22

Vitamin C

Biochemistry

Vitamin C (also called ascorbic acid) functions as an antioxidant and plays a role in immune function. It is essential for the synthesis of collagen (one of the major components of connective tissue) and carnitine. In addition, vitamin C has demonstrated antiviral and antibacterial effects *in vitro*; plays a role in microsomal hydroxylation reactions that catalyze cholesterol catabolism and detoxification of xenobiotic chemicals; and is involved in the metabolism of neurotransmitters.[1]

Clinical indications

Vitamin C may be useful for preventing and/or treating a wide range of conditions, as listed in Table 22-1.

Absorption and excretion

Fractional absorption of vitamin C decreases with increasing oral intake. When 15–30 mg was administered, approximately 90% was absorbed. In contrast, less than 50% was absorbed when the dose was increased to 1,250 mg. Clinical observations suggest that the capacity to absorb vitamin C increases during acute illness (see below, under Dosage and administration). Vitamin C is excreted primarily in the urine, and urinary excretion increases with increasing vitamin C intake.

Deficiency

Manifestations of severe vitamin C deficiency (scurvy) may include bleeding abnormalities (petechiae, perifollicular and subperiosteal hemorrhage, ecchymoses, purpura, bleeding gums, and hemarthrosis), bone pain, osteoporosis, arthralgias, myalgias, edema, ascites, orthostatic hypotension, parkinsonian symptoms (combined vitamin C and zinc deficiency), cardiomegaly, and electrocardiographic abnormalities suggestive of cardiac disease.[2–5] Fatigue, lassitude, and emotional changes (including depression and hypochondriasis) may precede the development of frank scurvy.[6]

Cardiac manifestations may also occur relatively early in the course of vitamin C depletion. Of 10 healthy volunteers (aged 21–34 years) given a vitamin C-deficient diet, 2 developed cardiac emergencies requiring immediate interruption of the experiment and hospitalization. These events occurred in the absence of overt signs of scurvy, and were similar to the observations of James Lind (a pioneer in the treatment of scurvy), who wrote in 1757, "Persons that appear to be but slightly scorbutic are apt to be suddenly and unexpectedly seized with some of its worse symptoms. Their dropping down dead upon an exertion of their strength, or change of air, is not easily foretold."[7,8]

Scurvy can mimic deep vein thrombosis, vasculitis, and systemic bleeding disorders.[9] Because the clinical features of scurvy are no longer well appreciated, scorbutic patients are often extensively evaluated for other disorders.

Table 22-1. Vitamin C may be useful for preventing and/or treating the following conditions

Cardiovascular
Atherosclerosis/ischemic heart disease
Hypertension
Thrombophlebitis

Dermatological
Furuncles
Herpes simplex
Herpes zoster
Immune thrombocytopenic purpura
Prickly heat
Senile purpura (topical)
Sunburn
Wrinkles, photoaging

Ear, nose, and throat
Allergic rhinitis
Sinusitis
Sudden sensorineural hearing loss

Gastrointestinal
Constipation
Gallstones
Gastritis
Peptic ulcer

Infectious disease
Acquired immunodeficiency syndrome
Colds
Diphtheria
Influenza
Leprosy
Measles
Infectious mononucleosis
Tuberculosis
Urinary tract infection

Musculoskeletal
Herniated disc
Muscle cramps
Osteogenesis imperfecta
Paget's disease (osteitis deformans)
Complex regional pain syndrome

Obstetrical and gynecological
Dysfunctional uterine bleeding
Leg cramps of pregnancy
Premature rupture of membranes

Ophthalmological
Conjunctivitis
Glaucoma
Uveitis

Psychiatric
Depression
Schizophrenia

Other
Asthma
Burns
Cancer
Critical illness
Diabetes
Gingivitis
Hepatitis
Hypoadrenalism
Infertility
Obesity
Opioid addiction
Post-exercise muscle soreness

Requirement

The Recommended Dietary Allowances (RDAs) for vitamin C, as established by the Food and Nutrition Board of the Institute of Medicine, are listed in Table 22-2. The RDAs for cigarette smokers are 35 mg/day higher than those for nonsmokers.[10]

As suggested below, the optimal level of vitamin C intake might be substantially higher than the RDA.

Table 22-2. Recommended Dietary Allowances for vitamin C[10]

Age	Males (mg/day)	Females (mg/day)	Pregnancy (mg/day)	Lactation (mg/day)
0–6 months	40*	40*	—	—
7–12 months	50*	50*	—	—
1–3 years	15	15	—	—
4–8 years	25	25	—	—
9–13 years	45	45	—	—
14–18 years	75	65	80	115
19 years and older	90	75	85	120
Smokers	Smokers require 35 mg/day more vitamin C than nonsmokers.			

*Adequate Intake

High-dose vitamin C: the evolutionary perspective

Irwin Stone, Linus Pauling, and others have argued that the level of vitamin C intake needed to promote optimal health is far greater than the RDA, and far greater than the amount found in a typical diet. To support this argument, Stone pointed out that humans are among a small group of species (including monkeys, guinea pigs, and an Indian fruit-eating bat) that are unable to synthesize vitamin C. The human liver contains the first 3 of the 4 enzymes involved in the biosynthesis of vitamin C from glucose. However, the fourth enzyme (L-gulonolactone oxidase) is missing, apparently because of mutations in the gene that encoded for that enzyme. There is evidence that this former gene now exists in the human genome as an inactive "pseudogene."[11]

Stone named this genetic defect hypoascorbemia, in reference to the abnormally low levels of vitamin C that can exist in species that are unable to synthesize vitamin C. He hypothesized that "full correction" of this inborn error of metabolism would require supplying the individual with as much vitamin C as the liver would be synthesizing if the genetic defect were not present. Among animals that synthesize vitamin C, the amounts produced per 70 kg of body weight per day are 1.8–4.9 g for unstressed rats, 15.2 g for stressed rats, 19.3 g for mice, 15.8 g for rabbits, 13.3 g for goats, 2.8 g for dogs, and 2.8 g for cats.[12–16] These amounts are 20–200 times greater than the RDA of 90 mg/day for adult males. It is possible that some benefit can be derived from having the blood and tissues saturated with vitamin C and from large amounts of the vitamin being excreted in urine and sweat. For example, because vitamin C has antiviral and antibacterial activity, excretion of large amounts in urine and sweat might help prevent urinary tract and cutaneous infections.

It might seem counterintuitive that mutants unable to synthesize vitamin C would have had a survival advantage over those capable of synthesizing the vitamin. However, studies in bacteria have shown that, in the presence of an ample supply of a particular essential nutrient, a mutant that is unable to synthesize the nutrient will win the competition for survival against the wild type that is capable of synthesizing the nutrient. That is because the mutant's cellular machinery has become streamlined by elimination of the need to manufacture certain enzymes.[17] There is evidence that before the development of agriculture, humans consumed primarily greens, which provided about 2.3 g/day or more of vitamin C. In this ascorbate-rich prehistoric metaphorical Garden of Eden, the loss of the capacity to synthesize vitamin C may indeed have been a survival advantage.

In reality, full correction of defective vitamin C biosynthesis is not possible, because one cannot duplicate with oral supplementation the steady release of large amounts of vitamin C from the liver into the bloodstream. As compared with maximum hepatic synthesis and release of vitamin C, oral administration of large doses of the vitamin probably results in lower serum vitamin C levels and more pronounced interactions (primarily in the gastrointestinal tract) with nutrients such as iron and copper. Nevertheless, the concept of hypoascorbemia as a genetic defect provides a theoretical framework to support the clinical observations of many practitioners that megadoses of vitamin C are useful for preventing and treating a wide range of health conditions.

Researchers skeptical of the value of high-dose vitamin C have pointed out that when vitamin C intake is high, further increases in intake produce only small increases in plasma or tissue levels of the vitamin. For example, increasing vitamin C intake from 200 mg/day to 2,500 mg/day raised the mean plasma vitamin C level by only 25%.[18] In addition, doubling the plasma vitamin C level increased the vitamin C concentration in the brain by only 10%.[19] However, as suggested by Pauling, the human body might be sensitive to small changes in plasma or tissue vitamin C levels. There are many examples of substances in body fluids for which a 10–25% change in the concentration has clinical consequences (e.g., glucose, sodium, calcium, chloride, and hemoglobin).[20] Therefore, the absence of dramatic changes in plasma and tissue vitamin C levels does not rule out the possibility that large doses of the vitamin can be beneficial.

Furthermore, vitamin C might have positive effects that are unrelated to an increase in plasma or tissue levels of the vitamin. It has been suggested that high intake of vitamin C induces the formation of enzymes that promote the metabolism of vitamin C to other compounds, some of which may be beneficial. For example, oxidation products of vitamin C had a greater anticancer effect in mice than vitamin C itself.[21]

Vitamin C nutritional status

Of 7,277 individuals (aged 6 years or older) participating in the National Health and Nutrition Examination Survey (NHANES) 2003–2004, 7.1% had vitamin C deficiency, as determined by serum vitamin C levels.[22] In NHANES 2009–2012, vitamin C intake was below the Estimated Average Requirement in 42–45% of participants.[23]

Children less than 1 year of age,[24] hospitalized patients,[25] the elderly (particularly those living in nursing homes), cigarette smokers, and low-income individuals are at increased risk of having low vitamin C status. People with gastroesophageal reflux may also be susceptible to developing vitamin C deficiency because of an aversion to acidic foods that are rich in vitamin C.[26]

Assessment of vitamin C status

Methods available to assess vitamin C status include dietary history and measurement of vitamin C levels in serum, leukocytes, and urine.[27–29] In patients who are not severely deficient, none of the laboratory tests by themselves are entirely reliable, and combining measurements may be more informative. In addition, serum vitamin C levels decline in response to inflammation, and serum vitamin C may be an unreliable indicator of vitamin C status when the C-reactive protein level is 5 mg/L or higher.[30] Considering the low cost and safety of vitamin C, a therapeutic trial is appropriate in many instances in lieu of laboratory testing.

Adverse effects

Gastrointestinal symptoms. The most common side effects of vitamin C are diarrhea and abdominal pain. These symptoms are dose-related and can be reduced or eliminated by decreasing the total daily dose, taking vitamin C in several divided doses throughout the day, taking the vitamin with food, or using buffered forms of vitamin C (e.g., sodium ascorbate or calcium ascorbate).

Kidney stones. It has frequently been claimed that ingestion of large doses of vitamin C can increase the risk of calcium oxalate kidney stones, because vitamin C is converted in part to oxalate. However, the hyperoxaluria associated with use of high-dose vitamin C was found to be due primarily to a laboratory artifact, resulting from the conversion of vitamin C to oxalate *ex vivo* (i.e., after it had left the body, while it was in the collection bottle). If there is a small increase in urinary oxalate resulting from ingestion of large doses of vitamin C, that increase might be counterbalanced by other effects of the vitamin. For example, vitamin C binds calcium in the urine, potentially reducing the formation of calcium oxalate crystals; produces a small increase in urinary acidity, thereby increasing calcium oxalate solubility; and possibly decreases urinary stasis by promoting diuresis. Observational studies have not provided any clear evidence that high vitamin C intake increases the risk of kidney stones. Moreover, practitioners who routinely used large doses of vitamin C did not observe kidney stones as a side effect. These points are discussed in greater detail (with references) in chapter 213.

Despite the apparent safety of vitamin C for the general population with respect to kidney stone risk, there are rare cases in which high-dose vitamin C appeared to cause a substantial increase in urinary oxalate levels. For example, a 25-year-old male with no history of kidney stones had a 350% increase in urinary oxalate excretion (which manifested as hematuria) while ingesting 8 g/day of vitamin C. Oxalate excretion was measured by a method that avoided artifactual increases.[31] This patient may have had a genetic abnormality of oxalate metabolism.

Triggering or exacerbating renal failure. Treatment with vitamin C has been associated with acute renal failure (apparently secondary to the deposition of calcium oxalate crystals; i.e., oxalate nephropathy) in people with preexisting renal disease or risk factors for oxalate nephropathy (such as prior gastric bypass surgery).

A 59-year-old woman with nephrotic syndrome and renal amyloidosis developed acute renal failure after intravenous administration of 45 g of vitamin C.[32] A 61-year-old man with bilateral ureteral obstruction and renal insufficiency secondary to metastatic prostate cancer developed acute renal failure after receiving 60 g of vitamin C intravenously over a 2-hour period.[33] A 70-year-old man with advanced renal insufficiency (estimated creatinine clearance, 19 ml/minute) became anuric, requiring the initiation of dialysis, after receiving 2.5 g of vitamin C intravenously over a 5-hour period.[34] The adverse effect of a relatively small dose of vitamin C in this patient may have been due to the advanced stage of his renal disease. As noted in chapter 204, even modest doses of vitamin C (such as 500 mg/day orally) can cause hyperoxalemia in patients with end-stage renal disease. A 69-year-old male developed oxalate nephropathy after taking 2 g/day of vitamin C for 2 years. He had 2 risk factors for oxalate nephropathy: a history of small-bowel resection (which can lead to increased intestinal oxalate absorption) and benign prostatic hyperplasia (which may have increased calcium oxalate crystal deposition in the renal tubules as a result of chronic urinary retention).[35] A 69-year-old woman with a history of Roux-en-Y gastric bypass and stage 3 chronic kidney disease developed acute renal failure secondary to oxalate nephropathy while supplementing with 1,000 mg/day of vitamin C.[36]

Other reports of vitamin C adversely affecting renal function are less convincing.

A 22-year-old woman with extensive small-bowel resection who required home parenteral nutrition developed hyperoxaluria and an elevated serum creatinine level while receiving 1.5 g/day of vitamin C in her parenteral nutrition solution.[37] However, in addition to causing artifactual elevations of oxalate levels, intravenous vitamin C has been reported to cause a false elevation of serum creatinine when measured by certain methods (see below, under Laboratory tests). In another case report, a 31-year-old male developed acute renal failure secondary to acute tubular necrosis after taking 5 g/day of vitamin C for an upper respiratory tract infection.[38] Since certain types of respiratory infections (such as influenza and Legionnaire's disease) have been reported to cause acute tubular necrosis, there is no clear evidence that vitamin C was the causative factor.

Iron overload. Because vitamin C increases the absorption of nonheme iron, vitamin C supplementation could worsen iron overload in people with increased body iron stores. Vitamin C may also increase iron-induced oxidative damage in patients with iron overload.[39]

Hemolysis in G6PD deficiency. In case reports, 4 patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency developed acute hemolysis after receiving intravenous vitamin C. The dosage regimens that caused hemolysis were a single 80-g dose, a single 30-g dose, 80 g on 2 consecutive days, and 30 g followed by 60 g 4 days later.[40–43] In one of these cases, hemolysis resulted in acute renal failure, which culminated in death. In another case report, a 9-month old infant with G6PD deficiency developed acute hemolytic anemia after receiving 2 g of vitamin C intravenously every 4 hours for 2 days for a presumed viral infection.[44] Patients should therefore be tested for G6PD deficiency before they are given large doses of vitamin C intravenously.

While the hemolytic effect of vitamin C in patients with G6PD deficiency is presumably dose-related, it is not known what dosage of intravenous vitamin C would be safe for these individuals. Numerous practitioners administer 1–5 g of vitamin C intravenously as a component of the Myers cocktail (chapter 340) without first testing for G6PD deficiency. Among the many thousands of patients who have received this treatment, there have been no reports of severe hemolytic episodes. However, it is possible that minor episodes of hemolysis have gone unrecognized.

There is also a report of 2 children with G6PD deficiency who developed severe hemolysis after consuming 8–10 servings of Tang and 2–3 glasses of a lemon-flavored soft drink (providing a total of 3–4 g of vitamin C) over a period of 4–6 hours. The authors of this report attributed the hemolysis to the vitamin C. However, Tang also contains tartrazine (FD&C Yellow #5), which may be metabolized to sulfanilic acid,[45] a precursor in the manufacturing of sulfa drugs. Since sulfa drugs are known to trigger hemolysis in people with G6PD deficiency, sulfanilic acid might have the same effect. In addition, tartrazine cross-reacts with aspirin, another potential cause of hemolysis in people with G6PD deficiency. Therefore, it remains uncertain whether oral administration of vitamin C can cause hemolysis.

"Rebound scurvy". When guinea pigs were given large doses of vitamin C and then put on a scorbutic diet, scurvy was more severe than in guinea pigs fed the scorbutic diet without first giving them large doses of vitamin C.[46] Presumably, there is a lag time before homeostatic mechanisms related to vitamin C absorption, excretion, and metabolism can adjust to an abrupt change in vitamin C intake. It would therefore be prudent for individuals taking large amounts of vitamin C who decide to reduce their dosage to do so gradually. A physician who had extensive experience using high-dose vitamin C stated that patients on long-term treatment with more than 4 g/day should not be deprived of the vitamin during emergency hospitalizations, and that they should have a Medic Alert type bracelet describing their increased vitamin C requirement.[47]

In a report published by Cochrane in 1965, 2 infants in Nova Scotia, Canada, developed scurvy despite consuming 60 mg/day of vitamin C, after their mothers had ingested 400 mg/day of vitamin C during pregnancy. The author of this report suggested that the use of these "large doses" of vitamin C may have resulted in rebound scurvy in the infants.[48] This potential adverse effect of vitamin C has been noted in a number of textbooks and review articles. However, for at least 2 reasons, Cochrane's conclusion that infantile scurvy was due to maternal ingestion of vitamin C is not credible.

First, while Cochrane did not mention how old his 2 patients were when they developed scurvy, an evaluation of 69 cases of infantile scurvy that were reported to the Canadian Pediatric Society around the same time period revealed that none developed the disease before 4 months of age.[49] Although vitamin C levels decline rapidly after abrupt discontinuation of the vitamin, they increase again within 10 days. If the infants described by Cochrane truly had "rebound scurvy," one would have expected them to become ill shortly after they were born, not many months later. Second, millions of women have consumed more than 400 mg/day of vitamin C during pregnancy (through diet and supplements) since 1965. During that time, not a single new case of rebound scurvy has been reported. Moreover, one practitioner who prescribed large doses of vitamin C to thousands of patients over a 23-year period did not see any cases of scurvy in the infants of mothers who took vitamin C during pregnancy.[50]

The most likely explanation why these children developed scurvy is that their mothers boiled the infant formula, thereby destroying most of the vitamin C.[51] Beginning in the early part of the twentieth century, physicians encouraged parents to heat-sterilize cow's milk in order to prevent summer diarrhea, which was one of the major causes of death in infants. Conscientious mothers, concerned about the dangers of germs for their baby, would in some cases re-boil even the sterilized milk they had purchased, just to "make quite sure." It was not appreciated that heat-sterilization of milk destroys most of the vitamin C. Infantile scurvy was an important public-health problem in Canada in the 1950s and 1960s, largely because many parents were feeding their infants nothing but evaporated milk, which is deficient in vitamin C. Some pediatricians recommended liquid vitamin C supplements, but these supplements were apparently added to the reconstituted milk, which may have then been boiled prior to giving it to the infant.

Thus, there is no convincing evidence that maintaining high vitamin C intake during pregnancy is detrimental to the infant.

Uricosuria and gout. Some, but not all, studies have found that vitamin C supplementation increases urinary excretion of uric acid and lowers serum uric acid levels (chapter 151). It has been hypothesized that vitamin C, like other uricosuric agents, could precipitate gout attacks in susceptible individuals by causing rapid migration of uric acid from tissues. However, practitioners who have administered large doses of vitamin C to thousands of patients to treat various medical conditions have not encountered any cases of

vitamin C-induced gout. In addition, a 20-year prospective study found that higher intake of vitamin C from food and supplements was associated with a lower incidence of gout. To obviate the theoretical concern that vitamin C could trigger a gout attack, when considering the use of high-dose vitamin C for a patient with a history of gout, it would be reasonable to begin with relatively modest doses and build up gradually.

Dental erosion. Chewing ascorbic acid tablets or otherwise allowing ascorbic acid to have direct contact with teeth can result in erosion of dental enamel.[52–55] Therefore, ascorbic acid tablets should not be chewed, and the use of chewable ascorbic acid preparations is discouraged. In addition, the teeth should be rinsed after ingestion of ascorbic acid crystals or powder. While one might expect that buffered forms of vitamin C would not erode dental enamel, there has not apparently been any research addressing that issue.

Treatment of cancer patients. There is one case report of tumor necrosis, hemorrhage, and subsequent death occurring in a cancer patient after a single intravenous dose of 10 g of vitamin C. Further information and precautions related to the use of high-dose vitamin C in cancer patients is presented in chapter 325.

Intravenous vitamin C. Adverse effects and precautions regarding intravenous administration of vitamin C are discussed above, and additional information is provided in chapter 341.

Drug interactions

Note: References for some of the information below are provided in chapter 342.

Aluminum-containing antacids. Co-administration of 2 g of vitamin C and aluminum hydroxide (an antacid), as compared with administration of aluminum hydroxide by itself, increased urinary excretion of aluminum, presumably because of an increase in intestinal aluminum absorption. In rats given aluminum hydroxide, co-administration of vitamin C increased the concentration of aluminum in liver, brain, and bone. These observations raise the possibility that vitamin C increases the absorption of other forms of aluminum as well. Since aluminum may play a role in the pathogenesis of osteoporosis and Alzheimer's disease, vitamin C should not be taken at the same time as aluminum-containing antacids.

Anesthetic agents. Interactions between vitamin C and anesthetic agents are discussed in chapter 336.

Antipsychotics (neuroleptics). Administration of vitamin C (500 mg twice a day) to a man with low vitamin C levels who was receiving the neuroleptic drug, fluphenazine, for bipolar disorder resulted in a 25% decrease in plasma fluphenazine levels and a deterioration of his clinical condition. In case reports, supplementation with vitamin C (2 g 3 times per day) appeared to reverse amenorrhea and irregular menses associated with neuroleptic use.

Aspirin. Aspirin increased urinary excretion of vitamin C and decreased platelet vitamin C concentrations. Vitamin C supplementation may therefore be beneficial for people on long-term aspirin therapy.

Contraceptives, oral. Some, but not all, studies found that the use of oral contraceptives decreased plasma vitamin C levels.

Doxorubicin. In guinea pigs, administration of vitamin C prevented the development of doxorubicin-induced cardiomyopathy. Vitamin C had no effect on the antitumor activity of doxorubicin in mice with experimentally induced tumors (chapter 325).

Glucocorticoids. In patients receiving large doses of glucocorticoids, administration of 2 g/day of vitamin C corrected glucocorticoid-induced defects in polymorphonuclear neutrophil function, an effect that might help prevent the increase in susceptibility to infections associated with long-term glucocorticoid use.

Indinavir. Supplementation with 1,000 mg/day of vitamin C decreased by 14–20% the steady-state plasma concentration of indinavir (chapter 309).

Interleukin-2. Treatment with interleukin-2 causes a marked decrease in plasma vitamin C levels. In one study, plasma vitamin C fell by 80% after the first phase of treatment and became undetectable in 8 of 11 patients as treatment progressed (chapter 325). The effect of vitamin C on the anticancer action of interleukin-2 has not been investigated.

Levodopa. In a case report, supplementation with vitamin C appeared to enhance the efficacy of levodopa (chapter 139).

Levothyroxine. In patients with a history of gastritis, ingestion of 500 mg of vitamin C along with levothyroxine appeared to increase the bioavailability of the drug.

Opioid narcotics. Interactions between vitamin C and opioid narcotics, and the use of vitamin C to treat opioid addiction, are discussed in chapter 276.

Propranolol. In healthy volunteers, administration of 2 g of vitamin C 30 minutes before a dose of propranolol significantly reduced the bioavailability of the drug. This effect appeared to be due to a combination of decreased drug absorption and an alteration in drug metabolism.

Proton pump inhibitors. Treatment with proton pump inhibitors decreased plasma vitamin C levels in healthy volunteers.

Ribavirin. In patients with chronic hepatitis C, supplementation with 2,000 mg/day of vitamin C and 2,000 IU/day of vitamin E prevented ribavirin-induced hemolytic anemia

during combination therapy with ribavirin and interferon alpha-2b, without compromising the efficacy of the treatment (chapter 122).

Tetracyclines. Administration of 500 mg of vitamin C along with 250 mg of tetracycline increased the blood level of tetracycline after 2 hours by 3- to 15-fold, compared with the level after administration of tetracycline alone. Similar effects were seen with oxytetracycline and chlortetracycline.

Warfarin. In case reports, 2 patients had an increase in their warfarin requirement while taking vitamin C (16 g/day in one case, dose not specified in the other case). In 5 other patients, administration of 1 g/day of vitamin C for 2 weeks had no effect on warfarin requirements. In animals, administration of vitamin C in doses up to 500 mg/kg/day did not alter the anticoagulant effect of warfarin. The case reports suggesting an interaction between vitamin C and warfarin may have been due to random fluctuations in coagulation parameters, rather than to an effect of vitamin C. However, the possibility that large doses of vitamin C interfere with warfarin cannot be ruled out.

Nutrient interactions

Iron. Vitamin C enhances the absorption of nonheme iron and also reverses the inhibitory effect of some foods on iron absorption (see chapter 30 for references). As little as 50 mg of vitamin C increased iron absorption in some studies. This interaction is useful for preventing and treating iron deficiency. However, vitamin C supplementation may worsen iron overload in patients with increased body iron stores, and may also increase iron-induced oxidative damage.

Copper. In animals, high intake of vitamin C (such as 1% of the diet) inhibited copper absorption and decreased tissue copper levels.[56,57] When the diet was deficient in copper, high vitamin C intake accelerated the development of copper deficiency.[58] In contrast, parenterally administered vitamin C had some supportive and some antagonistic effects on copper metabolism.[59]

In humans, supplementation with 500–600 mg/day of vitamin C had no clear effect on indices of copper status.[60–62] However, based on the results of animal studies, it would seem reasonable to administer a copper supplement (such as 2 mg/day) to individuals taking larger doses of vitamin C for long periods of time.

Vitamin B_{12}. One investigator reported that the addition of 500 mg of vitamin C destroyed 50–95% of the vitamin B_{12} in a homogenized meal *in vitro*. However, another group of researchers found that 500 mg of vitamin C did not destroy vitamin B_{12}, and they attributed the earlier findings to artifacts of the method used to measure vitamin B_{12} concentrations. One practitioner treated thousands of patients with large doses of vitamin C over a 35-year period and did not see a single case of vitamin B_{12} deficiency resulting from the use of vitamin C. In addition, among children taking an average of 1.65 g/day of vitamin C for 2 years to acidify their urine, there was no significant decrease in serum vitamin B_{12} levels (see chapter 20 for references).

An interaction between vitamins C and B_{12} may occur when these nutrients are present together in aqueous solution for parenteral administration. This issue is discussed in chapter 20.

Flavonoids. Certain flavonoids, such as rutin and quercetin, inhibited the oxidation of vitamin C *in vitro*.[63] In animals fed less than the minimum requirement of vitamin C, supplementation with rutin or quercetin reduced the number of hemorrhages.[64] Thus, certain flavonoids appear to have a sparing effect on vitamin C when vitamin C intake is low.

Vitamin E. Vitamins C and E function together as components of the antioxidant defense system. Studies in animals and humans suggest that supplementation with large amounts of either of these nutrients increases the requirement for the other.[65,66]

Selenium. Vitamin C appears to convert sodium selenite (a form of selenium used for supplementation) to elemental selenium, making it unavailable for absorption. This interaction occurred when 1 g of vitamin C was taken with sodium selenite on an empty stomach, but not when these nutrients were taken together with a meal.[67] Despite this interaction between sodium selenite and vitamin C supplements, consumption of a diet high in vitamin C was associated with an increased percent absorption of sodium selenite and increased retention of absorbed selenium, when compared with a diet low in vitamin C.[68] Vitamin C does not appear to interact with selenomethionine, another commonly used form of supplemental selenium.[69]

Other interactions

Aluminum. As noted above under Drug interactions, vitamin C may increase the absorption of aluminum. Since aluminum may play a role in the pathogenesis of osteoporosis and Alzheimer's disease, it would be prudent not to take vitamin C at the same time as aluminum-containing antacids or foods or beverages that may be high in aluminum (such as processed cheese, foods that contain baking powder, and beverages stored in aluminum cans).

Effect of vitamin C on laboratory tests

Glucose. Some,[70–72] but not all,[73] studies found that the glucose oxidase test for glycosuria (Diastix, Clinistix, Tes-tape) was inhibited by the presence of vitamin C in the urine in concentrations that can be achieved by oral administration of 300 mg/day of vitamin C. This test may therefore yield false-negative results in individuals who are taking vitamin C supplements or consuming a diet high in vitamin C.

False-negative results can be recognized by adding 1 drop of 0.5% glucose to the negative test area and seeing whether the area remains negative.

The addition of vitamin C to urine *in vitro* to achieve a concentration of 250 mg/dl produced a false-positive glucose test using the copper-reduction method (Clinitest). However, such high concentrations of vitamin C would be difficult to achieve with maximum tolerated oral doses of the vitamin. In healthy volunteers, vitamin C in doses up to 9 g/day did not cause false-positive tests using the copper-reduction method.[74–76]

Oxalate. The presence of large amounts of vitamin C in the urine can lead to a falsely elevated value for 24-hour urinary oxalate, because some vitamin C is converted to oxalate *ex vivo* (i.e., in the collection container). This spurious increase in urinary oxalate levels has led to the erroneous assumption that taking large doses of vitamin C causes kidney stones (see above). This *ex vivo* reaction can be prevented by adding 20 ml of concentrated hydrochloric acid to the collection container.[77] The *ex vivo* conversion of vitamin C to oxalate was also prevented by adding 20–25 mmol (7.44–9.3 g) of disodium EDTA and 0.2–0.6 mmol of sodium thimerosal to the collection container.[78]

Occult blood tests. Fecal excretion of as little as 55 mg/day of vitamin C can produce a false-negative stool test for occult blood. Tests that are affected include Hemoccult and similar tests that use guaiac, benzidine, or other diamino compounds as a color indicator. It has been recommended that patients discontinue vitamin C supplements for 48–72 hours prior to testing for occult blood.[79]

Vitamin C at a concentration of 25 mg/dl in urine prevented the detection of occult blood with Multi-Stix when the urine contained 10–20 erythrocytes per high-power field (HPF). At a urinary concentration of 35 mg/dl of vitamin C, occult blood was undetectable when the urine contained greater than 20 erythrocytes per HPF. Thus, vitamin C supplementation can give false-negative results for occult blood in urine.[80] Limiting supplemental vitamin C intake to 100 mg/day for a few days prior to testing the urine would presumably be sufficient to avoid a false-negative result.

Serum cholesterol and triglycerides. Vitamin C at concentrations within the physiologic range of 30–150 µmol/L caused a small but statistically significant artifactual decrease in total serum cholesterol and triglyceride concentrations, as measured by commonly used peroxidase-linked oxidative colorimetric methods.[81]

Effect of intravenous vitamin C. A 61-year-old man received an intravenous infusion of 30 g of sodium ascorbate just prior to the collection of a blood sample. Uric acid, cholesterol, and triglyceride levels were markedly depressed. In addition, serum creatinine was more than 3 times the upper limit of normal, but was normal when tested by a more specific method. Total iron-binding capacity was also falsely elevated. Serum sodium was elevated, apparently due to the high sodium content of the infusion. Similar laboratory abnormalities were seen in patients who received lower intravenous doses of vitamin C.[82] Intravenous administration of large amounts of vitamin C produces serum vitamin C concentrations far greater than those attainable with maximum tolerated oral doses. Therefore, except for the small effect on serum cholesterol and triglyceride levels (as noted above), one would not expect oral vitamin C administration to interfere with these laboratory measurements. It has been recommended that patients not have blood tests within 4 hours after receiving intravenous vitamin C.

Food sources

Good sources of vitamin C include citrus fruits, cantaloupe, broccoli, Brussels sprouts, cauliflower, and potatoes. Substantial amounts of vitamin C in food are lost during high-temperature cooking and during prolonged warming (such as keeping a meal warm at 75ºC [167ºF] for 4 hours).[83]

Preparations

Vitamin C is available as ascorbic acid (a weak acid) and in buffered forms (such as sodium ascorbate, calcium ascorbate, and other mineral ascorbates). Sodium ascorbate provides 131 mg of sodium per 1,000 mg of vitamin C, and calcium ascorbate provides 114 mg of calcium per 1,000 mg of vitamin C.[84] For some individuals, gastrointestinal side effects are less likely to occur with buffered vitamin C than with ascorbic acid. However, with large doses, the increased intake of sodium or calcium must be considered. I have often used a 50:50 mixture of ascorbic acid and buffered vitamin C (sodium ascorbate or calcium ascorbate) when administering large oral doses of vitamin C. One practitioner reported that, for some patients, sodium ascorbate was a more effective treatment than ascorbic acid for various allergy-related conditions (including asthma).[85]

One study found that the bioavailability of 500 mg of vitamin C from a natural source (a citrus extract that contained flavonoids and other substances) was somewhat greater than the bioavailability of 500 mg of synthetic vitamin C.[86] In addition to the sparing effect of flavonoids on vitamin C (as noted above under Nutrient interactions), flavonoids may have beneficial effects of their own. However, vitamin C from natural sources is more expensive than synthetic vitamin C, and some vitamin C products advertised as being "natural" contain only token amounts of flavonoids. Therefore, it might be preferable to use synthetic vitamin C for supplementation and to obtain additional flavonoids and other nutrients by consuming more fruits and vegetables.

Ester-C is a proprietary product that contains calcium ascorbate and small amounts of vitamin C metabolites, such as calcium threonate. A comparative trial in healthy volunteers found that Ester-C was not more bioavailable than ascorbic acid.[87]

Ascorbyl palmitate is a fat-soluble form of vitamin C manufactured by esterification of vitamin C to palmitic acid. While this product is promoted as being superior to ascorbic acid, there is no reason to assume that vitamin C is capable of exerting its usual biochemical effects in a fat-soluble environment where it is not normally present. Other antioxidants (such as vitamin E and vitamin A) are designed to function in fat-soluble environments, so it seems illogical to administer vitamin C in the form of ascorbyl palmitate.

Dosage and administration

For adults, the most frequently used dosages of vitamin C are 100–3,000 mg/day. Some practitioners have recommended much larger, "bowel tolerance" doses to treat certain conditions, such as acute viral infections. The bowel-tolerance dose is the dose just below that which produces diarrhea. It can be determined by taking vitamin C in progressively larger amounts (usually in 3–6 divided doses per day) until diarrhea occurs, and then reducing the dose slightly. According to one practitioner, the benefits of vitamin C become most pronounced as the bowel-tolerance level is approached. Patients are often able to tolerate much larger doses of vitamin C when they are ill than when they are well. As they improve, their bowel-tolerance limit decreases.[47,88]

Vitamin C is better tolerated when taken with food than when taken on an empty stomach. Taking vitamin C in 2 or 3 divided doses per day, as opposed to once a day, may increase the total amount absorbed and minimize the decline in serum vitamin C levels between doses. When administering large amounts of vitamin C, splitting it into multiple doses throughout the day may improve bowel tolerance and allow for a higher total daily dosage.

Information regarding intravenous administration of vitamin C is presented in chapter 341.

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23 *Vitamin D*

How this chapter is organized

Currently, there is disagreement among various practitioners and researchers regarding several issues: whether serum 25-hydroxyvitamin D is a reliable indicator of vitamin D status; how to define vitamin D deficiency and how prevalent it is; whether relatively high doses of vitamin D should be used to ensure "optimal" vitamin D status; what dose of vitamin D is safe for long-term use; and whether the assessment of vitamin D status should differ among different racial/ethnic groups. The first portion of this chapter will follow the same format used for other chapters on individual nutrients. At the end of the chapter the various controversies will be addressed.

Nomenclature and biochemistry

Vitamin D is a fat-soluble vitamin that functions as a prohormone (hormone precursor). Vitamin D_3 (also known as cholecalciferol) occurs naturally in fish and in small amounts in a few other foods (e.g., cheese, egg yolk, and beef liver), and is synthesized in the skin from 7-dehydrocholesterol after exposure to sunlight or other sources of ultraviolet light.