MONOGRAPH

Vitamin C: An Essential Nutrient For Human Health

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Abstract

Vitamin C must be obtained in the diet of humans as they are one of the few mammals that can't produce it endogenously. It has far-reaching effects as an antioxidant and as a cofactor in several metabolic functions including antioxidant defense, collagen synthesis, and nervous system health. Vitamin C insufficiency leads to impairment of blood vessel integrity, bruising, poor wound healing, excess bleeding, infection, oxidative stress, inflammation, joint pain, mood changes, and scurvy. Severe deficiency can lead to sudden cardiac death. Elevated levels of vitamin C are usually associated with high-dose intravenous administration. Excess vitamin C intake may be contraindicated in certain individuals including those with G6PD deficiency, oxalate kidney stones, and iron overload disorders.

This review will address:

- ✓ Vitamin C Overview
- ✓ Food Source and Intake of Vitamin C
- ✓ Signs and Symptoms of Vitamin C Insufficiency
- ✓ Risk Factors for Vitamin C Insufficiency
- ✓ Detoxification
- ✓ Stress
- ✓ Blood Cholesterol
- ✓ Cancer
- ✓ Diabetes
- ✓ Optimal Takeaways

Vitamin C Overview

Vitamin C is known as the "antiscorbutic vitamin." It is also called ascorbic acid, or ascorbate in its active anion form. Vitamin C is an essential nutrient for humans, one of the few mammals unable to synthesize it due to a lack of the enzyme L-gulonolactone oxidase. Therefore, vitamin C must be obtained in the human diet or through supplementation in order to sustain life (Maxfield 2020).

Vitamin C is a cofactor in several metabolic enzymes, including those involved in the metabolism of norepinephrine, collagen, carnitine, DNA, hypothalamic and gastrointestinal hormones, and other hormones. Vitamin C also supports (nonheme) iron absorption, prevents the formation of nitroso compounds, increases endothelium-dependent vasodilation, decreases neutrophil-induced oxidation, and quenches metabolic free radicals (Padayatty 2016). It protects intracellular proteins and DNA from oxidative damage as well (Van der Velden 2020).

The highest tissue concentrations of vitamin C are found in the adrenal and pituitary glands. Substantial amounts are also found in the brain, neurons, white blood cells, eyes, liver, kidneys, heart, lungs, pancreas, and muscle, including approximately 1,000-1,500 mg in skeletal muscle specifically. The total body pool of vitamin C is estimated to be 2-5 grams (Gropper 2021). Insufficient levels of vitamin C compromise enzyme activity and metabolism and lead to overt scurvy at levels below 0.2 mg/dL (11.4 umol/L) (Padayatty 2016).

The four main mechanisms controlling blood levels of vitamin C are gastrointestinal absorption, renal regulation, tissue accumulation, and rate of utilization (Levine 2011). However, suboptimal intake or excess stress, oxidation, or metabolic need can quickly deplete stores and compromise immunity, collagen synthesis, skin, blood vessel integrity, wound healing, energy levels, neurological function, and cardiometabolic health. Requirements appear to be higher in certain groups including smokers, the injured or critically ill, and those under increased stress.

Food Sources and Intake of Vitamin C

The consumption of fresh fruits and vegetables provides 90% of the vitamin C consumed by humans. Sources include citrus, berries, melon, broccoli, cauliflower, Brussels sprouts, cabbage, peppers, spinach, tomatoes, and potatoes (Maxfield 2020). Leafy greens (Abdullah 2022) and kiwis (Moritz 2020) are also excellent sources.

However, vitamin C is easily destroyed by heat, light, cooking, alkaline solutions, and oxidation, reducing its availability (Gropper 2021).

Photo byViktoria Slowikowska

Unfortunately, the current adult RDA of 75-90 mg/day may be inadequate as it underestimates the total body pool of vitamin C and is based on preventing overt deficiency instead of promoting health. The Tolerable Upper Intake Level of 2,000 mg is set to avoid the osmotic diarrhea that larger oral doses of vitamin C may cause. However, a level of 2,000 mg per day is commonly consumed without adverse effects.

Higher doses may be contraindicated in those with renal complications, iron overload disorders, and G6PD deficiency. However, in the critically ill, higher doses of 6-16 grams administered intravenously help reduce vascular permeability preserve endothelial function, maintain circulation, and improve hemodynamic stability and vasopressor sensitivity (Gropper 2021).

Signs and Symptoms of Vitamin C Insufficiency

Insufficient vitamin C intake can quickly lead to the depletion of normal body stores and levels in the blood. Clinical signs of deficiency occur when body stores drop below 350 mg and include impaired collagen synthesis in the skin, blood vessels, tendons, bone, and other tissues. Other signs of insufficiency include irritability, loss of appetite, poor wound healing, swollen bleeding gums, loss of teeth, soft malformed nails, corkscrew hairs, petechiae, bruising, capillary fragility, dry eyes, alopecia, nonalcoholic fatty liver disease (NAFLD), excess bleeding, and rheumatological disorders. Repletion with up to 2,000 mg per day loading dose for three days and then 500-1,000 mg per day can help correct a deficiency and restore blood levels. A serum level below 0.2 mg/dL (11.4 umol/L) is associated with severe vitamin C deficiency and scurvy (Maxfield 2020).

Since scurvy affects the skin and soft tissue, symptoms are wide-ranging and include musculoskeletal complaints such as fatigue, weakness, arthralgia, and myalgia; bruising, hemarthrosis, and bleeding throughout the body; significant collagen disruption with weakened leaking blood vessels; infection; and sudden cardiac death. Clinical signs of scurvy can occur within 30 days without sufficient vitamin C intake. While white blood cell concentration of vitamin C reflects long-term body stores, plasma vitamin C reflects recent intake, and clinical signs manifest as levels drop below 0.20 mg/dL (11.4 umol/L). One case study of a 72-year-old woman with a highly-processed diet, insufficient vitamin C intake, and 16-pound weight loss over 90 days revealed a plasma vitamin C below 0.05 mg/dL (2.84 umol/L). The patient presented with fatigue, malaise, weakness, falls, bruising, petechial rash, gingival inflammation and bleeding, painful ecchymosis, and low plasma vitamin A, E, B1, folate, iron, and hemoglobin. Some symptoms began to improve within 24 hours following supplementation with vitamin C and multivitamins. However, musculoskeletal symptoms may take two weeks to resolve (Amisha 2022).

Risk Factors for Vitamin C Insufficiency (Abdullah 2022)

- ✓ The elderly
- ✓ Those with alcohol use disorder, anorexia, or cancer
- ✓ Practicing food fads
- ✓ Those with presumed food allergies
- ✓ Receiving unsupplemented parenteral nutrition
- ✓ Those on restricted diets secondary to inflammatory bowel disease, gastrointestinal reflux, or Whipple disease
- ✓ Those who smoke tobacco products
- ✓ Taking medications such as aspirin, indomethacin, oral contraceptives, tetracyclines, and corticosteroids.
- ✓ Those who have renal failure due to filtration of water-soluble vitamin C during dialysis
- ✓ Those with a complication of interleukin-2 treatment of metastatic renal cell carcinoma
- ✓ Receiving liver transplants

Detoxification

Vitamin C also appears to be involved in the metabolism of the cytochrome P450 enzymes responsible for the breakdown and detoxification of drugs, food additives, pollutants, pesticides, and other carcinogens. Regeneration of other antioxidants, including glutathione and vitamin E, is another important role of vitamin C throughout the body as well as in the process of detoxification (Gropper 2021).

Stress

Vitamin C plays a protective role in stress. The adrenal glands maintain some of the highest concentrations of vitamin C in the body and release it quickly upon ACTH stimulation and before cortisol release. Taking oral doses of 1-3 grams of vitamin C daily may maintain plasma levels at concentrations close to those seen in the adrenal vein during ACTH stimulation. Consuming five servings of fresh fruits and vegetables daily can provide 200-250 mg of vitamin C. Depletion/repletion studies indicate that an intake of 100 mg of vitamin C per day increased plasma levels to 0.99 mg/dL (56 umol/L), and 400 mg/day increased levels to 1.23 mg/dL (70 umol/L) (Padayatty 2016). In animals that produce vitamin C endogenously, synthesis increases significantly under stress (Marik 2020).

Stress is considered a major trigger for anxiety and depression, conditions that have a strong association with oxidative stress. Vitamin C helps mitigate the damaging effects of oxidative stress as it concentrates in the brain, neuronal cells, and cerebrospinal fluid. It also plays an important role in myelin structure, glucocorticoid production, neurotransmitter metabolism, and brain electrical activity. Vitamin C insufficiency can compromise these functions and contribute to mood disorders. Administration of vitamin C in a number of clinical trials was found to blunt the excess cortisol response associated with stress, and in some cases decreased anxiety and improved mood. Researchers also note depression is associated with suboptimal vitamin C status and commonly occurs prior to the clinical manifestation of scurvy (Moritz 2020).

One randomized double-blind placebo-controlled study of 108 young adults assessed the response to stress in supplemented and unsupplemented individuals. Results indicate that 1,000 mg of sustained-release vitamin C administered three times per day significantly increased plasma vitamin C from a mean of 1.55 to 2.65 mg/dL (88 to 150 umol/L) versus a minor increase of 1.36 to 1.40 mg/dL (77.2 to 79.5 umol/L) in the placebo group. Reduced blood pressure, anxiety, and subjective stress, as well as faster cortisol recovery following psychological stress were also observed in the vitamin C group (Brody 2001).

Blood Cholesterol

Vitamin C is used therapeutically to improve blood lipid profiles, including the reduction of total cholesterol. Meta-analysis of 13 studies involving hypercholesterolemic subjects revealed that supplementation with at least 500 mg per day of vitamin C for at least four weeks significantly reduced LDL cholesterol and triglycerides and increased HDL cholesterol though not significantly. Analysis of 9 studies found a 25% reduction in coronary artery disease incidence in those taking at least 700 mg of vitamin C daily. The role of vitamin C in cholesterol metabolism includes preventing the oxidation of LDL, protecting HDL from oxidation, and enabling reverse cholesterol transport. Vitamin C's additional roles as an antioxidant and cofactor in collagen synthesis further extend its protective role in cardiovascular health (McRae 2008).

Cancer

Although oral intake of vitamin C via diet or supplementation does not increase plasma levels above 4.4 mg/dL (250 umol/L), intravenous administration can increase plasma vitamin C to pharmacological levels of 440 mg/dL (25 umol/L) and above, generating hydrogen peroxide and cytotoxic effects on cancer cells. Researchers suggest that the pro-oxidant effects of high-dose vitamin C may be effective in fighting pathogens such as bacteria and viruses as well (Levine 2011).

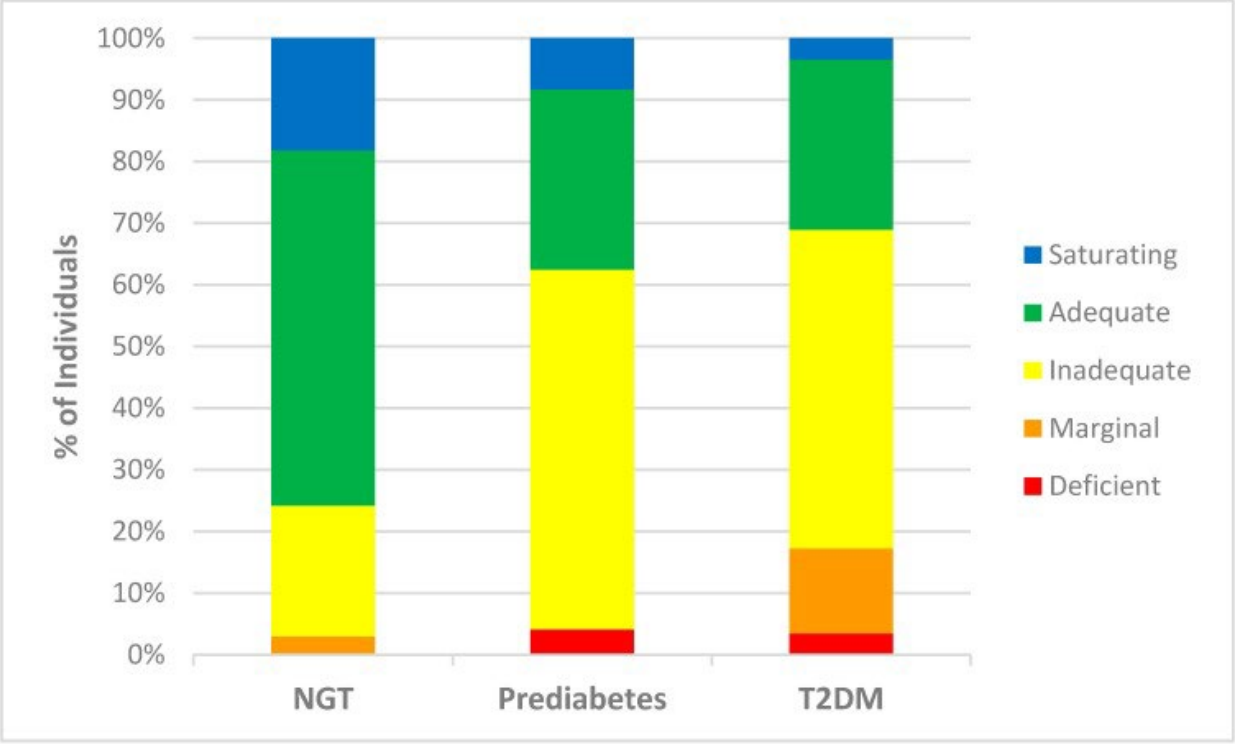
Inflammation and oxidative stress, commonly seen in cancer patients, deplete vitamin C and contribute to its insufficiency if not replaced. Clinical studies combining intravenous and oral vitamin C in cancer patients were found to be safe and effective in reducing inflammation and improving quality of life. In one observational retrospective study, the provision of 7.5 grams of IV vitamin C in addition to standard treatment in breast cancer patients significantly improved appetite, depression, fatigue, and sleep disorders (Klimant 2018).

A prospective interventional study of 60 newly diagnosed advanced cancer patients found that high-dose IV vitamin C (12.5-100 grams) twice weekly in addition to oral vitamin C 2-4 grams daily, significantly improved emotional, social, and physical function and decreased constipation, fatigue, and insomnia in two weeks. Significant cognitive function and pain improvement occurred after four weeks, with no observed adverse reactions despite 55% of subjects receiving concurrent chemotherapy. However, potential contraindications to IV vitamin C include G6PD deficiency, renal failure, history of kidney stones, oxaluria, anuria, severe pulmonary edema, low cardiac output, and dehydration. Researchers also suggest it may be prudent to allow clearance of IV vitamin C before administering chemotherapy. Pro-oxidant effects can occur at doses of IV vitamin C above 15 grams given over a short period and when blood levels exceed 53-70 mg/dL (3000-4000 umol/L) (Klimant 2018).

Diabetes

Individuals with diabetes tend to have lower vitamin C levels than non-diabetics, likely in part due to oxidative stress and increased antioxidant

requirements. One cross-sectional study of 89 individuals revealed significantly lower vitamin C levels in those with T2DM and prediabetes compared to those with normal glucose tolerance, i.e., 0.74 mg/dL (41.2 umol/L) and 0.85 mg/dL (48 umol/L) versus 1.01 mg/dL (57.4 umol/L). Those with T2DM and prediabetes had a higher incidence of overt vitamin C deficiency with levels below 0.19 mg/dL (11 umol/L), and far fewer had saturating levels of 1.3 mg/dL (74 umol/L) or above. An inverse relationship was observed between vitamin C levels in the blood and fasting glucose, hs-CRP, BMI, and smoking (Wilson 2017).



Plasma vitamin C status of individuals within study groups. Percentage of individuals from each study group [normal glucose tolerance (NGT), prediabetes, and type 2 diabetes mellitus (T2DM), including those taking no diabetes medication (fasting glucose ≥ 126 mg/dL (7.0 mmol/L) or on a regimen of Metformin only (T2DM)], classified as having saturating >1.24 mg/dL (70 µmol/L), adequate 0.9- 1.23 mg/dL (51.0–69.9 µmol/L), inadequate 0.42-0.89 mg/dL (24.0–50.9 µmol/L), marginal 0.19-0.4 mg/dL (11.0–23.9 µmol/L), and deficient below 0.19 mg/dL (11.0 µmol/L) plasma vitamin C concentrations (Lykkesfeldt 2010, Wilson 2017).

Source: Wilson, Renée et al. "Inadequate Vitamin C Status in Prediabetes and Type 2 Diabetes Mellitus: Associations with Glycaemic Control, Obesity, and Smoking." Nutrients vol. 9,9 997. 9 Sep. 2017, doi:10.3390/nu9090997 This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

Optimal Takeaways

- ✓ Vitamin C must be obtained in the diet as humans are unable to synthesize it as other mammals can
- ✓ Fresh fruits and vegetables are the best sources of dietary vitamin C
- ✓ Vitamin C in the body is concentrated in the adrenals, pituitary, brain, liver, kidneys, heart, lungs, eyes, pancreas, and muscle, with total body stores maintained between 2 and 5 grams
- ✓ Blood levels of vitamin C should be maintained above saturation levels of 1.3 mg/dL (74 umol/L)
- ✓ Signs of vitamin C insufficiency/deficiency include
  - Compromised collagen synthesis affecting the skin, nails, gums, blood vessels, bones, and joints
  - Excess bleeding and poor wound healing
  - Musculoskeletal complaints including fatigue, weakness, and muscle pain
  - Infection, oxidative stress, and compromised detoxification
  - Mood changes, anxiety, and depression
  - Loss of appetite
  - Impaired glucose tolerance
  - Dyslipidemia
- ✓ Supplementation may be indicated in those at increased risk for insufficiency including those experiencing excess stress or illness
- ✓ Oral intake above 2,000 mg at one time may cause osmotic diarrhea though higher doses of intravenous vitamin C are often well tolerated
- ✓ Contraindications to high-dose supplementation include G6PD deficiency, renal failure, and iron overload

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