

Vitamin C¹

Vitamin C (ascorbic acid) is a simple low-molecular-weight carbohydrate with an ene-diol structure that has made it a ubiquitous and essential water-soluble electron donor in nature. It is synthesized by all species except for higher-order primates, guinea pigs, and some bat, fish, and bird species. In all of the latter, the gene encoding for α -gulonolactone oxidase—the enzyme catalyzing the final step in the biosynthesis of ascorbic acid—has evolved into a nonfunctional state due to accumulation of mutations and/or deletions; consequently, these species rely on an adequate supply of vitamin C from their diet.

In all its known biologic functions, vitamin C acts as a reductant, i.e., it donates an electron to a substrate while itself being oxidized to an ascorbyl radical, a relatively stable free radical. Two molecules of ascorbyl free radical can dismutate into 1 molecule of ascorbate and 1 molecule of dehydroascorbic acid, the fully reduced and oxidized forms of vitamin C, respectively. To minimize the loss of vitamin C through metabolism and excretion, efficient retaining mechanisms have evolved, including ascorbate recycling, in which dehydroascorbic acid is rapidly reduced to ascorbate intracellularly by glutathione (another cellular reductant) or the selenoenzyme, thioredoxin reductase, and active renal reabsorption by the sodium-dependent vitamin C transporter (SVCT)². Vitamin C absorption, tissue distribution, and excretion are tightly controlled by tissue-specific, active transport through SVCT1 and SVCT2. If vitamin C intake in humans is in excess of ~400 mg/d, a homeostatic state is reached with maximal plasma steady-state concentrations of ~60 to 90 μ mol/L and intracellular concentrations ranging from 0.5 to 10 mmol/L, depending on the tissue. The highest concentrations of vitamin C are found in the brain, eye, and adrenal gland.

The biologic role of vitamin C is related to its reduced form, ascorbate, and can be separated into enzymatic and nonenzymatic functions. The best-known enzymatic function of vitamin C is probably as cofactor for the ferrous [Fe(II)] and 2-oxoglutarate dependent dioxygenases in collagen synthesis. These enzymes catalyze the hydroxylation of lysine and proline residues in unfolded procollagen chains, which are the building blocks of the triple-helical structure of mature, functional collagen. Ascorbate also serves as an electron donor for various enzymes catalyzing carnitine and norepinephrine biosynthesis, peptide hormone amidation, and tyrosine metabolism. Ascorbate-mediated hydroxylation of hypoxia inducible factor 1 α (HIF-1 α) regulates the transcription of several genes encoding proteins involved in iron homeostasis, angiogenesis, and cell proliferation.

More recently, several studies have shown that vitamin C plays an important role in vascular function. Ascorbate mod-

ulates vasorelaxation by increasing NO synthesis or bioavailability in a number of ways (1). Endothelial NO synthase (eNOS) generates NO, which diffuses to the smooth muscle cell layer of the vascular wall and mediates dilation through its interaction with soluble guanylyl cyclase. Tetrahydrobiopterin is a cofactor for eNOS activity, and vitamin C appears to recycle tetrahydrobiopterin from its oxidized form(s), thereby sustaining the enzyme's activity. Moreover, vitamin C may affect NO bioavailability through ascorbate-mediated denitrosylation and phosphorylation of eNOS. Other roles of vitamin C in vascular function include modulating the endothelial cell barrier and regulating the activity of NADPH oxidases (NOXs) involved in inflammatory gene response.

In addition to its roles in the above enzymatic processes, ascorbate is a powerful antioxidant with the ability to reduce or "scavenge" many (patho)physiologically relevant free radicals and reactive oxygen species. In addition, vitamin C can regenerate vitamin E (α -tocopherol) from its oxidized form (α -tocopheryl radical), allowing vitamin C to indirectly inhibit lipid peroxidation. Ascorbate can also reduce urate and glutathione radicals as part of the antioxidant network in cells and extracellular fluids. Although the clinical importance of ascorbate's antioxidant action is difficult to assess, a considerable experimental literature has shown that vitamin C effectively protects biologic macromolecules from oxidative damage that might otherwise causally contribute to the initiation and progression of several chronic and acute diseases (2).

Deficiency

The clinical hallmark of severe and prolonged vitamin C deficiency is scurvy, which is fatal if left untreated. The symptoms of impaired wound healing, gingivitis, perifollicular hemorrhages, ecchymoses, and petechiae have been known for centuries and are largely related to impaired collagen biosynthesis and perhaps HIF-1 α hydroxylation. Other symptoms of severe vitamin C deficiency are malaise and fatigue or lethargy, which may be difficult to diagnose clinically. These symptoms can be explained by impaired carnitine biosynthesis resulting in decreased fatty acid transport and subsequent β -oxidation in mitochondria required for ATP production and decreased synthesis of the neurotransmitter norepinephrine. The enzymatic synthesis of both carnitine and norepinephrine involves hydroxylation steps that depend on vitamin C for full enzyme activity (2). Whereas vitamin C deficiency is mainly caused by poor diet, several additional risk factors have been identified, including smoking, pregnancy, low socioeconomic status, genetic predisposition, old or young age, strenuous exercise, and clinical conditions

associated with metabolic syndrome, such as hypertension, diabetes, and obesity.

Dietary Recommendations

Based on the vitamin C intake required to achieve near-saturation of plasma and leukocytes with minimal urinary excretion, and adjusted for body mass, an RDA of 75 and 90 mg/d for women and men, respectively, was established by the U.S. Institute of Medicine (IOM) in 2000. In addition, the RDA for pregnant and breastfeeding women (≥ 19 y) was set at 85 and 120 mg/d, respectively. No RDA was established for infants; instead, the Adequate Intake of vitamin C was set at 40 mg/d for infants up to 6 mo of age, and 50 mg/d for infants up to 12 mo. For older children, the recommendation is based on estimated body mass in relation to an adult: 15 mg/d for children up to 3 y of age, 25 mg/d for children up to 8 y, and 45 mg/d for children up to 13 y. The RDA for teenagers is based on gender: 75 and 65 mg/d for boys and girls 13–17 y of age, respectively (3).

It has long been recognized that smokers and individuals exposed to environmental tobacco smoke (“passive” smokers) have a lower vitamin C status than nonsmokers. This is believed to be partly due to poor dietary habits but also due to the oxidizing properties of tobacco smoke per se, resulting in an increased turnover of vitamin C. Consequently, the IOM recommends that smokers get an additional 35 mg/d of vitamin C. No increased RDA has been established for passive smokers, but they are strongly encouraged to ensure that they meet the standard RDA.

Recent data suggest that the current RDA for vitamin C set by the IOM for men and women may be too low. On the basis of a comprehensive review of the scientific evidence from human metabolic, pharmacokinetic, and observational studies as well as phase 2 randomized controlled trials, it was concluded that 200 mg/d is the optimum intake of vitamin C for the majority of the adult population to maximize the vitamin’s potential health benefits with the least risk of inadequacy or adverse health effects (4).

Food Sources

Fruit and vegetables are good sources of vitamin C, and ~90% of the daily intake in the general population comes from these sources. The content varies between species, but citrus fruit, kiwi, mango, and vegetables such as broccoli, tomatoes, and peppers are all rich sources of vitamin C. Because vitamin C degrades when heated and during storage, the processing and preparation procedures should be considered when estimating dietary intake of vitamin C. A total of 5–9 servings of fresh, minimally processed, or frozen fruit and vegetables per day is estimated to equal ~200 mg of vitamin C. The presence of vitamin C in dietary products other than fruit and vegetables is typically due to its addition as a preservative to processed foods to protect against oxidation. In areas where vegetation is sparse, such as the arctic regions, people have traditionally relied on alternative sources of vitamin C, such as medicinal herbs (herbal

teas and tinctures from rose hips, pine needles, and tree barks) and animal organs, such as raw liver and whale skin.

Clinical Uses

The current RDA for vitamin C largely exceeds the amount necessary to prevent scurvy (~10 mg/d). However, given the possible severity of events associated with scurvy, urgent replacement therapy is suggested when clinical signs or symptoms of vitamin C deficiency are identified. Oral supplementation with 500 mg/d will be adequate in milder cases, but parenteral therapy may be required in severe cases and in cases of impaired intestinal function or lack of compliance. Subclinical vitamin C deficiency is difficult to detect because the typical symptoms, fatigue and lassitude, are nonspecific. Overt vitamin C deficiency can be seen in malnourished populations, including those with chronic conditions, poor dietary habits, malabsorption, or chemical dependencies.

A considerable epidemiologic literature has found associations between poor vitamin C status and increased risk of developing cardiovascular diseases (CVDs), including coronary heart disease, ischemic stroke, and hypertension (5). Those with near-saturated plasma vitamin C concentrations appear to have the lowest CVD risk, suggesting that intakes greater than the RDA are required to achieve these health benefits. However, properly designed randomized controlled trials have not yet been conducted to either confirm or reject a causal link between vitamin C status and CVD. Thus, prophylactic supplementation of high-risk individuals is not currently recommended by the medical community. In contrast, a considerable number of large intervention studies have confirmed that supplementation of already well-nourished individuals has no additional health benefits.

Another clinical use of vitamin C is to increase nonheme-iron absorption. In the small intestine, vitamin C reduces dietary iron and allows for efficient transport across the intestinal epithelium. Food sources of vitamin C or supplements, when consumed with iron, may lead to increased hemoglobin production in anemic patients. Recent work at the NIH and the University of Iowa has suggested that gram-doses of intravenously administered vitamin C may have merit in cancer therapy in conjunction with standard chemotherapy. This beneficial effect of intravenous vitamin C may be due to ascorbate autooxidation and the generation of hydrogen peroxide, which is selectively toxic to cancer cells.

Toxicity

Vitamin C is generally safe and well tolerated, even in large doses. The IOM set the Tolerable Upper Intake Level for oral vitamin C ingestion at 2 g daily for adults based on gastrointestinal disturbances observed in some individuals at higher doses. High amounts of vitamin C intake have been associated with an increased risk of kidney stones, although the evidence is mixed and inconsistent. The current recommendation is to avoid vitamin C supplementation in those susceptible to

kidney stone formation. Vitamin C consumed with iron could increase the risk of iron overload in susceptible individuals. Patients with these conditions should not avoid eating fruit and vegetables but limit their intake of iron instead. Vitamin C has been reported to cause hemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency, but these reports have not been substantiated.

Recent Research

The so-called antioxidant hypothesis of the 1980s promising a long and healthy life from an abundant intake of antioxidants, including vitamin C, has long been replaced by the view that the health benefits of vitamin C are derived from its role in a number of key reactions within immune function, metabolism, and other enzymatic and nonenzymatic reactions (see above). Thus, emerging evidence indicates that even marginal vitamin C deficiency may impair normal perinatal neurogenesis, affect fetal programming of adult disease risk, and increase the risk of cardiovascular and all-cause mortality. Several genetic variants have been identified in SVCTs, haptoglobin, and glutathione S-transferases that may influence plasma vitamin C status or uptake into tissues. More recent studies have investigated how these polymorphisms may interact with low dietary vitamin C concentrations to increase chronic disease risk (6).

Jens Lykkesfeldt*

Faculty of Health and Medical Sciences,
University of Copenhagen, Denmark

Alexander J. Michels

Balz Frei

Linus Pauling Institute, Oregon State University, Corvallis, OR

* To whom correspondence should be addressed. E-mail: jopl@sund.ku.dk.

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²Abbreviations used: CVD, cardiovascular disease; eNOS, endothelial NO synthase; HIF-1 α , hypoxia inducible factor 1 α ; IOM, Institute of Medicine; NOX, NADPH oxidase; SVCT, sodium-dependent vitamin C transporter.

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