

# Vitamin C Neglect in Hemodialysis: Sailing between Scylla and Charybdis

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## Key Words

Vitamin C · Hemodialysis · Oxalosis, systemic

## Abstract

In our efforts to meet the vitamin C requirements of dialysis patients we confront a medical dilemma – do we allow the patient to become depleted of vitamin C, with the accompanying hematological and other consequences (Scylla), or do we provide for adequate tissue levels of vitamin C, which has been thought to carry the risk of oxalosis (Charybdis). Many practitioners are certain that either one outcome (deficiency) or the other (oxalic acid toxicity) is inevitable, and much like Odysseus, no safe course is to be found. The recent accumulating evidence that vitamin C improves the management of anemia in dialysis patients compels us to find a safe passage through this dilemma. The serious vitamin C deficiency seen in many patients may also contribute to poor oral health and chronic fatigue. The evidence for oxalosis from vitamin C supplements stems from hemodialysis as practiced 20 years ago. Investigators using this therapy are not observing systemic oxalosis, and the most current data support the conclusion that vitamin C therapy is safe for dialysis patients. The question will be resolved by controlled trials that address both vitamin C effectiveness and safety.

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In the Odyssey, the task set to Odysseus is to sail between the sea monster at Scylla and the whirlpool at Charybdis. In the myth, a course away from one is virtually certain to lead to the other, although the myth opens the possibility that extraordinary seamanship might lead to safe passage. Are we faced with the same delicate balance in providing appropriate levels of vitamin C for dialysis patients?

Limited dietary intake of vitamin C has long been a major issue in dialysis therapy [1]. Most dietary vitamin C is provided by foods such as orange juice, strawberries, and broccoli, which are rich in potassium. Since hyperkalemia is a major risk factor for dialysis morbidity and mortality [2], the renal dietitian often instructs the patient to limit intake of potassium-rich foods [3]. Many of the best sources of vitamin C are excluded by these guidelines, and low dietary vitamin C intake can readily occur. The problem is aggravated by vitamin C losses during dialysis, which may remove several hundred milligrams of vitamin C in a single dialysis treatment [4, 5]. Normal plasma vitamin C levels in the nondialysis population are 30–60  $\mu\text{M}$  [6]. By contrast, plasma vitamin C in dialysis patients is frequently  $<10 \mu\text{M}$  [7], and may be as low as 2  $\mu\text{M}$  [Handelman, in preparation]. Vitamin C deficiency may be seen as Scylla, the sea monster that would doom the ship.

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The appropriate response to restricted vitamin C intake from diet is to provide dietary vitamin C supplements. But here we are faced with the specter of Charybdis, the whirlpool. The metabolism of vitamin C includes the formation of oxalic acid, which has limited solubility in human tissues. When the plasma concentration of oxalate exceeds 40  $\mu\text{M}$ , there is at least the possibility of oxalate crystals forming in a variety of tissues, including retina, skin, joints, and cardiac muscle. This syndrome, called primary oxalosis, is often found in children with a metabolic defect that forms excessive oxalate in the liver. Primary oxalosis often leads to early kidney failure and death, and is only treatable by liver transplantation. Prior to the advent of reliable high-flux dialysis therapy, some cases of oxalosis were observed in patients with end-stage renal disease [8, 9]. Following implementation of 3 $\times$ /week dialysis therapy, with weekly standardized Kt/V >2, oxalate deposits could not be detected in a thorough biochemical analysis of biopsy and autopsy material from hemodialysis patients [10], and no case reports of oxalate deposition have been reported in recent years in dialysis patients as a result of vitamin C supplement use. However, the usual guidance provided in nephrology textbooks and manuals on renal nutrition is to 'limit dietary vitamin C supplements to 60 mg/day, to avoid oxalosis' [11]. For many patients, this dosage has not achieved the normal range of plasma vitamin C, and deficiency is widespread. For many in nephrology, oxalosis (Charybdis) seems the greater peril, and vitamin C deficiency (Scylla) is accepted as unavoidable.

### Vitamin C Effects on Erythropoiesis

The management of anemia utilizes much of the resources dedicated to patients on dialysis; hemoglobin, ferritin, transferrin saturation, erythropoietin therapy and the intravenous administration of iron complexes (IV-iron) are reviewed extensively for each patient, with dose adjustments monthly or even at more frequent intervals. Improved vitamin C status may lead to improved anemia management in these patients. The biochemistry of vitamin C and iron are intimately related; at the level of the gastrointestinal tract, vitamin C helps maintain iron as  $\text{Fe}^{2+}$ , which is more soluble than  $\text{Fe}^{3+}$  at the alkaline pH of the small intestine, and is more readily absorbed across the intestinal mucosa [12, 13]. However, the iron requirements of dialysis patients are greater than most persons with normal renal function, and several investigations [14, 15] have reported that oral iron supple-

ments have limited ability to meet the iron needs of these patients. The consensus among dialysis clinicians is therefore that IV-iron is obligatory in these patients, although further study may document the beneficial effects of dietary vitamin C on utilization of oral iron.

Vitamin C can affect mobilization of iron from Kupffer cells and other sites in the reticuloendothelial system (RES). When storage iron accumulates beyond the requirement of the body for iron, it may be converted from ferritin to hemosiderin, a form of iron with limited bioavailability, which can accumulate in the bone marrow of dialysis patients [16]. Studies in guinea pigs have shown that vitamin C aids the conversion of hemosiderin iron to ferritin iron [17], which can be exported from the storage cell and carried on transferrin to sites of red blood cell synthesis in the bone marrow. In Bantu siderosis [18], administration of dietary vitamin C supplements led to a significant increase in serum iron, indicating that vitamin C was helping to mobilize stored iron in these patients. During the initial phase of vitamin C therapy in siderotic subjects, there was an accelerated release of urinary oxalic acid [19], consistent with conversion of vitamin C to dehydroascorbate by interaction with stored ferric ion, followed by catabolism of dehydroascorbate to oxalate. Dialysis patients may also accumulate excess iron stores in the gastrointestinal mucosa [20], which could lead to rapid breakdown of vitamin C provided by the diet, and limit the impact of supplemental vitamin C on plasma vitamin C levels.

IV-iron may only be partially utilized for Hb synthesis in dialysis patients. A dose of 1 g iron could theoretically produce 300 g Hb, which should increase Hb to 15 g/dl, from a baseline value of 10 g/dl. But the usual outcome of a standard 1-gram course of IV-iron administered to hemodialysis patients is to increase Hb to only 11 g/dl [14, 21], which indicates that 20% of the iron was available for Hb production. In a 1-year study of chronic kidney disease patients (stage 3 renal failure), a 2.4-gram IV-iron regimen led to 10–20% of the predicted increment of Hb in the bloodstream [22]; the remainder may have gone into long-term storage in the reticuloendothelial system, and accumulation of large deposits of hepatic iron has been documented in hemodialysis patients after prolonged IV-iron therapy [23].

The interactions of vitamin C with intravenous iron complexes provide *in vitro* evidence for potentially positive actions of vitamin C supplements in hemodialysis patients. These iron complexes contain relatively little 'free' iron, about 1–5% [24], and there is probably limited immediate release of iron to the bloodstream after injec-

tion. The iron complexes are generally taken into the lysosomal apparatus within a few hours [25, 26], and the iron is released following decomposition of the complex within the storage cell [27]. However, at mildly acidic pH (ca. 4–5), which is the pH of the lysosomal vacuole [28], vitamin C can release large amounts of the iron content from the complexes, and as much as 60% of the iron can be solubilized in several hours [Handelman, in preparation]. Improved vitamin C status could assist in utilizing IV-iron after its uptake into the lysosome.

These actions of vitamin C have been exploited in several longitudinal studies that used intravenous vitamin C to improve erythropoiesis and decrease erythropoietin (EPO) requirements in patients with low Hb levels [29–31]. These investigators selected patients who required high-EPO doses and who had elevated ferritin levels, indicative of a state of EPO resistance. Intravenous vitamin C (1,000–3,000 mg/week) was able in many of these patients to reduce EPO requirements and increase blood Hb levels, although negative results have also been reported [32]. Similar effects of high plasma vitamin C were observed in a cross-sectional study of plasma vitamin C and EPO requirements [33].

### **Do Hemodialysis Patients Also Show Symptoms of Scurvy?**

Since dialysis patients can have plasma vitamin C concentrations of  $<10 \mu\text{M}$ , the occurrence of scurvy is a possible outcome. Dialysis patients often have gingivitis, which is usually diagnosed as periodontal disease [34], but vitamin C deficiency should be considered, since bleeding gums are a major scorbutic symptom. Dialysis patients frequently complain of fatigue; since fatigue is an

early symptom of scurvy [35], the role of vitamin C deficiency should be further explored [36]. Scurvy is also associated with increased bone resorption [37], and impaired resistance to infection. Many of the symptoms of scurvy are seen in dialysis patients, and therefore specific diagnosis has been difficult to achieve. To resolve this controversy, a controlled trial of vitamin C supplements in patients with low plasma vitamin C levels is warranted to examine its effect on scurvy-like symptoms.

### **Finding a Safe Path between Scylla and Charybdis**

Multiple factors contribute to vitamin C deficiency in dialysis patients: dietary restriction, losses during dialysis, and fear of oxalosis. This uncertainty is compounded by difficulties in measurement of plasma vitamin C, which is very unstable in the blood sample [38, 39]. Currently, plasma vitamin C is rarely determined. Standardized clinical methods for measuring plasma vitamin C are urgently needed, which would allow measurement of vitamin C to be done as a routine procedure to assess vitamin C status.

The improved Hb response to iron therapy seen in many patients indicates that there is a true Scylla of vitamin C deficiency; is there likewise a true Charybdis of oxalosis in hemodialysis patients? There has been no evidence for at least 10 years that dialysis patients are harmed by increased doses of vitamin C, but this worry persists among nephrologists. Controlled studies of the impact of vitamin C supplements on the occurrence of oxalate deposits are needed, and then perhaps we can show that the whirlpool has vanished with modern dialysis treatment, and practitioners can sail safely on with the use of supplemental vitamin C.

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