Vitamin C

Introduction

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. It is required for the synthesis of collagen, which is a critically important structural component of blood vessels, tendons, ligaments, and bone. Also, vitamin C is necessary for the synthesis of carnitine, a small molecule that is essential for the transport of fat into cellular organelles such as mitochondria, where the majority of fat oxidation occurs.

Vitamin C is a highly effective antioxidant, especially in the acidic environment of the stomach. In this way, it may be important in blocking production of compounds such as nitrosamines, most of which are known carcinogens (Tricker and Preussmann 1991). This action is consistent with the lower rates of stomach cancer in persons with high vitamin C intakes (Scanlan 2000).

Unlike most mammals and other animals, humans do not have the ability to make their own vitamin C. Therefore it must be obtained from the diet (Higdon 2004). The intestinal absorption of vitamin C is regulated by at least one dose-dependent active transporter (National Institutes of Health [NIH] 2013). Cells accumulate vitamin C via a second specific transport mechanism. In vitro studies show that oxidized vitamin C (dehydroascorbic acid) enters cells via some facilitated glucose transport and is then reduced internally to ascorbic acid. The physiological importance of oxidized vitamin C uptake is unknown.

Overall vitamin C concentrations in the tissues and plasma are tightly controlled. At oral intakes above 1 g per day, vitamin C uptake falls off to less than 50 percent, and unmetabolized vitamin C is excreted in the urine (NIH 2013). It does not necessarily follow that unabsorbed vitamin C provides no benefit; for example, decreases in nitrosamine production may be beneficial in reducing stomach cancer risk.

Safety Considerations

Vitamin C has very low toxicity and is not believed to cause serious adverse effects at high intakes. The most common complaints after very high intakes of vitamin C are diarrhea, nausea, abdominal cramps, and other gastrointestinal effects related to the osmotic effect of unabsorbed vitamin C in the intestine (Institute of Medicine [IOM] 2000).

Although large intakes of ascorbic acid may cause transient gastroenteritis or diarrhea in some individuals, several more serious adverse effects have been purported in books and review articles. These effects have not been supported by the evidence in regard to oral consumption (Hathcock and Rader 1990; IOM 2000), but fears about them continue to persist. The following sections review the main hypothesized adverse effects and the evidence surrounding them.

Conditioned Scurvy

This spurious phenomenon has been so widely cited in review articles that it has become unsupported "conventional wisdom." It is said to result from a conditioning of adults who have had large intakes of vitamin C and in infants whose mothers consumed large amounts during pregnancy, such that blood levels are rapidly depleted to scorbutic levels after discontinuation of ascorbic acid.

Detailed review, including bibliographic tracing, does not substantiate this phenomenon (IOM 2000). High intakes result in accelerated clearance, but this does not result in blood levels lower than normal and nowhere near scorbutic levels (Schrauzer and Rhead 1973; Tsao and Leung 1988). A paper commonly cited in support of conditioned scurvy in infants whose mothers took vitamin C was speculative and did not provide data that supported such a relationship (Cochrane 1965). Oral scurvy due to withdrawal from high vitamin C intakes was reported in another paper (Siegel et al. 1982), but the diagnosis was not confirmed, the time to onset was suspiciously short, and no plasma vitamin C determinations were made. In summary, conditioned scurvy has not been substantiated, despite very large numbers of people taking vitamin C quantities of 1 g or more over the last 40 years.

Oxalate Kidney Stones

Early reports of large increases in urinary oxalate levels following high intakes of vitamin C speculated that oxalate production increased with high intakes of ascorbic acid in an analytical procedure that involved heat (Hoffer 1985). More recent reports based on better assay procedures have indicated a small but significant increase in oxalate excretion (10 to 15 mg, still within the normal range) by persons consuming 1,000 mg of ascorbic acid daily (Levine et al. 1996), though this result might be caused by the instability of ascorbic acid in the urine during collection, storage, or analysis. Some reports assert that ascorbic acid is a risk factor for calcium oxalate kidney stones (Urivetzky et al. 1992). Other research involving alternative sample handling procedures found no increase with a different preparation of ascorbic acid at intakes of up to 8 g per day (Fituri et al. 1983). One study found that oxalate production occurred only in the urine sample in vitro with oral ascorbic acid intakes of up to 10 g (Wandzilak et al. 1994).

A significant contribution of high ascorbic acid intakes to urinary oxalate is not established (Costello 1993), and the association of oxalate kidney stones with higher ascorbic acid intakes remains speculative (Gerster 1986). Indeed, the available epidemiological evidence suggests the exact opposite: a decreased risk of oxalate kidney stones with increased intake of vitamin C. For example, a prospective epidemiological study found the relative risk of oxalate renal stones to be decreased for men consuming 1,500 mg or more vitamin C in comparison with those consuming less than 250 mg (Curhan et al. 1996). These data provide further support for an earlier retrospective study (Fellstrom et al. 1989) that produced similar results. An authoritative review found no risk of oxalate kidney stones in relation to vitamin C intake (IOM 2000).

Increased Uric Acid Excretion

Similar to the increased oxalate concern, it has been theorized that a large increase in urate excretion could increase the risk of urate renal stones. For example, a significant increase in uric acid excretion has been reported with vitamin C intakes of 1,000 mg and higher (Levine et al. 1996), and a single dose of 4 g ascorbic acid has been reported to increase fractional clearance of uric acid (Stein et al. 1976). Five other studies, however, show no effect on uric acid excretion of

vitamin C intakes of up to 12 g per day (IOM 2000). The clinical effects of the increased uric acid production, if any, have not been identified.

Pro-Oxidant Effects, Excessive Iron Absorption, and Excessive Iron Release

A potential for harm from high intakes of ascorbic acid through pro-oxidant effects has been widely discussed (Herbert 1993; Herbert 1994; Herbert et al. 1996), but an authoritative review discredited such claims (IOM 2000). Some research (Kondo et al. 1988) has been cited (Herbert et al. 1996) as demonstrating that an ascorbate-driven free radical reaction damages cells. This research, which used in vitro studies with phagocytes, found increased release of iron from senescent erythrocytes by the phagocytes only at abnormally high ascorbic acid concentrations. The concentrations used were more than tenfold above the highest plasma ascorbic acid levels of subjects consuming 1,000 to 2,500 mg of ascorbic acid per day (Levine et al. 1996). The hypothesis that high intakes of ascorbic acid will produce direct pro-oxidant effects is not consistent with the data on iron release and contrasts with the antioxidant effects of vitamin C observed under a wide variety of conditions (Frei 1991).

The concept that the enhancement of iron absorption by ascorbic acid leads to excess iron-related disease has also been suggested (Herbert et al. 1996) based on the iron-heart disease hypothesis (Sullivan 1981; Salonen et al. 1992). This hypothesis—that high iron status produces an increased risk of heart disease—is not supported by subsequent evidence and evaluation (Aronow 1993; Baer et al. 1994; Liao et al. 1994; Morrison et al. 1994; Moore et al. 1995; Sempos et al. 1996). Furthermore, ascorbic acid intakes of 2,000 mg per day for 2 years did not cause excessive iron uptake (Cook et al. 1994). And intakes of up to 10,000 mg per day for up to 3 years have been observed in clinical trials without side effects (Bendich and Langseth 1995). These findings provide additional evidence that high ascorbic acid intake is unlikely to produce any iron-related increase in heart disease. Moreover, endogenous ascorbate prevented, rather than promoted, lipid peroxidation in iron-overloaded plasma (Berger et al. 1997).

Vitamin B_{12} Destruction

The in vitro observation of the apparent destruction of vitamin B_{12} by ascorbic acid (Herbert and Jacob 1974) has been erroneously interpreted as an adverse effect of vitamin C. Vitamin C intakes of up to 4 g per day have no effect on vitamin B_{12} status (Afroz et al. 1975; Ekvall et al. 1981). A major review found no evidence that vitamin B_{12} antagonism is a credible adverse effect of vitamin C (IOM 2000).

Erosion of Dental Enamel

Chewable vitamin C tablets, used daily, have been reported to lead to erosion of dental enamel because of the acidity of ascorbic acid (pH of 2.8) and the abrasiveness of the tablets (Guinta 1983). However, this result occurs only if the tablets have not been properly formulated to a pH of approximately 4 to 5 using sodium ascorbate or another buffering agent. Chewable vitamin C supplements that are properly buffered do not cause dental enamel erosion.

Gastrointestinal Distress

The only concretely documented adverse effects of high vitamin C intakes are gastrointestinal symptoms such as nausea, abdominal cramps, and diarrhea of osmotic origin (Miller and Hayes 1982). When these effects occur, the vitamin C dosage is usually 3,000 mg per day or higher, taken at one time; but a few individuals respond at single doses as low as 1,000 mg (IOM 2000). This effect results from a direct osmotic effect of unabsorbed ascorbic acid and can usually be avoided by taking the vitamin as a buffered salt rather than as a free acid. The symptoms usually disappear within a week or two with no further consequences.

Official Reviews

IOM (2000). The IOM found no credible reports of adverse effects other than gastrointestinal distress related to irritation and osmotic diarrhea from large doses. For these effects, the IOM

identified a LOAEL of 3,000 mg per day but, because of the mild and transient nature of the effects, selected a UF of 1.5, thus deriving a UL of 2,000 mg per day.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM also found no credible reports of adverse effects other than mild gastrointestinal distress and diarrhea. The EVM applied a standard toxicological default UF of 3, setting a guidance level of 1,000 mg per day.

European Food Safety Authority (EFSA 2004). In April 2004, EFSA released a risk assessment for ascorbic acid that included some evidence of oxidative damage. Their report noted that genotoxicity was supported by oxidative damage that could occur in the presence of transition metal ion. However, EFSA theorized that such effects were countermanded by the antimutagenic effects in a variety of systems. Vitamin C would be expected to be antimutagenic because of its antioxidant properties, and there are several types of data consistent with this effect. EFSA concluded that the data are insufficient to establish a UL for vitamin C. It was noted, however, that doses of vitamin C up to about 1 g in addition to normal dietary intakes are not associated with adverse gastrointestinal effects, but that such effects may occur at higher intakes (3 to 4 g per day). There are no data on the gastrointestinal absorption or tolerability of esterified forms of vitamin C.

CRN Recommendations

Vitamin C has an extremely low potential for toxicity. Multigram supplements have been widely used for decades, with only mild and transient gastrointestinal effects such as irritation, bloating, and diarrhea. The adverse gastrointestinal effects of very high intakes justify the establishment of a UL at 2,000 mg per day.

CRN also identified a LOAEL of approximately 3,000 mg. Given the mild, transient, and self-correcting nature of the adverse effects, CRN considers an uncertainty factor of 1.5, as identified by the IOM, to be ample.

The IOM and the EVM set their ULs at 1,000 mg per day, but neither considered in detail the role of individual dosages versus total intake. CRN recommends a UL of 2,000 mg per day but spread out into at least two doses. Single doses should not exceed 1,000 mg in order to avoid undesirable gastrointestinal effects.

Quantitative Summary for Vitamin C

CRN UL, supplemental intake	2,000 mg/day
IOM UL, total intake	2,000 mg/day
EFSA UL, total intake	Not determined
EC, supplement maximum	Not determined
EVM, guidance level, supplemental intake	1,000 mg/day

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