Criteria and Recommendations for Vitamin C Intake

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Recommendations for vitamin C intake are under revision by the Food and Nutrition Board of the National Academy of Sciences. Since 1989 when the last recommended dietary allowance (RDA) of 60 mg was published, extensive biochemical, molecular, epidemiologic, and clinical data have become available. New recommendations can be based on the following 9 criteria: dietary availability, steady-state concentrations in plasma in relationship to dose, steady-state concentrations in tissues in relationship to dose, bioavailability, urine excretion, adverse effects, biochemical and molecular function in relationship to vitamin concentration, direct beneficial effects and epidemiologic observations in relationship to dose, and prevention of deficiency. We applied these criteria to the Food and Nutrition Board's new guidelines, the Dietary Reference Intakes, which include 4 reference values. The estimated average requirement (EAR) is the amount of nutrient estimated to meet the requirement of half the healthy individuals in a life-stage and gender group. Based on an EAR of 100 mg/d of vitamin C, the RDA is proposed to be 120 mg/d. If the EAR cannot be determined, an adequate intake (AI) amount is recommended instead of an RDA. The AI was estimated to be either 200 mg/d from 5 servings of fruits and vegetables or 100 mg/d of vitamin C to prevent deficiency with a margin of safety. The final classification, the tolerable upper intake level, is the highest daily level of nutrient intake that does not pose risk or adverse health effects to almost all individuals in the population. This amount is proposed to be less than 1 g of vitamin C daily. Physicians can tell patients that 5 servings of fruits and vegetables per day may be beneficial in preventing cancer and providing sufficient vitamin C intake for healthy people, and that 1 g or more of vitamin C may have adverse consequences in some people.

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RECOMMENDATIONS FOR VITAMIN C intake are under revision by the Food and Nutrition Board of the National Academy of Sciences. Since the last recommendations for vitamin C intake issued in 1989, extensive biochemical, molecular, epidemiologic, and clinical data have been published. This article reviews the role of vitamin C in metabolic processes, discusses criteria used for recommended ingestion of vitamin C, and presents recommendations for vitamin C intake.

VITAMIN C AND HUMAN METABOLIC PROCESSES

Vitamin C (ascorbic acid, ascorbate) is an essential micronutrient involved in many biologic and biochemical functions. Humans cannot synthesize vitamin C because they lack the last enzyme in the biosynthetic pathway. Known functions of vitamin C are accounted for by its action as an electron donor, or reducing agent (FIGURE 1).

Vitamin C is a specific electron donor for 8 enzymes.[1,2] Three enzymes participate in collagen hydroxylation and 2 participate in carnitine biosynthesis. Dopamine β-monooxygenase is necessary for biosynthesis of the catecholamine hormone norepinephrine, peptidylglycine α-monooxygenase is necessary for amidation of peptide hormones, and 4-hydroxyphenylpyruvate dioxygenase participates in tyrosine metabolism.

Vitamin C also has non–enzymatic-reductive functions in chemical reactions (Figure 1). Based on its redox potential, and its free radical intermediate, vitamin C is a chemical reducing agent (antioxidant) in many intracellular and extracellular reactions. Most have been described in vitro, but because they are oxidation-reduction reactions they may not require vitamin C specifically in vivo. In vitro chemical oxidation reactions involving iron or copper may not be relevant in vivo because these divalentcations are protein bound in vivo. The type or amount of oxidant necessary to induce an experimental effect of vitamin C in vitro may be irrelevant in vivo because that oxidant or its selected concentration might not occur. Although in certain experimental systems ascorbate has pro-oxidant activity, there is little evidence for such activity in vivo.[3,4]

See also Patient Page.

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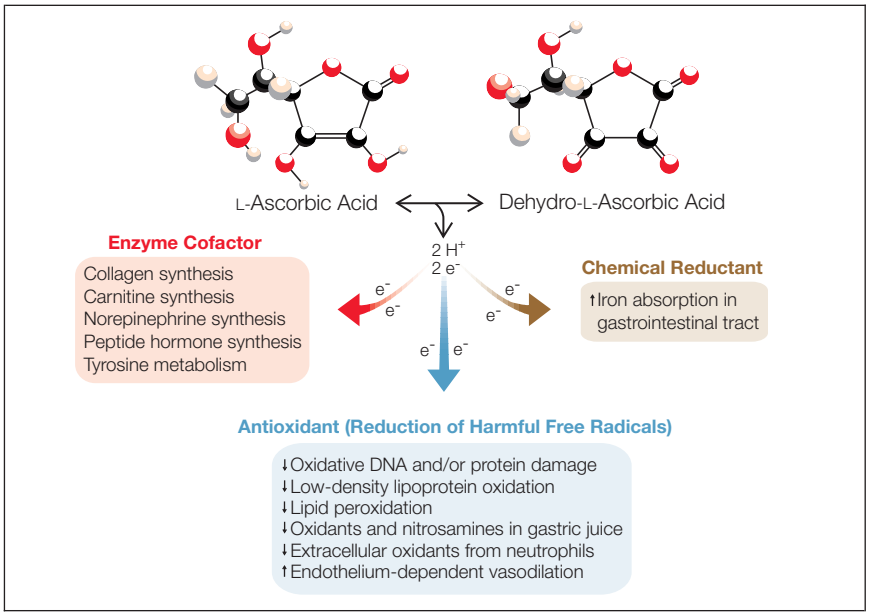
One example of vitamin C action as an extracellular chemical reducing agent is its prevention of low-density lipoprotein (LDL) oxidation.[5-7] Low-density lipoprotein is atherogenic after structural modification. A major pathway of LDL modification may be oxidative modification due to lipid peroxidation, and vitamin C inhibits metal-catalyzed LDL oxidation in many experimental systems in vitro.[5-7] The likely mechanism is that vitamin C reduces aqueous free radicals. Regeneration of oxidized α-tocopherol (vitamin E) on LDL by vitamin C has also been proposed, but this mechanism may have less importance for LDL protection.[5] Vitamin C could also decrease oxidative damage in vascular walls.[5] In contrast to protective effects of ascorbate on LDL in vitro, effects in vivo are inconsistent.[8-10]

As an extracellular reducing agent, vitamin C may reduce harmful oxidants in gastric juice. In normal humans, vitamin C concentrations in gastric juice are approximately 3-fold higher than in plasma. Ascorbate secretion is impaired when gastric mucosa is inflamed, as in *Helicobacter pylori* gastritis. With hypochlorhydria, as in atrophic gastritis, vitamin C secretion can be absent.[11] Because vitamin C in the stomach or duodenum could quench reactive oxygen metabolites or prevent formation of mutagenic N-nitroso compounds, gastric juice vitamin C might confer protection against gastric cancers.[12] However, vitamin C concentrations were normal in gastric juice of patients at risk for familial gastric cancer.[13] High vitamin C dietary intake correlates with reduced gastric cancer risk.[14] Like other epidemiologic observations for vitamin C and cancer risk, it is uncertain if either vitamin C itself or other components of foods that contain vitamin C confer protection.

Vitamin C promotes iron absorption in the small intestine.[15] Vitamin C enhances absorption of soluble nonheme iron, either by reducing it or preventing its chelation by phytates or other food ligands. Vitamin C increases iron absorption 1.5- to 10-fold, depending on iron status, the test meal, and ascorbate dose. Iron absorption can be doubled by 25- to 50-mg ascorbate in the meal, and ascorbate can double iron absorption in iron-deficient patients. Although iron absorption is decreased without gastric acid, as in atrophic gastritis and achlorhydria, it is unknown whether ascorbate increases iron absorption in these conditions.

Figure 1. Actions of Vitamin C



Oxidation of vitamin C (L-ascorbic acid) sequentially releases 2 donor electrons that become available for biochemical reactions observed in vivo and/or in vitro. In the molecular diagrams, carbon atoms are black; oxygen, red; and hydrogen, white. Up and down arrows mean an increase or decrease in level.

INGESTION CRITERIA

The current RDA for vitamin C is 60 mg/d, which was set in 1980 and unchanged in 1989. The current RDA was based on preventing scurvy with a 4-week margin of safety, on the threshold of urine excretion, on estimates of vitamin C absorption, on losses associated with food preparation, and on estimated rates of depletion, turnover, and catabolism.[16,17] The experimental data for this RDA were incomplete.[1,18] Controlled inpatient data were from a depletion-repletion study of 5 prisoners who received limited vitamin C doses.[19] Artifact and insensitivity, especially at low values, limited accuracy of vitamin C assays.[20] Catabolism estimates were inaccurate because catabolism varied at different vitamin C amounts.[1]

Since the last RDA was set, abundant new data are at hand concerning vitamin C biochemistry, molecular biology, epidemiology, pharmacokinetics, and metabolism in different clinical conditions. The following criteria can be used as a basis for recommended ingestion of vitamin C.[2,18,21]

Dietary Availability

Vitamin C is found in many fruits and vegetables[22] (TABLE), but is a labile micronutrient.[15,23,24] Estimates of vitamin C amounts in foods depend on season, transport of the food, shelf time prior to purchase, storage, and cooking practices. For example, supermarket broccoli compared with wholesaler broccoli can lose 33% of its vitamin C, and boiling vegetables can cause 50% to 80% loss. Cooking vegetables with minimal water or in a microwave oven will decrease vitamin C losses.[23,24]

As a supplement, ascorbate is available in tablet and powder forms, with a wide dose range. Ascorbate is part of many multivitamin formulations and is in supplements with selected vita-

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mins, commonly sold as antioxidant supplements. Vitamin C absorption from supplements depends on tablet binders and dose. Effects of food and sustained-release preparations on absorption are uncertain.

Vitamin C is readily available in foods in industrialized countries, and intake is governed by food selection. The US Department of Agriculture and the US National Cancer Institute's guidelines are similar, with recommendations for eating at least 5 fruits and vegetables daily.[25] If these recommendations are followed, daily vitamin C intake will be 210 to 280 mg, depending on food content factors. For supplement users, vitamin C intake is dependent on the supplement chosen.

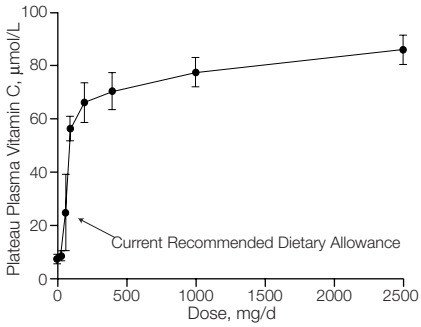
Information from the third US National Health and Nutrition Examination Survey (NHANES III, 1988-1991) indicates that median vitamin C consumption from foods for US men is 84 mg/d, and for women, 73 mg/d (children excluded).[26] However, approximately 25% of women and 33% of men ingested less than 2.5 servings of fruits and vegetables daily. Mean vitamin C intake for men and women was higher than median intake, suggesting that some people ingested much more vitamin C than the median. Data from surveys of specific populations on mean dietary intake show that approximately 25% of 9- to 10-year-old girls had vitamin C intake below the RDA of 45 mg for their age,[27] and less than 15% of Latino children ingested the recommended intake of fruits and vegetables.[28] Data from NHANES II indicated that 20% to 30% of US adults ingested less than 60 mg/d of vitamin C.[29,30] Comparison of NHANES II and NHANES III data indicates that vitamin C intake from foods is increasing slightly, but a substantial number of people ingest vitamin C from foods at or below the present US RDA.[26,31]

Most intake data do not include vitamin C consumption from supplements, used by 40% to 50% of the US population.[32] Supplements may change total vitamin C intake.[32] It is uncertain whether individuals who take supplements are those who already ingest vitamin C from foods or whose vitamin C intake is otherwise low. National surveys have not provided quantitative estimates of total nutrient intakes based on food consumption plus dietary supplements.[26]

Table. Food Sources of Vitamin C

Source (Portion Size)	Vitamin C, mg
Fruit	
Cantaloupe (1/4 Medium)	60
Fresh grapefruit (1/2 Fruit)	40
Honeydew melon (1/8 Medium)	40
Kiwi (1 Medium)	75
Mango (1 Cup, sliced)	45
Orange (1 Medium)	70
Papaya (1 Cup, cubes)	85
Strawberries (1 Cup, sliced)	95
Tangerines or tangelos (1 Medium)	25
Watermelon (1 Cup)	15
Juice	
Grapefruit (1/2 Cup)	35
Orange (1/2 Cup)	50
Fortified Juice	
Apple (1/2 Cup)	50
Cranberry juice cocktail (1/2 Cup)	45
Grape (1/2 Cup)	120
Vegetables	
Asparagus, cooked (1/2 Cup)	10
Broccoli, cooked (1/2 Cup)	60
Brussels sprouts, cooked (1/2 Cup)	50
Cabbage	
Red, raw, chopped (1/2 Cup)	20
Red, cooked (1/2 Cup)	25
Raw, chopped (1/2 Cup)	10
Cooked (1/2 Cup)	15
Cauliflower, raw or cooked (1/2 Cup)	25
Kale, cooked (1 Cup)	55
Mustard greens, cooked (1 Cup)	35
Pepper, red or green	
Raw (1/2 Cup)	65
Cooked (1/2 Cup)	50
Plantains, sliced, cooked (1 Cup)	15
Potato, baked (1 Medium)	25
Snow peas	
Fresh, cooked (1/2 Cup)	40
Frozen, cooked (1/2 Cup)	20
Sweet potato	
Baked (1 Medium)	30
Vacuum can (1 Cup)	50
Canned, syrup-pack (1 Cup)	20
Tomato	
Raw (1/2 Cup)	15
Canned (1/2 Cup)	35
Juice (6 Fluid oz)	35

Figure 2. Plateau Vitamin C Concentrations as a Function of Dose



Subjects ingested less than 5 mg of vitamin C daily from dietary sources. When subjects' vitamin C plasma concentrations decreased to approximately 7 µmol/L, each of 7 repletion doses were administered in succession. Doses of 15 to 1250 mg were administered twice daily. Subjects achieved steady-state for each dose before the next dose was administered. Data represent fasting morning samples. Plateau concentration was defined as the mean of 5 or more samples drawn over at least 7 days with 10% SD or less. The first sample included in all plateau determinations was 90% or more of the final plateau mean. Used with permission from the Proceedings of the National Academy of Sciences.[33]

Steady-State Concentrations

Before 1996, steady-state plasma vitamin C concentrations as a function of dose were uncertain. Prior inpatient and outpatient investigations of vitamin C metabolism were incomplete or had design limitations.[1,2] In 1996 new pharmacokinetic data about vitamin C were published, based on results from 7 men aged 20 to 26 years who were inpatients for 4 to 6 months at the US National Institutes of Health.[33] To solve measurement problems of earlier studies, vitamin C was measured by high-pressure liquid chromatography with coulometric electrochemical detection.[20] Steady-state concentration for each dose was based on the pharmacological definition and occurs when the amount of vitamin absorbed equals the amount of vitamin eliminated.[34] Vitamin C in water was administered either in the fasting state or at least 90 minutes before meals. The pharmacokinetic data showed a steep sigmoidal relationship between vitamin C dose and steady-state plasma concentration (FIGURE 2). Plasma concentrations produced by the current US RDA of 60 mg were on the bottom third of the steep sigmoidal portion of the curve; the 200-mg dose was the first dose beyond the steep portion of the curve; the 200-mg dose produced approximately 80% saturation of plasma; and plasma

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saturation occurred at the 1000 mg/d dose. Average plasma vitamin C concentrations over 24 hours will be slightly higher than the steady-state predose concentrations, but to calculate them requires complex fitting of the data to a multicompartment model of vitamin C distribution.[35]

The 1996 National Institutes of Health study also measured vitamin C concentrations in neutrophils, monocytes, and lymphocytes at each total daily dose from 30 to 2500 mg.[33] All cell types saturated at the 100 mg/d dose. Cells saturated at lower doses compared with plasma. An explanation is that ascorbate accumulation in cells is mediated by active transport, which saturates (achieves V_{max}) at approximately 60 to 70 µmol/L. The ascorbate dose producing a plasma concentration of approximately 60 µmol/L is 100 mg/d. In contrast, plasma saturated at the 1000-mg/d dose, which produced a plasma concentration of approximately 80 µmol/L. Other factors affecting plasma saturation are bioavailability and renal excretion.

Bioavailability

Bioavailability is a measure of efficiency of gastrointestinal tract absorption. Most investigators estimated vitamin C bioavailability indirectly because of difficulty obtaining true bioavailability data.[36] Oral absorption was compared with urine excretion or absorption of one form of vitamin C vs another. In the National Institutes of Health study, at each steady-state, true bioavailability was studied for 1 dose, which was that total daily dose producing steady-state.[33] For example, the 200-mg/d dose was administered as 100 mg twice daily. At steady-state, bioavailability sampling was for 200 mg given once. Vitamin C bioavailability at steady-state for each dose was approximately 100% for 200 mg, 73% for 500 mg, and 49% for 1250 mg (FIGURE 3).

Although it was likely that bioavailability was complete at doses of less than 200 mg, calculations could not be made using direct area under the curve ratios[33] (Figure 3). Bioavailability calculations using area under the curve ratios assume that there is a constant volume of distribution and constant clearance for the test substance.[34] At vitamin C doses of less than 200 mg, these assumptions were not valid, probably as a consequence of multicompartment distribution.[35] Methods to determine bioavailability at vitamin C doses of less than 200 mg require complex models that account for nonlinearity in clearance and volume of distribution.

When these factors were accounted for in a new model,[35] bioavailability was calculated as 89% for 15 mg, 80% for 100 mg, 72% for 200 mg, 63% for 500 mg, and 46% for 1250 mg. Based on the model, a total daily vitamin C dose of 200 mg ingested in divided doses would have nearly complete bioavailability.

Similar to steady-state plasma concentration data, true bioavailability data for vitamin C were based on its administration in the fasted state as a pure substance. There are no data for true bioavailability of vitamin C when administered with foods or in compounds found in foods. It remains possible that food components such as glucose will inhibit vitamin C absorption, which would decrease bioavailability and shift ascorbate dose-concentration curves to the right. If this occurred, to obtain the dose-plasma concentration relationships observed for pure vitamin C, the amounts of vitamin C ingested from foods would have to be higher.

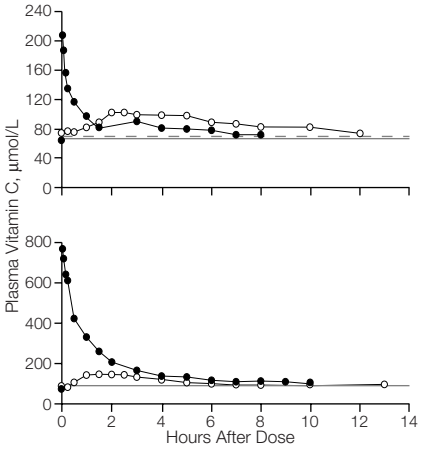
Urinary Excretion of Vitamin C

Vitamin C undergoes glomerular filtration and renal reabsorption.[37] Ascorbate probably passes unchanged through glomeruli and undergoes concentration-dependent active tubular reabsorption by a vitamin C transport protein. When the transport protein reaches saturation (achieves V_{max}), remaining vitamin C is not transported and is excreted in urine. It is unknown whether vitamin C is actively secreted into renal tubules distal to the reabsorption site. There is no known renal mechanism for dehydroascorbic acid filtration and reabsorption, since there is probably no dehydroascorbic acid in normal human plasma.

Vitamin C is not bound to plasma proteins, and is dialyzable.[38] Patients receiving dialysis require vitamin C replacement, but ideal replacement amounts are uncertain. If vitamin C is not replaced, scurvy can occur. In patients with renal insufficiency not requiring dialysis, it is unknown whether vitamin C utilization is affected by metabolic abnormalities associated with renal insufficiency and whether there is impaired vitamin C filtration or reabsorption.

Before 1996 there were few data describing urine excretion of vitamin C at steady-state concentration for a given dose.[2,19,37] Urine excretion of vitamin C for each dose was measured at steady-state concentration in the National Institutes of Health study. In 6 of 7 volunteers, no urine excretion occurred at vitamin C doses of less than 100 mg/d. At 100 mg, approximately 25% of the dose was excreted, and at 200 mg approximately 50% of the dose was excreted. At higher doses, such as of 500 mg and 1250 mg, only part of the in-

Figure 3. Vitamin C Bioavailability in Plasma



Bioavailability is shown for 1 subject at 200 mg (top) and at 1250 mg (bottom). For each dose, vitamin C was administered at zero time (8 AM) orally and samples were obtained as shown. After 24 hours the same dose was given intravenously and samples were obtained as shown. Dashed lines indicate baselines. Bioavailability sampling was performed at steady-state for the total daily dose. Bioavailability was the ratio of the area of the oral dose (area under the $curve_{po}$) divided by the area of the intravenous dose (area under the $curve_{iv}$). See "Bioavailability" for details. Used with permission from the Proceedings of the National Academy of Sciences.[33]

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gested dose was absorbed, but almost the entire absorbed amount was excreted. These data show that at steady-state, vitamin C doses of more than 500 mg have little impact on body stores.[33] The threshold dose for vitamin C excretion is 100 mg/d, and the threshold plasma concentration for excretion is approximately 55 to 60 µmol/L.

Adverse Effects

Vitamin C has few toxic effects, and adverse effects are related to dose.[39] Diarrhea or abdominal bloating can occur when several grams are taken at once, although there are no indications for such doses. With guaiac-based tests, false-negative results for detecting stool occult blood occur with intake of 250 mg of vitamin C.[40] Vitamin C intake from all sources should be less than 250 mg for several days prior to stool testing. Vitamin C also can cause false-negative test results in detecting gastric occult blood.[41]

Vitamin C enhances iron absorption. Patients may have iron overload due to hemochromatosis, thalassemia major, sideroblastic anemia, or other diseases requiring multiple red blood cell transfusions.[42] While theoretically possible for vitamin C to enhance iron overload or harm individuals with these disorders, patients with hemochromatosis should not be discouraged from eating fruits and vegetables.[42-44] Although uncertain, it is unlikely that vitamin C induces iron overabsorption in healthy people. For iron-replete subjects who consumed foods that contained iron, 2 g of ascorbate did not increase iron stores, suggesting that ascorbate does not induce overabsorption of iron.[45] Patients with hemochromatosis are homozygous for the disease-causing gene. It is unknown whether subjects who are heterozygous for the gene have enhanced iron absorption from vitamin C. However, iron overload is rare compared with the prevalence of people heterozygous for the disease-causing gene. If ascorbate caused iron overload in heterozygotes, a higher incidence and prevalence of iron overload should be observed than is now found. Therefore, it is unlikely that vitamin C induces iron overabsorption in people heterozygous for hemochromatosis.

Data are conflicting concerning the effect of ascorbate on urate excretion. Hyperuricosuria occurred when some patients received a large dose of ascorbate intravenously,[46] although contradictory findings were reported.[47] Transient hyperuricosuria occurred when 3 g of vitamin C was given.[48] The conflicting findings may be due to lack of steady-state for vitamin C, differences in plasma concentrations, or duration of vitamin C administration.[33] In all reports hyperuricosuria was absent at vitamin C doses of less than 1 g.

A product of vitamin C catabolism is oxalate. Its excretion in relationship to vitamin C intake has been controversial, in part because of oxalate assay techniques. In assays used before 1987, artificial oxalate elevation occurred due to inadvertent ascorbate conversion to oxalate in stored samples.[49,50] Despite better assays, controversy remains.[33,51-56] Taken together, the data show that oxalate excretion is probably increased at vitamin C doses of 1 g or more daily in some healthy people, although consequences are unclear. In people with underlying hyperoxaluria, oxalate excretion is accelerated by ascorbate doses of 1 g or more, and for these people megadoses could be harmful.[53,55] Because hyperoxaluria can be occult, and oxalate excretion can be increased by vitamin C in some healthy people, safe vitamin C intake is less than 1 g/d.

Hyperoxalemia in patients receiving dialysis was induced by vitamin C when it was administered intravenously in repeated 1-g doses,[57] but there is no rationale for such use. Vitamin C daily doses of 500 mg or more could possibly produce hyperoxalemia in patients receiving dialysis. Ideal vitamin C intake for patients receiving dialysis is unknown, but intake probably should not exceed 200 mg/d.

Hemolysis occurred after vitamin C was administered intravenously in patients with glucose-6-phosphate dehydrogenase deficiency.[58,59] Hemolysis also occurred in subjects with glucose-6-phosphate dehydrogenase deficiency who received at least 6 g of ascorbate as a single oral dose.[60] We know of no clinical indication for such doses. If it is necessary to administer ascorbate intravenously, patients should first be screened for glucose-6-phosphate dehydrogenase deficiency.

Harmful effects have been mistakenly attributed to vitamin C, including hypoglycemia, rebound scurvy, infertility, mutagenesis, and destruction of vitamin B_{12}. Health professionals should recognize that vitamin C does not produce these effects.[1]

Biochemical and Molecular Function in Relationship to Vitamin Concentration

There are no definitive data showing that vitamin C concentrations directly enhance biochemical or molecular function in human tissues, or that higher vitamin C concentrations confer benefit. Only indirect information is available regarding dose-function relationships.

The plasma concentration corresponding to the current RDA of 60 mg/d is 24 µmol/L and is close to K_m for vitamin C transport. By contrast, the plasma concentration corresponding to 200 mg/d is 66 µmol/L, a concentration at which vitamin C transport achieves V_{max} and tissues saturate.[61] Whether this is beneficial is unknown. Because vitamin C saturation has no apparent adverse consequences, ideal intake might be that amount producing maximum V_{max} for beneficial biochemical functions that are vitamin C-dependent.[62] Such functions include proline and lysine hydroxylation for wound healing and bone formation, oxidant quenching, carnitine synthesis for fatty acid metabolism, and perhaps synthesis of some hormones.

Oxidation of LDL in vitro is inhibited by vitamin C concentrations above 40 to 50 µmol/L.[6,7] However, in vitro oxidation assays may not be related to oxidation conditions in vivo, and it is unproven whether vitamin C prevents LDL oxidation in vivo.

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When neutrophils encounter bacteria, neutrophils are activated to produce oxidants, which leak outside neutrophils and oxidize extracellular vitamin C to dehydroascorbic acid.[63,64] Dehydroascorbic acid is immediately transported into neutrophils by glucose transporters and then reduced to vitamin C by the glutathione-dependent protein glutaredoxin.[65,66] Because ascorbate oxidized extracellularly is recycled intracellularly, the process is called ascorbate recycling. During ascorbate recycling, extracellular ascorbate quenches extracellular oxidants, and large increases in intracellular vitamin C occur at the same time intracellular oxidants are formed. Neutrophil-generated oxidants could damage neutrophils and impair bacterial killing and also damage surrounding tissue. Thus, oxidant quenching by ascorbate should be beneficial, but it is unknown whether vitamin C or its recycling will enhance neutrophil function. Vitamin C recycling is near maximal at an extracellular concentration of 75 µmol/L.[64]

Nitrosamines are formed in the gastrointestinal tract under certain conditions and can be harmful. Nitrosamine formation may be decreased by vitamin C doses of 200 mg/d,[67] but whether this has clinical benefit remains to be determined.

Beneficial Dose Effects

Diets with 200 mg or more of vitamin C from fruits and vegetables are associated with lower cancer risk, especially for cancers of the oral cavity, esophagus, stomach, colon, and lung.[11,14,68,69] Five servings of fruits and vegetables appear to be protective. However, consumption of vitamin C as a supplement in experimental trials did not decrease the incidence of colorectal adenoma and stomach cancer.[11,70,71] Fruit and vegetable intake may be associated with lower cancer risk not because of vitamin C alone but perhaps because of interactions between ascorbate and bioactive compounds in these foods, or because of compounds independent of vitamin C, or because of characteristics of people who eat fruits and vegetables.[14,69]

Data describing the association of vitamin C consumption with health maintenance or disease outcome are conflicting. For example, vitamin C supplement use for more than 10 years was associated with lower cataract risk,[72] but findings were observational, sample size was small, and other nutrients or behaviors could have explained the results.[73] Other reports concerning cataract prevention by vitamin C are inconsistent.[74-81] Effects of ascorbate intake on coronary heart disease are also inconclusive.[9,10,82-89]

Some inconsistencies may be explained by relating results to intake rather than to plasma or tissue concentrations. Because of the steep relationship between vitamin C plasma concentration and daily intake of 100 mg or less, control subjects may have already been close to saturation for vitamin C, additional doses would cause minimal increases in concentrations, and an effect would not be expected.[33,71] Conversely, small differences in vitamin C intake of less than 100 mg have substantial consequences for plasma concentrations (Figure 2).[33] Thus, instead of correlating population outcomes to vitamin C intake, it may be preferable to correlate outcomes to measured vitamin C concentrations in plasma or tissues.[90]

Data relating disease outcome to vitamin C concentrations are available for cardiovascular disease and stroke. Vitamin C plasma concentrations were not related to risk of death due to coronary heart disease but were for stroke[91]; were associated with increased risk for coronary artery disease only with marked deficiency[92,93]; and had little[94] or no significant effect on ischemic heart disease and stroke after adjustment for other risk factors.[10,87] In one study, a higher plasma vitamin C concentration was associated with lower mortality only for those with high dietary plus supplemental intake of vitamin C,[82] suggesting vitamin C itself was not responsible. In another study, plasma vitamin C concentrations of more than 60 µmol/L vs 6 to 23 µmol/L were associated with decreased risk of heart disease and stroke.[89] In this and another study in which vitamin C appeared to be protective,[91] the measurement techniques overestimate vitamin C values at low concentrations,[20] and the findings may indicate that vitamin C is protective only compared with deficiency. Taken together, the data show that only marked vitamin C deficiency is associated with coronary heart disease, and although vitamin C might have a protective effect against stroke, the findings are inconclusive due to imperfect measurement techniques.

Other than to treat deficiency, beneficial effects of vitamin C on clinical outcomes have not been conclusively demonstrated. It might be possible to determine such effects in clinical conditions in which vitamin C concentrations are low and then repleted. Vitamin C plasma concentrations compared with controls are low in smokers, patients recovering from surgery, and patients with sepsis, human immunodeficiency virus (HIV) infection, critical illnesses requiring intensive care, acute respiratory distress syndrome, and pancreatitis.[95-101] The significance of low vitamin C concentrations in these patients is unknown. Circulating oxidants presumably oxidize ascorbate in those who smoke, are critically ill, have acute respiratory distress syndrome, or have pancreatitis. It is uncertain if oxidation occurs in vivo or occurs only as plasma is prepared. The effect of altered renal function on ascorbate economy in these patients is also unknown. For example, low ascorbate postoperatively could be caused by a transient increase in vitamin C renal excretion, but this remains unproven.

For patients with low vitamin C concentrations, will increasing concentrations change outcome? For many conditions it is either difficult to address this question directly or the issue has not been considered adequately. Because of complexities in identifying patients who will develop adult respiratory distress syndrome, pancreatitis, sepsis, or critical illness, it is difficult to test effects of vitamin C prospectively. Whether increasing vitamin C

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concentrations will ameliorate smoking-associated diseases remains unknown. Preliminary evidence indicated vitamin C had a small effect on decreasing viral load in patients infected with HIV, without altering HIV-associated infections.[98] In elderly patients with decubitus ulcers and low vitamin C concentrations, patients who received 500 mg of vitamin C had improved healing compared with controls.[102] The effect remains unproven because only 8 patients were in each group and vitamin C concentrations in supplemented patients were much higher than those found by others.[103] There are few data relating changes in vitamin C concentration to susceptibility to bacterial or viral infections.[64,104] To advance understanding, conditions in which vitamin C concentrations are low should be identified and tested prospectively to determine whether increasing vitamin C concentrations affects outcome.

Pauling[104] advocated vitamin C doses of many grams for preventing and treating the common cold. However, the patients who derived benefit, a slight reduction in cold incidence, were a small subset who were probably vitamin C deficient.[104] Gram doses of vitamin C do not have a place in prevention or treatment of colds. However, physicians can screen for occult vitamin C deficiency by asking about intake of fruits, vegetables, and vitamin supplements.

Prevention of Deficiency

The first symptom or sign of vitamin C deficiency is fatigue, the "lassitude" of scurvy.[105] Fatigue is subtle, precedes other symptoms and signs, occurs at plasma concentrations below approximately 20 µmol/L, and resolves above this concentration.[33] Steady-state plasma concentrations achieved by 60 mg/d will prevent deficiency for 10 to 14 days if vitamin C ingestion suddenly ceased. Steady-state plasma concentrations of 55 to 60 µmol/L, achieved by 100 mg/d, will probably prevent deficiency for 1 month if vitamin C ingestion suddenly ceased[33] (M. Levine, MD, and Y. Wang, MD, unpublished data, 1999).

RECOMMENDATIONS FOR INGESTION

In 1998, the Food and Nutrition Board of the National Academy of Sciences developed new classifications for providing estimates of nutrient intakes.[106] The concept of RDAs was expanded to the new guidelines, the Dietary Reference Intakes, which include the following reference values: estimated average requirement (EAR), RDA, adequate intake (AI), and tolerable upper intake level (UL). The criteria for estimating recommended ingestion of vitamin C can be applied to each of these Dietary Reference Intakes categories.

EAR and RDA

The Food and Nutrition Board defined the EAR as the amount of nutrient estimated to meet the nutrient requirement of half the healthy individuals in a life-stage and gender group.[106] For the selected criterion used as the basis of the EAR, half the individuals would have values above the EAR value and half below. Using the EAR definition, the RDA is arbitrarily calculated by taking the EAR plus 2 SDs. When the SDs of the EAR are not known, a coefficient of variation is arbitrarily assumed to be 10%, and the RDA is therefore 1.2 × EAR.

The EAR is difficult to calculate for vitamin C because most clinical studies have not been based on EAR principles. One EAR calculation is based on vitamin C saturation in neutrophils, which are saturated at an intracellular vitamin C concentration of 1.3 mmol/L. The EAR is that dose at which 50% of subjects' neutrophils are saturated and is 100 mg/d.[33] The RDA calculation is: 100 mg (EAR) + 20 mg (0.2 × EAR) = 120 mg (RDA). Another EAR calculation is based on urine excretion of vitamin C at steady-state. In healthy men at steady-state, vitamin C excretion first occurs at 100 mg/d.[33] It is assumed that a selected value of urine excretion represents the EAR, that this value occurs near the threshold of urine excretion, and that the value can be considered as fractional excretion of vitamin C. If the selected value of fractional excretion is 23% excreted daily at steady-state, at the 100 mg dose half of the men would have urine excretion above this value and half below. Thus, the EAR is 100 mg/d, and the RDA is 120 mg/d.

Adequate Intake

The Food and Nutrition Board can decide that an EAR is indeterminate, and an AI is used in place of an RDA. Adequate intake is an intake level based on observed or experimentally determined approximations of nutrient intake by a group of healthy people.[106] The primary use of the AI is as a goal for the nutrient intake of individuals.

One AI calculation uses criteria of the current RDA of 60 mg.[16,17] As noted earlier these criteria are (1) protection against deficiency for 1 month if vitamin C ingestion suddenly ceased, (2) the dose representing the threshold of urine excretion, and (3) a dose that replaces catabolic losses. Data are available for the first 2 criteria but not the third. When these data are used as the basis of an AI, 100 mg/d will prevent deficiency for 1 month and is the threshold dose for urine excretion. Catabolism calculations cannot be performed because modeling cannot account for multicompartment catabolism and because catabolism varies as a function of repletion state, so that catabolic estimates calculated at 1 steady-state may not be relevant at another.[1,35]

Another AI calculation, based on the criteria discussed herein, is 200 mg/d provided by 5 servings of fruits and vegetables. This amount is available in US diets now.[25] The first amount beyond the steep portion of the dose-concentration curve for plasma is 200 mg/d but plasma saturation is not induced at this amount and instead occurs at 1000 mg/d.[33] Tissues probably will be saturated at 200 mg/d, without apparent harm. Bioavailability is near maximal for 100 mg twice daily, at least for pure vitamin C. The estimate of 200 mg/d accounts for the possibility that vitamin C bioavailability from foods might decrease compared with pure vitamin C. At the 200-mg/d dose, urine excretion of vitamin C is beyond the excretion threshold, but fractional excretion is less than 1. There are no known adverse ef-

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fects of vitamin C at this dose.[53] Although uncertain, it is possible that there are biochemical benefits due to the concentrations achieved by the 200-mg/d dose. Vitamin C transport will achieve V_{max} in tissues,[61] LDL oxidation might be decreased compared with lower doses,[6,7] ascorbate recycling as a protective mechanism in neutrophils might be optimized,[64] and decreased nitrosation in the gastrointestinal tract might result from this dose.[67] Also, intake of 5 servings of fruits and vegetables is associated with decreased cancer risk.[14,69] Finally, 200 mg of vitamin C will prevent deficiency for more than 1 month if ingestion suddenly ceased.[33] There is no certain benefit from vitamin C at this dose compared with lower ones, except for prevention of scurvy with a safety margin. A recommendation of 200 mg from 5 fruits and vegetables daily will make intake recommendations similar to those of the US Department of Agriculture and National Cancer Institute.[25]

Mean fruit and vegetable intake for most people decreased slightly between 1965 and 1991.[107] From 1991, when the National Cancer Institute began its 5-a-day program, mean intake increased modestly in 1994 from approximately 3.1 to 3.6 servings per person per day.[31] Health professionals are the preferred source for nutrition information by household managers, but only one third of those surveyed used health professionals as a source.[26] Therefore, physicians may have untapped potential to provide nutrition information to their patients.

Fruit and vegetable intake may be difficult for patients with diseases that impair food intake, absorption, or bioavailability. Five servings could underestimate vitamin C needs in patients with accelerated metabolism.[99] For patients unable or unwilling to consume fruits, vegetables, or vitamin C-fortified foods and beverages, a supplement containing 200 mg of vitamin C should suffice.

Tolerable UL

The Food and Nutrition Board defines UL as the highest level of daily nutrient intake that does not pose risk or adverse health effects to almost all individuals in the population.[106] As intake increases above UL, risk of adverse effects increases. Because patients with preexisting hyperoxaluria may have increased risk of nephrolithiasis at vitamin C doses of 1 g or more, and because this dose might increase oxalate excretion in some healthy people, UL of vitamin C should be less than 1 g/d.[33,53,55]

CONCLUSION

Revised recommendations for vitamin C intake are based on new data, new criteria for devising recommendations, and new guidelines termed Dietary Reference Intakes. Recommended intake of vitamin C can be increased from 60 mg to 100 mg to 200 mg/d, depending on the criteria selected and the Dietary Reference Intakes guidelines. Whenever possible, vitamin C intake should come from fruits and vegetables and physicians should encourage their patients to eat 5 servings of fruits and vegetables daily. Vitamin C doses of 1 g or more could have adverse consequences in some people, and physicians should counsel patients to avoid these doses.

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