury. Amikacin may also have contributed to the development of renal failure. He showed no signs of renal recovery for up to 2 months after the initial insult. During this time period, the patient was receiving total parenteral nutrition with a large amount (1 g/day) of vitamin C.
Renal biopsy performed after 50 days of prolonged oliguria revealed extensive oxalate deposition. Calcium oxalate deposits are sometimes seen in renal biopsies of patients with acute renal failure; however, extensive deposition as in this case is unusual. After the reduction of vitamin C supplementation and commencement of daily dialysis, the patient's urinary flow rapidly increased and his plasma creatinine level began to return to normal. One year later, postmortem results showed no evidence of oxalosis in the kidneys or other internal organs. These findings make the possibility of underlying abnormality of oxalate metabolism unlikely and suggest that the renal oxalate deposits we observed were probably a consequence of vitamin C overdose. The delay in renal recovery was possibly the result of oxalate deposits in the kidney. Recovery of renal function was enhanced by the removal of oxalate with intense dialysis and by the decrease in oxalate production by limiting the amount of vitamin C supplementation. Hemodialysis itself has been implicated, however, as a cause of delayed recovery from acute renal failure secondary to loss of vascular autoregulation (13).

**Vitamin C Metabolism**

Vitamin C is a precursor of oxalic acid. Isotope studies indicate that vitamin C is oxidized to a monodehydroascorbic acid, which exists in very small concentrations (14). This is then oxidized to dehydroascorbic acid, a stable lactone, which is hydrolyzed to 2,3 diketogluconic acid, which in turn is metabolized to oxalic acid and L-threonic acid (Figure 4). Vitamin C, as well as other water-soluble vitamins, is often given to patients on chronic hemodialysis to prevent deficiency (15). It is also added as a reducing agent to the dialysate fluid in some centers to remove chloramine, which can cause hemolysis. In people with normal renal function, excess vitamin C is excreted by the kidney. In patients receiving conventional hemodialysis, 66% of vitamin C is removed during dialysis (15). High vitamin C levels may occur in such patients if the vitamin load exceeds the removal rate of hemodialysis (16). This could increase the oxalate load through increased metabolism into 2-3-diketogluconic acid. The recommended daily allowance of vitamin C for adults is 60 mg (17), whereas the daily requirement of vitamin C for patients undergoing conventional hemodialysis has been estimated to be 100 to 200 mg (16,18). A positive correlation has been found between the dose of vitamin C supplementation and serum oxalate levels in hemodialysis patients (19,20). In addition, patients undergoing hemodialysis have been reported to have high plasma oxalate levels, compared with control subjects (21).
Oxalate Metabolism

Oxalate is present in many plants, such as tea and green leafy vegetables, but very little is absorbed through the gastrointestinal tract. The colon is believed to be the major site of reabsorption (23), which appears to be an active carrier-mediated, anion-exchange process. OH\(^-\) and Cl\(^-\) ion exchangers have been shown to play an important role in oxalate absorption in the intestine (24). Increased absorption is seen in certain small-bowel diseases and in patients who have undergone small-bowel bypass (25, 26). Oxalate is excreted exclusively in the urine as an end-product of metabolism (27). It is filtered and secreted in the proximal tubule, as demonstrated by micropuncture techniques (28, 29). There is no evidence to suggest that oxalate is metabolized in humans. Under normal conditions, urinary oxalate is derived primarily from glyoxalate, ascorbic acid, and dietary oxalate (27) (Figure 4). Oxalate forms a wide variety of salts, the most important of which is calcium oxalate. The pathogenesis of oxalosis may be related to its poor water solubility. The nephrotoxicity of oxalate is believed to be related to a direct toxic effect on the renal tubules and interstitium, as well as to the development of oxalate stones (30). Additional insights into cellular mechanisms of oxalate nephrotoxicity have recently been reported. Lieske et al. have shown that calcium oxalate crystals are endocytosed by renal epithelial cells and promote a proliferative response (31). This proliferative response was blocked by
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nephrocalcin, a glycoprotein that inhibits calcium oxalate nucleation and aggregation. In other studies, investigators demonstrated that calcium oxalate crystals are rapidly internalized by renal epithelial cells, giving a possible explanation to crystal retention in the kidney (32). In more recent data, calcium oxalate has been shown to stimulate specific genes in renal tubular cells, including the connective tissue growth factor gene (33). Stimulation of connective tissue growth factor gene expression may explain the interstitial fibrosis that is commonly found in patients with underlying disorders of oxalate metabolism.

Causes of Secondary Oxalosis

Two compounds, ethylene glycol (34) and methoxyflurane (35,36), that cause increased oxalate production, marked hyperoxaluria, and renal oxalate deposition, are well-known causes of acute renal failure. Renal insufficiency attributed to oxalate deposits has been reported with massive administration of vitamin C (37–39). Oxalosis secondary to vitamin C administration has also been reported in patients with acute renal failure who are undergoing hemodialysis. Friedman et al. (40) reported a patient with hemolytic uremic syndrome who was undergoing hemodialysis, and who received 0.5 g/day of vitamin C in the hyperalimentation fluid. He developed hyperglycemia and died of sepsis, and at autopsy was found to have extensive calcium oxalate deposits in the pancreas and the kidneys. These and other causes of secondary oxalosis are summarized in Table 1.

Oxalosis in Patients with Chronic Renal Failure

Though it is not commonly seen in such cases, oxalosis has been reported in chronic hemodialysis patients. Moderate to severe oxalate deposits in various organs were encountered more frequently in patients who were maintained for longer periods on hemodialysis (41). Salyer and Hutchins (42) reported renal and myocardial oxalate deposits in 70% of patients maintained on chronic hemodialysis. There was a positive correlation between the presence of oxalate deposits, the extent of myocardial fibrosis, and the development of heart failure. These researchers also found that hemodialysis was more effective than peritoneal dialysis in ameliorating oxalate deposits. Fayemi et al. (43) studied the extent of oxalate deposits at autopsy in various organs in 80 hemodialysis patients. In this series, the most frequently involved organs were kidneys, thyroid, and myocardium. Less prominent deposits were found in the spleen, lungs, male genitalia, bone, central nervous system, and

Figure 3. Postmortem renal histology showing no evidence of oxalate deposits (1 yr after the initial renal biopsy). (Hematoxylin-eosin stain; original magnification, ×10).
CONCLUSION

Vitamin C is essential for patients on hemodialysis; however, the use of excessive amounts of this vitamin should be avoided. Vitamin C overdose may cause secondary oxalosis, which could further worsen the renal insult and delay recovery of renal function in patients with acute renal failure. Secondary oxalosis is sometimes seen in patients undergoing hemodialysis, and may play a role in the morbidity and mortality associated with uremia. The available data suggest that a daily dose of 200 mg of vitamin C should be sufficient to prevent ascorbate deficiency in dialysis patients. Studies of vitamin C clearance, using high-efficiency, biocompatible membranes, should be performed to identify the amount of vitamin C that can be safely administered to hemodialysis patients without inducing toxicity.

REFERENCES

2. Chlebeck PT, Milliner DS, Smith LH: Long-term prognosis in primary hyperoxaluria type II. Am J Kidney Dis

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**TABLE 1. Causes of secondary oxalosis**

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Increased Intake</td>
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<tr>
<td>- Ascorbate overdose</td>
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<td>- Ethylene glycol intoxication</td>
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<td>- Methoxyfluorane</td>
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<td>- Excessive dietary intake of dark leafy vegetables, rhubarb, citrus fruits, or tea</td>
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<tr>
<td>Increased Absorption</td>
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<td>- Inflammatory small-bowel disease</td>
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<td>- Status after partial small-bowel resection</td>
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<td>- Status after small-bowel bypass surgery</td>
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<tr>
<td>Decreased Excretion</td>
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<tr>
<td>- Prolonged acute renal failure, chronic renal failure</td>
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<tr>
<td>Vitamin Deficiency</td>
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<tr>
<td>- Thiamine</td>
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<td>- Pyridoxine</td>
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Ascorbic acid

Dehydroascorbic acid ↔ Monodehydroascorbic acid ↔ Ascorbic acid

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Figure 4. Oxalate and ascorbic acid metabolic pathway. (Modified from Coe FL, Nephrolithiasis: Pathogenesis and Treatment, Year Book Medical Publishers, Inc., Chicago, 1978:147.)
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