

The Role of Vitamin C in Orthopedic Trauma and Bone Health

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Abstract

Vitamin C is an essential micronutrient with an adult daily recommended intake of 75 mg for women and 90 mg for men. Smokers should consume an additional 35 mg per day because of the increased oxidative stresses from cigarette smoke.

Observational data support the hypothesis that high dietary intake and supplementation with vitamin C may reduce the risk of hip fractures in postmenopausal women.

Results of 2 high-quality trials support use of vitamin C 500 mg daily for 50 days as prophylaxis against complex regional pain syndrome after wrist fracture treated conservatively and operatively. Observational evidence exists for similar treatment after foot and ankle surgery.

The role of vitamin C in preventing osteoarthritis has tremendous potential, though results in animal and human studies are controversial. The heterogeneous results and the lack of prospective trials preclude any recommendation at this time.

teoarthritis. In this article, we review the basics of vitamin C metabolism and summarize the evidence surrounding the role of vitamin C supplementation in orthopedics.

Sources and Metabolism

Vitamin C is found naturally in many fruits and vegetables (Table 1) and is a common fortification in cereals, juices, and multivitamins. Daily recommended intake (Table 2) depends on age and smoking status. Absorption occurs in the distal small intestine, with blood plasma vitamin C concentrations reflecting dietary intake. Pharmacokinetic studies have shown that vitamin C concentrations are tightly regulated through absorption, tissue accumulation, and renal resorption, with plasma concentrations rarely exceeding 100 $\mu\text{mol/L}$ without additional supplementation.¹⁷ Although the usual dietary doses of 100 mg/d (adult) are almost completely absorbed, producing a plasma concentration of 60 $\mu\text{mol/L}$, higher intake results in an increasingly smaller fraction absorbed.^{1,18} Intake of more than 1000 mg/d results in less than 50% absorption¹⁹ (unmetabolized vitamin C is excreted in stool and urine¹). Even at higher doses, vitamin C has low toxicity³; the most common complaints are diarrhea, nausea, and abdominal cramps caused by the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract.¹

Vitamin C Deficiency

The relationship between vitamin C deficiency and the development of scurvy has been documented for centuries. Symptoms are described in the ancient Egyptian, Greek, and Roman literature.²⁰ Ascorbic acid is essential for normal collagen function, as it is a required cofactor for enzymatic transfer of hydroxyl groups to select proline and lysine residues during procollagen formation. Hydroxylysine contributes to the intermolecular cross-links in collagen, and hydroxyproline stabilizes the triple-helix structure of collagen.²¹ Insufficient vitamin C during this process results in collagen that is non-cross-linked, nonhelical, structurally unstable, and weak.²¹ Clinical manifestations of scurvy stem from an underlying impairment of collagen production causing a systemic decrease in connective tissue integrity, capillary fragility, poor wound healing, fatigue, myalgias, arthritis, and even death.²² Vitamin C deficiency has also been implicated as a cause of diffuse bleeding in surgical patients with normal coagula-

L-ascorbic acid, more commonly known as vitamin C, is an essential micronutrient used in numerous metabolic pathways. It functions physiologically as a water-soluble antioxidant by virtue of its high reducing power, playing a key role in the function of leukocytes, protein metabolism, and production of neurotransmitters.¹⁻³ Vitamin C also contributes to musculoskeletal health through biosynthesis of carnitine and collagen⁴ and enhancement of intestinal absorption of dietary iron⁵ from plants and vegetables. Unlike most animals, humans are unable to synthesize this essential vitamin and therefore require intake from natural dietary sources or supplements.⁶ The ability of vitamin C to prevent or treat disease has been an area of research interest since the vitamin was identified and isolated by Szent-Györgyi in the 1930s.⁷⁻¹⁶ Research in orthopedic surgery has focused on the effects of vitamin C on fracture healing, its potential use in preventing complex regional pain syndrome (CRPS), and its role in the pathophysiology of os-

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Table 1. Selected Food Sources for Vitamin C^a

Food Source	Milligrams (mg) per serving	Percent (%) DV ^b
Red pepper, sweet, raw, ½ cup	95	158
Orange juice, ¾ cup	93	155
Orange, 1 medium	70	117
Grapefruit juice, ¾ cup	70	117
Kiwifruit, 1 medium	64	107
Green pepper, sweet, raw, ½ cup	60	100
Broccoli, cooked, ½ cup	51	85
Strawberries, fresh, sliced, ½ cup	49	82
Brussels sprouts, cooked, ½ cup	48	80
Grapefruit, ½ medium	39	65
Broccoli, raw, ½ cup	39	65
Tomato juice, ¾ cup	33	55
Cantaloupe, ½ cup	29	48
Cabbage, cooked, ½ cup	28	47
Cauliflower, raw, ½ cup	26	43
Potato, baked, 1 medium	17	28
Tomato, raw, 1 medium	17	28
Spinach, cooked, ½ cup	9	15
Green peas, frozen, cooked, ½ cup	8	13

^aData from US Department of Agriculture (USDA) National Nutrient Database for Standard Reference;⁷⁵ table reprinted with permission from National Institutes of Health.⁷⁶
^bDV = Daily Value. DVs were developed by the US Food and Drug Administration (FDA) to help consumers compare the nutrient contents of products within the context of a total diet. The DV for vitamin C is 60 mg for adults and children aged 4 years and older. The FDA requires all food labels to list the percent DV for vitamin C. Foods providing 20% or more of the DV are considered to be high sources of a nutrient.

tion parameters secondary to capillary fragility.²³ In the United States, the 2003–2004 National Health and Nutrition Examination Survey (NHANES) measured serum vitamin C concentrations in 7277 noninstitutionalized patients 6 years old or older.²⁴ Age-adjusted incidence of subnormal serum vitamin C levels (<28 µmol/L) was 19.6%, and incidence of frank vitamin C deficiency (<11.4 µmol/L) was 7.1%. Reported rates of vitamin C deficiency in hospitalized patients are much higher, with 47% to 60% having subnormal values (<28 µmol/L) and 17% to 19% being vitamin C–deficient (<11.4 µmol/L).^{22,25} Identified risk factors for hypovitaminosis C include advanced age, obesity, low socioeconomic status, unemployment, male sex, and concomitant alcohol and tobacco consumption.^{22,24,25}

Table 2. Recommended Dietary Allowances for Vitamin C^a

Age, y	mg			
	Male	Female	Pregnancy	Lactation
1-3	15	15	—	—
4-8	25	25	—	—
9-13	45	45	—	—
14-18	75	65	80	115
19+	90	75	85	120
19+, smoker	125	110	120	155

^aData from Institute of Medicine, Food and Nutrition Board;⁷⁷ table reprinted with permission from National Institutes of Health.⁷⁸

Fracture Healing and Prevention

The effects of vitamin C deficiency on bone healing have been studied with animal models as early as the 1940s.^{26,27} Early experiments using guinea pigs demonstrated failure of bone graft incorporation, delayed collagen maturation, and decreased collagen and callus formation in scorbutic animals compared with controls that received vitamin C supplementation.^{26,27} Based on his work with guinea pigs, Bourne²⁶ reported in 1942 that vitamin C deficiency significantly inhibited the reparative process in damaged bone and that patients with fractures should receive vitamin C supplementation. Building on this early research, Yilmaz and colleagues²⁸ found faster histologic healing for tibia fractures in a rat model for animals that received a single injection of vitamin C 0.5 mg/kg compared with a nonscorbutic control group, and Sarisözen and colleagues²⁹ showed significantly accelerated histologic bone formation and mineralization at the fracture site for rats that received vitamin C supplementation. Moreover, Kipp and colleagues³⁰ found that scorbutic guinea pigs had lower bone mineral density (BMD), decreased bone mineral content, and impaired collagen synthesis of articular cartilage and tendons compared with nondeficient controls.

Besides promoting bone formation, vitamin C improves the mechanical strength of callus formation. Alcantara-Martos and colleagues³¹ used an osteogenic disorder Shionogi (ODS) rat model to examine the effects of vitamin C intake on femoral fracture healing. This particular animal model is unable to produce its own vitamin C. The groups with lower serum vitamin C levels demonstrated lower mechanical resistance of the fracture callus to torsional loads 5 weeks after fracture. Moreover, the group that received vitamin C supplementation showed higher histologic grade of callus formation and demonstrated faster healing rates. The authors suggested that subclinical vitamin C deficiency can delay fracture healing and that vitamin C supplementation in nondeficient patients would improve bone healing.

Other research has demonstrated a link between vitamin C and mesenchymal cell differentiation. Mohan and colleagues³² used an *sfx* mouse model to show that vitamin C deficiency results in decreased bone formation secondary to impaired

osteoblast differentiation, diminished bone density, and development of spontaneous fractures. The authors indicated that not only is vitamin C essential for maintenance of differentiated functions of osteoblasts, but deficiency during early active growth may affect peak BMD levels in humans. Additional studies have demonstrated the role of vitamin C in endochondral bone formation through both induction of osteoblast differentiation and modulation of gene expression in hypertrophic chondrocytes.³³⁻³⁶ Chronic vitamin C deficiency has been found to depress osteoblast function and differentiation of chondrocytes.³⁷ More recently, Kim and colleagues³⁸ examined the effect of vitamin C insufficiency in *GULO*-deficient mice, which are unable to synthesize ascorbic acid. Ascorbic acid insufficiency over 4 weeks led to decreased plasma levels of osteocalcin and bone formation in vivo as well as significantly diminished metaphyseal trabecular bone. Despite all the evidence demonstrating the importance of vitamin C in bone formation and maintenance, many of the underlying processes in this relationship have yet to be determined.

Bone Mineral Density

Several observational studies have found a positive association between vitamin C intake and BMD in postmenopausal women. In a retrospective, cross-sectional study by Hall and Greendale,³⁹ a positive association was found between vitamin C intake and BMD of the femoral neck in 775 participants in the Postmenopausal Estrogen/Progestin Interventions trial. After calcium intake, physical activity level, smoking, estrogen use, age, and body mass index were adjusted for, each 100-mg increase in dietary vitamin C was associated with a 0.017 g/cm² increase in BMD. Wang and colleagues⁴⁰ found a positive association between dietary vitamin C intake and femoral neck BMD in a retrospective analysis of 125 postmenopausal Mexican American women. Other observational studies have reported that decreased intake of vitamin C is associated with osteoporosis⁴¹ and increased rates of BMD loss⁴² and that supplementation with vitamin C may suppress bone resorption in postmenopausal women.⁴³

The results of these studies contrast with the findings of Leveille and colleagues,⁴⁴ who examined the relationship between dietary vitamin C and hip BMD in 1892 postmenopausal women. Although the authors found that women (age, 55-64 years) using vitamin C supplements for more than 10 years had an average BMD 6.7% higher than that of nonusers, they did not find any association between dietary vitamin C intake and BMD. Moreover, NHANES III also found inconsistent associations between vitamin C and BMD among 13,080 adults surveyed in the United States.⁴⁵ Although for premenopausal women dietary ascorbic acid was associated with increased BMD, for postmenopausal women with a history of smoking and estrogen replacement, it was actually associated with lower BMD values. For other subgroups in the study, the relationship was also inconsistent or nonlinear.

The exact mechanism by which ascorbic acid contributes to BMD is not fully delineated. However, it likely is related to the known role of vitamin C in collagen formation, bone matrix

development, osteoblast differentiation, and its antioxidant effects limiting bone resorption.^{44,46}

Hip Fractures

Besides demonstrating positive effects of vitamin C on bone healing and BMD, epidemiologic studies have found evidence of a protective effect of vitamin C on hip fracture risk. In a study of the Swedish Mammography cohort, 66,651 women (age, 40-76 years) were prospectively followed.⁴⁷ The authors found that the odds ratio (OR) for hip fractures among smokers with a low intake of vitamin E (median intake, ≤ 6.2 mg/d) was 3.0 (95% CI, 1.6-5.4) and for vitamin C (median intake, ≤ 67 mg/d) was 3.0 (95% CI, 1.6-5.6). Moreover, in smokers with a low intake of both vitamins E and C, OR increased to 4.9 (95% CI, 2.2-11.0). In addition, the Utah Study of Nutrition and Bone Health matched 1215 cases of hip fractures in patients who had ever smoked (age, >50 years) with 1349 controls and found that vitamin C intake above 159 mg/d had a significant protective effect on the incidence of hip fracture; however, a graded relationship was not observed.⁴⁸ Despite the inconsistencies in the NHANES III study regarding the relationship between vitamin C and BMD, Simon and Hudes⁴⁵ found that serum vitamin C was associated with lower risk for self-reported fracture in postmenopausal women who had ever smoked and had a history of estrogen therapy (OR, 0.51; 95% CI, 0.36-0.70). Finally, Sahni and colleagues⁴⁹ followed 958 Framingham cohort men and women (mean age, 75 years) over 17 years and found that those in the highest tertile of total vitamin C intake (median, 313 mg/d) had significantly fewer hip fractures and nonvertebral fractures compared with those in the lowest tertile of intake (median, 94 mg/d). Dietary vitamin C intake was not associated with fracture risk in this study.

Complex Regional Pain Syndrome

Type 1 CRPS is a debilitating condition characterized by severe pain, swelling, and vasomotor instability. It is commonly precipitated by an injury or surgery to an extremity and is a dreaded sequelae in orthopedics,⁵⁰ with incidence rates of 10% to 22% in wrist fractures⁵¹⁻⁵³ and 10% after foot and ankle surgery.⁵⁴ Although the pathophysiology of CRPS remains unknown, dysregulation and increased permeability of the vasculature caused by free radicals are thought to play an important role.⁵⁵ In dermal burns, high doses of vitamin C therapy slowed progression of vascular permeability and therefore reduced extravascular leakage of fluids and protein.^{56,57} The ability of vitamin C to prevent CRPS has been studied in only a handful of trials.

In a double-blind trial, Zollinger and colleagues⁵¹ randomized 127 conservatively treated distal radius fractures to receive either vitamin C 500 mg or placebo daily for 50 days starting on day of injury. Incidence of CRPS (using the diagnostic criteria proposed by Veldman and colleagues⁵⁸) at 1-year follow-up was 22% in the placebo group and 7% in the vitamin C group (95% CI for difference, 2%-26%). Complaints while wearing the cast and fracture type increased the risk for developing CRPS. This initial study was followed up by a prospective, ran-

domized, double-blind multicenter trial by the same authors,⁵² who had 416 patients with 427 wrist fractures receive either placebo or vitamin C 200 mg/d, 500 mg/d, or 1500 mg/d for 50 days. This follow-up study included both operative (11%) and nonoperative (89%) distal radius fractures. Incidence of CRPS was 10.1% in the placebo group and 2.4% in the vitamin C group ($P < .002$). Although there was an appreciable drop in the relative risk (RR) of developing CRPS between the vitamin C 200-mg/d and 500-mg/d groups (0.41-0.17), there was no additional benefit in the 1500-mg/d group. Pooling the data for these 2 randomized trials showed that the overall RR for developing CRPS was lower with vitamin C supplementation (RR, 0.28; 95% CI, 0.14-0.56; $P = .0003$).⁵⁹

Results of the 2 trials by Zollinger and colleagues^{51,52} have been met with several concerns.⁶⁰⁻⁶² As a corollary to the unclear etiology of CRPS, several different sets of diagnostic criteria exist, and the criteria are somewhat subjective and imprecise. Although both trials used the Veldman criteria,⁵⁸ the incidence of CRPS in the placebo group dropped unexpectedly between trials, from 22% to 10.1%, and the results may have been different had other criteria been used. Moreover, the idea that toxic oxygen radicals have a role in CRPS and that vitamin C can scavenge these radicals is based on limited data.⁶¹ In the absence of a clear pathophysiologic explanation, some surgeons have been reluctant to treat patients with vitamin C supplementation.

Cazeneuve and colleagues⁵³ also studied the effect of vitamin C supplementation on CRPS in patients with distal radius fractures treated with reduction and intrafocal pinning. Group 1 consisted of 100 patients (treated from 1995 to 1998) who did not receive vitamin C supplementation, and group 2 consisted of 95 patients (treated from 1998 to 2002) who received vitamin C 1000 mg/d for 45 days starting on day of fracture. Patients were followed for up to 90 days after surgery. Incidence of CRPS type 1 was 10% in the untreated group and 2.1% in the group that received vitamin C supplementation.

Vitamin C prophylaxis for CRPS has also been studied in foot and ankle surgery. Besse and colleagues⁵⁴ prospectively compared 2 chronologically successive groups that received (235 feet) or did not receive (185 feet) vitamin C 1000-mg/d supplementation for 45 days. Incidence of CRPS type 1 as diagnosed with International Association for the Study of Pain (IASP) criteria dropped from 9.6% to 1.7% with vitamin C supplementation. In a case series, Zollinger and colleagues⁶³ examined CRPS type 1 rates after performing cementless total trapeziometacarpal semiconstrained joint prosthesis implantations for trapeziometacarpal arthritis. Forty implantations were performed in 34 patients. All patients received vitamin C 500 mg/d for CRPS prevention starting 2 days before surgery for 50 days. There were no cases of CRPS in the postoperative period, according to Veldman or IASP criteria. Although the results of the studies by Cazeneuve and colleagues⁵³ and Besse and colleagues⁵⁴ agree with those of the distal radius fracture trials by Zollinger and colleagues,^{51,52} the quasi-experimental design and the lack of blinding and randomization temper the conclusions that can be drawn because of the risk for significant bias.

In a recent systematic review examining the effectiveness of

vitamin C supplementation in preventing CRPS in trauma and surgery in the extremities, Shibuya and colleagues⁶⁴ concluded that taking at least 500 mg of vitamin C daily for 45 to 50 days after injury or surgery may help decrease the incidence of CRPS after a traumatic event.

Osteoarthritis

Damage caused by free radicals has long been thought to play an important role in osteoarthritis (OA).⁶⁵⁻⁶⁷ A cross-sectional study in knee OA found that amounts of joint fluid antioxidants were lower in patients with severe arthritis than in those with intact cartilage, further implicating free radicals in the pathophysiology of OA.⁶⁸ Use of vitamin C for prophylaxis against development or progression of OA is therefore a hot research topic. Thus far, animal studies have had mixed results—several showing a chondroprotective effect of vitamin C^{69,70} and others finding either no effect or even a positive association with the development of arthritis.⁷¹

The literature on human subjects, chiefly observational studies, is just as controversial. Wang and colleagues⁴⁰ found vitamin C intake associated with both a 50% risk reduction of bone marrow lesions on magnetic resonance imaging over a 10-year interval (OR, 0.5; 95% CI, 0.29-0.87) and inversely associated with the tibial plateau bone area. Similarly, the Clearwater Osteoarthritis Study, which followed 1023 patients (age, >40 years), showed that participants who took vitamin C supplements were 11% less likely to develop radiographic evidence of OA (RR, 0.89; 95% CI, 0.85-0.93).⁷² Nonetheless, other studies have failed to show such associations⁷³ or have demonstrated the opposite effect. Chaganti and colleagues⁷⁴ analyzed levels of vitamins C and E in the Multicenter Osteoarthritis Study (MOST) cohort of 3026 men and women (age, 50-79 years) and found higher vitamin levels were not protective against incidence of radiographic whole-knee OA and may even have been associated with increased risk.

Conclusion

Vitamin C is an essential micronutrient and a powerful water-soluble antioxidant in numerous biochemical pathways that influence bone health. It has been implicated in the biology of fracture healing, and vitamin C supplementation has been proposed as prophylaxis against hip fractures based on observational data. Results of 2 high-quality double-blind randomized trials support use of vitamin C as prophylaxis against CRPS in wrist fractures treated conservatively and operatively; the evidence for foot and ankle surgery is weaker. Use of vitamin C in OA prevention has tremendous potential, though animal and human study results are controversial. Heterogeneous results and lack of prospective trials preclude any recommendation at this time.

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