Vitamin C Function and Status in Chronic Disease

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■ **ABSTRACT**

Vitamin C is an essential dietary nutrient required as a co-factor for many enzymes, and humans are among the few animals that lack the ability to synthesize the compound from glucose. The reduced form of the vitamin, ascorbic acid, is an especially effective antioxidant owing to its high electron-donating power and ready conversion back to the active reduced form. Concentrations of the vitamin in body tissues and fluids are regulated through interactions of intestinal absorption, cellular transport, and excretion. The amount of vitamin C needed to prevent scurvy is very small and easily obtained in nearly all Western diets. There is great interest in the clinical roles of vitamin C because of evidence that oxidative damage is a root cause of, or at least associated with, many diseases. Population studies show that individuals with high intakes of vitamin C have lower risk of a number of chronic diseases, including heart disease, cancer, eye diseases, and neurodegenerative conditions. However, these results may simply reflect a more healthful diet or lifestyle for individuals with a high vitamin C intake. At present, data from controlled clinical trials have not established that higher intakes of vitamin C alone will help prevent chronic degenerative diseases. However, the evidence that ascorbic acid acts as an important antioxidant in many body tissues is convincing. The new higher Recommended Dietary Allowance (RDA) for vitamin C of 75 mg for women and 90 mg for men is, for the first time, based on the vitamin's role as an antioxidant as well as protection from deficiency. In healthy people, amounts greater than the RDA do not appear to be helpful. Vitamin C nutriture may be more important for people with certain diseases or conditions. High intakes of the vitamin are generally well tolerated; a Tolerable Upper Level was recently set at 2 g based on gastrointestinal upset that sometimes accompanies excessive intakes. *Nutr Clin Care.* 2002;5:66–74 ■

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BIOCHEMISTRY, METABOLISM, AND PHYSIOLOGIC FUNCTION

Vitamin C is a water-soluble vitamin that exists in the body primarily in its reduced form, ascorbic acid. The oxidized from of the vitamin, dehydroascorbic acid (DHA), also has antiscorbutic (scurvy preventive) activity because it is easily reduced intracellularly to ascorbic acid (Figure 1). The ability of the vitamin to provide electrons and be readily converted back to its reduced form by glutathione accounts for its particular effectiveness as an in vivo antioxidant.

The intestinal absorption of ascorbic acid is regulated by a dose-dependent active transport process.[1] At nutritional intakes of 30–180 mg per day approximately 70–90% is absorbed, whereas absorption falls to less than 50% at intakes greater than 1 g per day. The vitamin is transported into

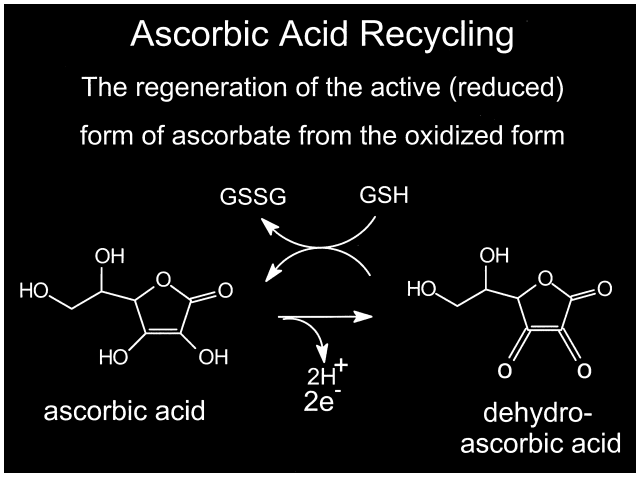

Figure 1. Oxidation of ascorbic acid to dehydroascorbic acid and reversible reduction of dehydroascorbic acid by glutathione (GSH). GSSG = oxidized glutathione.

cells primarily as DHA, and is reduced intracellularly to ascorbic acid. Of the 2 optical isomer forms, only the L form naturally occurs. The D form, isoascorbic or erythorbic acid, provides antioxidant but little or no antiscorbutic activity.

Because metabolism of the vitamin is regulated by several mechanisms, small intakes are conserved and large amounts can be tolerated without ill effects.[2] Absorption is efficient at vitamin C intakes below 100 mg per day, and little or no ascorbate is excreted in the urine. The oxidized or "spent" form of the vitamin is readily reduced back to ascorbic acid so that only small amounts are lost through catabolism (5–45 mg per day). At larger intakes, absorption becomes less efficient and unmetabolized ascorbic acid is excreted in the urine. Total human body content of the vitamin ranges from 300 mg at near scurvy to a maximum of approximately 2 grams. The concentration of the vitamin in body tissues and fluids varies greatly, with high levels maintained in leukocytes, eye, adrenals, pituitary, and brain, whereas low levels are found in plasma and saliva.

Vitamin C functions physiologically as a reversible reductant and antioxidant in the aqueous fluid and tissue compartments. The vitamin is specifically required for the activity of 8 human enzymes involved in collagen, hormone, amino acid, and carnitine synthesis or metabolism.[3] As a co-factor for prolyl and lysyl hydroxylases, ascorbate is an essential part of the molecular cross-linking that gives collagen its elasticity. The importance of ascorbate for connective tissue synthesis is indicated by physical symptoms of scurvy that involve deterioration of elastic tissue: bleeding gums, petechiae, and joint pain.

Ascorbic acid is also involved in the synthesis or modulation of some components of the nervous system, the microsomal drug-metabolizing system, synthesis of corticosteroids and carnitine, and conversion of cholesterol to bile acids.[4]

Because of its ability to donate electrons and be readily regenerated, ascorbate is an effective antioxidant *in vivo.* The vitamin efficiently neutralizes reactive oxygen and nitrogen species such as hydroxyl, peroxyl, and superoxide radicals, as well as peroxynitrite, nitroxide radicals, singlet oxygen, and hypochlorite.[5] This action provides direct antioxidant protection to tissues subjected to high free-radical stress such as phagocytes, eye, brain, stomach, and sperm. The vitamin also provides antioxidant protection indirectly by regenerating other biologic antioxidants such as glutathione, α-tocopherol, and flavonoids to their active state.

VITAMIN C AND IMMUNE FUNCTION

The many roles that vitamin C plays in immune response can be broadly classified into 2 functional areas: (1) the role of ascorbic acid in neutralizing reactive oxygen species created by phagocytes during their oxidative destruction of foreign microbes and (2) effects of ascorbate on various components of the immune system. The importance of ascorbate as a protective antioxidant during leukocyte phagocytosis was used as part of the justification for the new higher Recommended Dietary Allowance (RDA) for vitamin C: 75 and 90 mg for adult women and men, respectively.[5]

The critical antioxidant role of vitamin C in cell-mediated immune function is indicated by its tightly controlled regulation in leukocytes. Vitamin C is concentrated in leukocytes by a facilitated cellular transport system that results in leukocyte ascorbate concentrations among the highest in the body. Leukocytes are especially effective in recycling ascorbate, for example, regenerating the active reduced form of the vitamin (ascorbic acid) from the spent or oxidized form (dehydroascorbic acid).[1] Exposure of isolated neutrophils to microbial pathogens increases the rate of ascorbate recy-

cling up to 30-fold. *In vitro* studies show that ascorbate effectively neutralizes reactive oxidants created by phagocytes to destroy invading bacteria. Concentrations of ascorbate normally found in plasma have been shown to inhibit the potentially damaging effects of hypochlorous acid and superoxide, two of the powerful oxidants generated by activated neutrophils and monocytes, without hampering bactericidal activity.[5]

In vitro evidence indicates that vitamin C may modulate leukocyte phagocytic action, blastogenesis, immunoglobulin production, chemotaxis, and adhesiveness.[6] Overall, the results have generally not been consistent in that some studies report positive effects of the vitamin, whereas others report no effect. In clinical studies, many of the above immune functions were stimulated; however, a similar mix of positive and no-effect results are reported. Of studies that tested the effect of vitamin C supplements given to healthy adults, both positive and no-effect results were noted for measures of cell-mediated immunity, for example, lymphocyte proliferation capability and delayed dermal sensitivity. This mix of results was seen in studies of the elderly as well as younger adults. In the only human-depletion experiment, vitamin C deficiency resulted in decreased delayed dermal sensitivity but had no effect on lymphocyte proliferation capability.[5] Trials to assess the effect of pharmacologic doses of vitamin C (≥1 g per day) on the occurrence and course of the common cold showed no effect or only a modest benefit to duration or severity in some groups.[7] Among special populations, vitamin C supplements have been reported to decrease the incidence of upper respiratory infections in runners[8] and the immune response of patients with staphylococcus-infected boils.[9]

In summary, the evidence indicates that vitamin C plays an important role in immune function. Mechanisms for such roles are largely unknown, but likely include the vitamin's antioxidant effects, direct antimicrobial action, and/or effects on various immune system modulators such as histamine and prostaglandins. The mixed results seen for *in vitro* and clinical studies are likely due to methodological differences in assessing immune functions, and to the study of well-nourished individuals who therefore show no response to additional vitamin C intake.

HUMAN NUTRITION

Deficiency Syndromes

Severe vitamin C deficiency leads to scurvy, which is characterized by swollen and bleeding gums, follicular hyperkeratosis, petechiae, ecchymoses, impaired wound healing, joint effusions, arthralgia, dry eyes and mouth, coiled hairs, depression, and sudden death.[5,10] Fatigue and inflammation of the gums are two early signs of vitamin C deficiency.[5] Impaired collagen synthesis is believed to be responsible for the connective tissue and hemorrhagic manifestations of scurvy. In addition, because of low plasma ascorbate, oxidative damage to some blood coagulation factors may contribute to hemorrhagic symptoms.[5] Alterations in iron or carnitine metabolism may be involved in scorbutic weakness and fatigue. Impaired neurotransmitter synthesis and metabolism may be involved in psychological symptoms.[2] Scurvy develops with serum ascorbate concentrations of less than 12 μmol/L (0.2 mg/dL) and leukocyte concentrations of less than 410 μmol/L (7 mg/dL).[11] Vitamin C deficiency in infants (Moeller-Barlow disease) leads to impaired bone formation, hemorrhagic symptoms, and anemia.[5,11] Although scurvy is rare in developed countries, it is sometimes seen in people with low consumption of fruits and vegetables, those with special or poor diets, and those involved in alcohol or drug abuse. In the United States, men—especially elderly men—have lower blood ascorbate concentrations than women, and vitamin C deficiency is more prevalent in low socioeconomic groups.[5] Blood ascorbate levels are higher in premature fetal blood and decline rapidly after birth.[12] Human milk is sufficient in vitamin C and formulas are fortified with the vitamin such that scurvy in infants is rare.[2]

Dietary Requirement and Intakes

The minimum vitamin C requirement to prevent scurvy is approximately 10 mg per day.[5] The previous RDA for vitamin C, 60 mg per day for adults, aimed to provide a total body pool of ascorbate (eg, 900–1,500 mg) that prevented scurvy for several weeks during low vitamin C intake and periods of physiologic or other stress that may increase the requirement.[5] To provide antioxidant protection, the new RDA for vitamin C was set at 75 mg per day for females and 90 mg per day for males.[5] This

intake should maintain near-maximum neutrophil ascorbate concentrations with little urinary excretion. Because women have smaller lean body mass and maintain higher plasma ascorbate concentrations at a given intake, it was estimated that they have a lower vitamin C requirement than men.[5] A recent report providing leukocyte ascorbate data, however, argues that women have the same requirement as men and that their RDA should be increased to 90 mg per day.[13]

Some epidemiologic studies have shown that elderly, especially institutionalized elderly, have lower vitamin C status than young adults.[5] These low levels were mainly due to low dietary intake; however, low levels in institutionalized elderly may be due to clinical conditions such as recurrent infections. A decline in plasma ascorbate with age was not found in other studies. The RDA for vitamin C for the elderly is therefore the same as that for the young adult.[5]

In most studies, smokers had lower plasma ascorbate levels than nonsmokers, even after adjustment for vitamin C intake.[5] This is due to increased ascorbate catabolism or use owing to the oxidative stress of smoking.[2] In one study, moderate vitamin C supplementation of smokers significantly increased plasma ascorbate.[14] Smokers are estimated to require an additional 35 mg per day of vitamin C.[5] Passive smoke exposure also decreases plasma ascorbate levels, so intake of the full vitamin C RDA is advised for individuals with regular exposure.[5]

In pregnancy, hemodilution and active transfer of vitamin C to the fetus causes a decline in plasma ascorbate levels. Vitamin C deficiency during pregnancy is associated with increased risk of infections, premature rupture of the membranes, premature birth, and eclampsia. Therefore, the requirement for pregnant women is estimated to be 10 mg per day higher than for nonpregnant women.[5] On average, vitamin C produced in milk during the first 6 months of lactation provides 40 mg per day.[15] *Lactating women* require 115 (≤18 years old) or 120 (>18 years old) mg per day of vitamin C.[5]

Status Assessment Methods

There are no reliable functional tests to determine human vitamin C status. Status assessment is therefore mainly based on static methods. Measurements of plasma and leukocyte ascorbate levels are the most practical and reliable static tests. Assessment of total body vitamin C pool or measurement of changes in serum ascorbate or urinary ascorbate excretion following an oral vitamin C load can provide more information, but these tests are not practical for large-scale population studies. Plasma ascorbate levels correlate directly with recent dietary vitamin C intake and with leukocyte ascorbate levels.[2] The response of leukocyte levels to dietary vitamin C intake is slower, but leukocyte ascorbate levels better reflect ascorbate tissue content and the body pool. The plasma ascorbate test is easy, reliable, and requires less blood, and is therefore preferred for large population studies. Measurements of whole-blood or erythrocyte ascorbate levels are less sensitive indicators of vitamin C deficiency. Urinary ascorbate levels are not good status measures because they do not correlate linearly with vitamin C intake. Lack of urinary ascorbate, however, can confirm severe vitamin C deficiency. Guidelines for interpreting plasma and leukocyte ascorbate concentrations are shown in Table 1.

VITAMIN C AND CHRONIC DISEASE

Vascular Disease

Vitamin C, especially with tocopherol, inhibits low-density lipoprotein oxidation, a process that is believed to be involved in the formation of atherosclerotic plaques.[11] In several epidemiologic studies, plasma ascorbate levels were inversely associated with coronary vascular disease (CVD) and stroke.[5,16] In the Second National Health and Nutrition Examination Survey (NHANES), the relative risk of CVD and stroke was decreased by 26% with serum ascorbate concentrations of 63–153 μmol/L (1.1–2.7 mg/dL) compared with concentrations of 6–23 μmol/L (0.1–0.4 mg/dL).[5] Lower vitamin C status is related to several CVD risk factors, such as male gender, age, smoking, hypertension, high serum total cho-

Table 1. Guidelines for Interpretation of Blood Vitamin C Concentrations[2]

	Plasma μmol/L (mg/dL)	Mixed Leukocytes nmol/10^8 cells (μg/10^8 cells)
Adequate	> 23 (> 0.4)	> 114 (> 20)
Low	11.4–23 (0.2–0.4)	57–114 (10–20)
Deficient	< 11.4 (< 0.2)	< 57 (< 10)

lesterol, and low high-density lipoprotein levels.[11] However, these population studies can not establish causality. High dietary intake of vitamin C is a marker for a healthful diet or lifestyle. Data from clinical trials are therefore needed to determine the effect of vitamin C intake on CVD.

Many studies have shown beneficial effects of high doses of ascorbic acid on endothelial-dependent vasodilation.[17,18] In four studies, 1,000–2,000 mg of oral ascorbic acid or 25 mg per minute of ascorbic acid infusion increased vasodilation 45–220% in patients with CVD. Similar results were found in patients with diabetes, hypercholesterolemia, and hypertension, as well as in healthy adults.[17–20] Ascorbic acid improves both endothelial function and insulin sensitivity in patients with CVD.[21] The mechanism by which ascorbic acid improves vasodilation has not been definitively established, but this effect is attributed to the vitamin's ability to promote the synthesis and/or prevent the oxidative degradation of the endothelial-derived relaxing factor, nitric oxide (NO).[18] Some beneficial effects of ascorbic acid supplements on thrombotic risk of CVD and impaired endothelial function in women with pre-eclampsia have also been reported.[17,22] In other studies, vitamin C intake was not associated with a lower risk of CVD.[5] A randomized placebo-controlled trial of the effect of vitamins C and E on 3-year progression of carotid atherosclerosis in Finnish adults showed significant benefit from combined vitamin C and E supplementation, but not with either vitamin C or E alone.[23]

Cancer

Most case-control studies have found an inverse association between vitamin C intake from fruits and vegetables and cancers of the oral cavity, larynx-pharynx, esophagus, lung, stomach, and colon-rectum.[17] Of the hormone-dependent cancers, only breast cancer was inversely associated with vitamin C intake. In cohort studies, an inverse relationship between vitamin C intake and cancer risk was seen in populations consuming up to approximately 110 mg per day, but the relationship was generally not found in populations consuming higher intakes. This suggests a level of vitamin C intake above which tissues may be saturated and can derive no further benefit toward cancer prevention.[17] Antioxidant action of ascorbic acid inhibits the formation of carcinogenic N-nitroso compounds that are implicated in gastric and lung cancer.[17] Vitamin C is actively secreted in the gastric juice, and patients with gastritis and *Helicobacter pylori* infection have decreased gastric juice ascorbate. Results from several studies indicate that vitamin C supplementation of these patients increases gastric ascorbate, decreases cancer biomarkers and oxidative damage in the gastric mucosa, and may decrease gastric cancer risk.[5] In intervention trials, by contrast, ascorbic acid supplementation had no effect on colorectal adenoma and stomach cancer.[16] Some evidence suggests that vitamin C may help prevent cancer by enhancing the immune response and accelerating the detoxification of carcinogens.[24]

Diabetes

Diabetic patients have lower plasma ascorbate levels and altered turnover of the vitamin that cannot be explained by low dietary intake.[2,10] Evidence suggests that oxidative stress has an important role in diabetic complications, and increased oxidative stress and hyperglycemia may accelerate *in vivo* ascorbate destruction.[2,11] In one study, ascorbic acid supplementation resulted in improvement of glycemic control and vascular health, and decreased glycosylated hemoglobin and erythrocyte sorbitol.[10] Results of another study suggest that supplementation with ascorbic acid may modulate insulin activity in diabetic patients.[11]

Eye Disease

The eye contains a high ascorbate concentration that protects against photolytically generated free-radical damage that may lead to cataracts and macular degeneration.[2] Two case-control studies indicated 70–75% reduced risk of cataract with vitamin C intakes of greater than 300 mg per day. In addition, plasma ascorbate concentrations greater than 90 μmol/L were associated with a 71% lower risk of cataract. The results of ascorbic acid supplementation for 10 years or more showed risk reductions of greater than or equal to 45%.[17] In one clinical trial, however, intake of 120 mg per day in conjunction with 30 μg Mo per day for 5 years had significant benefit only when it was consumed with a multivitamin and mineral supplement.[17] The results of NHANES I showed that high intakes of vitamin A and vitamin C were inversely associated with mac-

ular degeneration, but this was not confirmed in clinical trials.[25] Lens concentrations of ascorbate are affected by vitamin C intake. Intakes between 150 and 250 mg per day may saturate eye tissues.[17] However, some adverse effects of ascorbic acid supplementation on lens opacities owing to the Maillard reaction or ascorbate metabolism byproducts have been suggested.[2]

Neurodegenerative Diseases

Iron-induced oxidative stress has been implicated in the pathogenesis of Parkinson's and Alzheimer's diseases.[26] Accordingly, high levels of ascorbate in the brain may be important for protection against oxidative damage.[2] Two studies revealed lower plasma ascorbate concentrations in patients with Alzheimer's disease despite adequate dietary intake.[17] A prospective study in 633 people 65 years of age or older showed that consumption of high-dose vitamin E and vitamin C supplements may lower the risk of Alzheimer's disease.[27] In addition, a pilot study of high-dose ascorbic acid and α-tocopherol indicated that the point at which levodopa became necessary for patients with Parkinson's disease was delayed by antioxidant treatment.[11] By contrast, some evidence suggests that ascorbic acid *in vitro* may exert a pro-oxidant effect in brain tissue under certain conditions.[2]

OTHER DISEASES AND CONDITIONS

Asthma and Respiratory Conditions

Along with glutathione, ascorbic acid is one of the major antioxidants in lung tissue and lining fluid.[28] Antioxidant protection in the lung is important because of its constant exposure to oxygen and reactive air pollutants such as ozone and nitrogen oxides. Ascorbate also protects against secondary oxidative damage that may result from lung phagocytes activated by the immune/inflammatory response. Decreased concentrations of ascorbate have been reported in the lung lining fluid of persons with mild asthma[29] and ozone exposure.[30] In addition to its possible role as a protective antioxidant, vitamin C may improve respiratory function or airway reactivity by virtue of its antihistamine effect, or its ability to improve bronchial smooth muscle relaxation via modulation of prostaglandin and/or NO synthesis.[28]

Results of some population studies have shown direct links between vitamin C nutriture and improved pulmonary function or airway reactivity.[31] In cross-sections of European populations, 1-second forced expiratory volumes and forced vital capacity were directly related to vitamin C intake or blood plasma ascorbate concentrations in both women and men.[32,33]

Results from clinical trials testing the effect of vitamin C supplementation on lung function and airway reactivity have been mixed. Administration of the vitamin to asthmatics resulted in beneficial effects in some trials and no effects in other trials.[28] Vitamin C supplements reduced airway reactivity to exercise in 9 of 20 patients, but did not affect at-rest airway reactivity as observed in other studies.[34] Modest vitamin C supplementation of 200 mg per day in elderly hospital patients admitted with acute respiratory infections resulted in significantly increased leukocyte ascorbate concentrations and improved clinical outcomes in those receiving the vitamin as opposed to those who received a placebo.[35] Overall, the evidence shows that vitamin C is an important antioxidant for lung tissue and that increased vitamin C intake may benefit some individuals with respiratory or airway reactive conditions, especially those with low vitamin C status.

Periodontal Health

As discussed, clinical symptoms of scurvy include inflamed and bleeding gums, which are likely due to reduced activity of ascorbate-requiring enzymes involved in the cross-linking of collagen. Vitamin C deficiency can adversely affect the permeability of the gingival sulcular epithelium as well as the structural integrity of gingival tissue.[36] Experimental studies support the conclusion that severe or moderate vitamin C deficiency is associated with increased gingival inflammation and bleeding.[37] Gingival deterioration during vitamin C deficiency appears to be due to negative effects on the gingival structural and/or microvascular tissue rather than alterations in the pathogenic microflora associated with gingivitis.[38] However, supplemental vitamin C given to well-nourished populations generally has shown little or no affect on periodontal integrity or risk of developing gingivitis.[39] Epidemiologic studies have mostly shown no relationship between vitamin C intake and periodontal disease;[36]

however, analysis of NHANES III survey data showed a weak, but statistically significant, relationship between vitamin C intake and periodontal disease in former and current smokers.[40] Overall, the data suggest that improving vitamin C nutriture may ameliorate some aspects of periodontal disease in individuals with low vitamin C intake, but likely has little effect on the large segment of the population that is well nourished.

Fertility

Some evidence suggests that vitamin C plays a role in reproductive function and that additional vitamin C intake may improve fertility in some individuals. Ascorbate accumulates in both ovary and testis, and treatment of some men with vitamin C supplements improved sperm qualities and reproductive outcome.[41] Proposed mechanisms by which vitamin C may affect reproductive functions include its role as an antioxidant and as a co-factor for collagen and hormone synthesis.[42]

Other Conditions

Vitamin C has been reported to be involved in a variety of other disease conditions.[2,10] As a co-factor for collagen synthesis, ascorbic acid is one of the micronutrients that is important for wound and burn healing. Low plasma ascorbate concentrations along with high levels of malondialdehyde (a lipid peroxidation product) have been reported in ambulatory peritoneal dialysis patients.[43] Results from a rat study suggest that vitamin C treatment may improve the microvascular dysfunction of patients with septic syndrome.[44] Vitamin C supplements have been reported to benefit patients suffering from pancreatitis and certain bone diseases. Vitamin C status has been linked to *other conditions*, including anemia, heavy metal toxicity, mental depression, idiopathic thrombocytopenic purpura, gastrointestinal ulcers and hemorrhage, menorrhagia, habitual abortion, premature birth, and premature rupture of fetal membranes.

TOXICITY

Ascorbic acid provokes little or no ill effects even when taken in gram amounts.[45] This is due to the nontoxic nature of the vitamin and the body's ability to regulate physiologic concentrations by alterations in intestinal absorption, renal excretion, and cellular transport. With very large doses (>3 g), ascorbate that is not absorbed in the upper intestine may cause osmotic diarrhea and gastrointestinal disturbances. This is the basis for setting the Tolerable Upper Level (UL) for adults at 2 g per day.[5] The UL is the highest level of daily nutrient intake likely to pose no risks of adverse health effects in almost all individuals.

A variety of adverse effects have been suggested to occur with very high intakes (>1g per day) but the totality of evidence does not currently support such effects as legitimate concerns. Because catabolism of ascorbate produces oxalate, ingestion of large amounts of the vitamin may increase plasma or urine oxalate, and this has raised concern about increased risk for renal stone formation. However, controlled studies of large populations of healthy women and men showed no associations between high vitamin C intakes and kidney stones.[46,47]

High concentrations of ascorbate, especially in combination with the redox active metals iron or copper, provoke oxidant damage in many *in vitro* systems; however, this adverse effect has not been shown to occur *in vivo.* High vitamin C doses given to guinea pigs[48] and healthy adults[49–51] (even those with iron overload) resulted in antioxidant rather than pro-oxidant effects. Other unsubstantiated reports of adverse effects of large vitamin C intakes include systemic conditioning, excess iron absorption, and vitamin B_{12} antagonism. Renal-stone formers and people with hemochromatosis and glucose-6-phosphate dehydrogenase deficiency are advised to avoid high intakes of the vitamin.[5]

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