Original Scientific Paper

Vitamin C:

Evidence, application and commentary

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ABSTRACT

Vitamin C is classically seen as a vitamin taken in small doses to prevent scurvy and support the immune system. However, there is increasing evidence showing that vitamin C has a much greater role to play in human health, particularly when supra-physiological doses are administered either orally or intravenously for patients with a wide range of conditions, including infections, cancer, cardiovascular diseases, wounds, diabetes and anaemia. Few incidences of severe adverse effects have been reported following vitamin C administration. The role of vitamin C in disease intervention at doses higher than previously considered relevant should be thoroughly investigated in a clinical setting.

Keywords

Ascorbic acid; humans; antioxidants; factors, immunologic

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Introduction

Scurvy (first recorded by Hippocrates circa 400BC) has been a plague for centuries, especially during long-distance travel. James Lind was famous for recommending that the British Navy should give all sailors daily rations of citrus to prevent scurvy, but it was not until 1932 that Albert Szent-Györgyi recognised the vitamin C (ascorbic acid) in citrus as the cure for scurvy,[1] and that scurvy is the result of severe vitamin C deficiency.

Irwin Stone explained that humans lacked the enzyme, L gulonolactone oxidase, essential for producing vitamin C. He also proposed that while a small amount of vitamin C from foods was enough to prevent clinical scurvy, it was not enough to prevent sub-clinical scurvy which may be expressed as a wide range of diseases that improved with large doses of vitamin C.[2]

In the 1940s Frederick Klenner was giving 'megadoses' of vitamin C (in the form of sodium ascorbate) to patients with polio, diphtheria, herpes, chickenpox, influenza, measles, mumps, pneumonia, viral encephalitis and Shiga toxin poisoning. He used intravenous doses supplemented by additional oral

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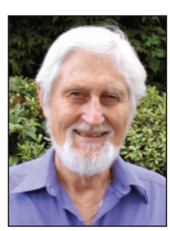

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doses in adults and used intramuscular injections for young children. The only side effects he noted were a few people who vomited soon after receiving oral vitamin C; those people were given vitamin C intravenously without a problem.[3]

In the late 1960s, Linus Pauling became an advocate for 'megadoses' of vitamin C; Pauling recommended a daily oral intake of at least two grams.[4] In the 1970s he worked with Ewan Cameron in the intravenous and oral use of vitamin C as a cancer therapy.[5]

In 1981 Robert Cathcart published his observations on providing more than 9000 patients with high doses of vitamin C. He described his therapy for patients with mononucleosis, acute hepatitis, bacterial and viral infections, allergies, trauma, surgery, burns, back pain, scarlet fever and herpes. Some of his patients took more than 200 grams per day orally when very sick. He also warned that stopping vitamin C therapy suddenly could cause a relapse in their original condition.[6]

For the last 25 years, Hugh and Neil Riordan and James Jackson have been developing a protocol for providing the appropriate dose of vitamin C to patients with cancer. The protocol is based on accurately monitoring blood serum vitamin C concentrations and altering the dose of vitamin C so that therapeutic effects are achieved and maintained.[7] Several case studies, small clinical trials and in vitro experiments have been published, suggesting that vitamin C at the correct dosage has anti-cancer effects.[8-23]

Table 1. Vitamin C synthesis in other mammals and extrapolation to the equivalent intake in humans

Species (Reference)	Weight (kg)	Synthesis (mg/kg/day)	Extrapolation (mg/70kg/day)
Rat (28)	0.15	26	1820
Dog (29)	10	81	5670
Goat (30)	90	190	13300

How vitamin C works

Vitamin C is essential for humans because it has several critical functions as an enzyme cofactor and an antioxidant. As an enzyme cofactor, vitamin C is involved with collagen synthesis, carnitine synthesis, converting dopamine to noradrenalin, cholesterol metabolism and formation of bile acid, steroid metabolism and tyrosine metabolism.[24]

Vitamin C is a potent electron donor and reducing agent and also acts as a water-soluble antioxidant. As an antioxidant, vitamin C helps maintain DNA, proteins, lipids, enzymes and other antioxidants in their normal form. It does this by scavenging oxygen and nitrogen radicals and reducing metal ions.[24]

Vitamin C is transported from blood plasma into cells either as ascorbic acid through sodium-dependent transporters, or as dehydroascorbic acid through glucose transporters. Dehydroascorbic acid is then reduced to ascorbic acid within the cell.

When cells are stressed, they increase the concentration of vitamin C inside the cells to protect them from damage. When the vitamin C has been depleted, cells do not function as efficiently and immune responses are also impaired. A regular intake of vitamin C is needed to keep replenishing the cells so that they can perform essential functions and repair cellular damage.[25]

Vitamin C works together with other antioxidants such as glutathione, lipoic acid, coenzyme Q10 and vitamin E to maintain a continual antioxidant supply that can protect cells against free radicals.[26]

Rationale for vitamin C supplementation

Humans are one of the few mammals not able to convert glucose into ascorbic acid in the body. Primates, guinea pigs, fruit-eating bats, some birds and some fish also lack this ability due to a mutation in the L-gulono-γ-lactone oxidase gene. This gene encodes the critical enzyme needed for the last step in the synthesis of vitamin C.[27]

Other animals that can produce their own vitamin C do so in either their liver or kidneys. The amount of ascorbic synthesized daily has been measured in several species. These animals can also significantly increase their vitamin C synthesis when exposed to conditions that place their body under stress, such as disease, toxic chemicals or injury. Extrapolation from other species gives an estimate of the daily requirement for vitamin C in humans for maintaining health.

Like humans, primates are also prone to scurvy and must also obtain vitamin C from the diet to stay healthy.[31] Wild spider monkeys consume about 106mg vitamin C/kg/day (equivalent to 7420mg for a 70kg adult human) while wild mountain gorillas consume about 30mg/kg/day (equivalent to 2100mg for a 70kg adult human).[32] The official recommendation for humans is that less than 100mg vitamin C per day is adequate for most people. For a 70kg adult, this is the equivalent of roughly 1mg/kg/day. As shown from the data above, this is significantly less than for other mammals that either produce their own vitamin C or obtain vitamin C from their food. Although the minimum requirement for vitamin C in humans is known, the optimal requirement is still under investigation.

There has been much debate about the benefits of obtaining vitamins and nutrients from fresh food or from supplements. Table 2 lists a number of good food sources of vitamin C.

Ideally, we would all eat a plentiful and wide variety of fresh fruit and vegetables containing all the nutrients our bodies need for optimal health. However, there are several reasons why this ideal is not achieved: fruit and vegetables may have variable levels of vitamin C (see Table 3) due to the use of fertilisers, pruning, premature harvesting, processing, cooking and storage;[34] cost and inaccessibility of nutritious fruit and vegetables are barriers for some people, particularly in lower socioeconomic groups;[35] and food choices are influenced by the convenience of ready-to-eat foods, family habits, advertising and peer pressure.[36]

The New Zealand Ministry of Health recommends at least three servings of vegetables and two servings of fruit per day to obtain sufficient nutrients. The 2002/2003 New Zealand Health Survey found that only 32% of adult males and 51% of adult females were following this recommendation.[40] For people not obtaining sufficient nutrients from their diet, additional supplementation of vitamins and minerals may help to protect good health. However, supplements should not replace a healthy diet. Multivitamins may help many people to meet their nutritional needs, but taking large doses of single vitamins is not recommended except under medical supervision.

Intravenous and oral vitamin C

A number of fruits and vegetables contain milligram quantities of vitamin C. Fruit and vegetables will prevent scurvy in healthy people but when the body is stressed by injury or illness, larger quantities of vitamin C are needed. In this situation additional oral or intravenous vitamin C may be more beneficial. Robert Cathcart recommended oral vitamin C for patients with a wide variety of medical conditions. His policy was that people should increase the oral dose until reaching 'bowel tolerance' (diarrhoea), and then reduce the dose slightly. In some severe conditions, some people could tolerate more than 200 grams of vitamin C in divided doses over a 24-hour period.[6]

Pharmacokinetic studies have found that the amount of vitamin C reaching blood plasma from oral intake is limited to a maximum of about 220μmol/L in healthy people. With intravenous administration, the digestive system is bypassed and plasma concentrations of more than 15000μmol/L can be achieved.[41] For large doses of vitamin C, intravenous administration is better tolerated than oral as it can be provided as a single dose with less likelihood of discomfort. Also, in situations such as cancer, intravenous administration is more effective at increasing the plasma concentration to high levels thought to be cytotoxic to cancer cells. Vitamin C for intravenous administration should always be sodium ascorbate and not ascorbic acid as it needs to be buffered to neutral pH.

Possible adverse effects

The material safety data sheet for vitamin C indicates that skin contact or inhalation may cause mild irritation, and large oral doses may cause diarrhoea, gastrointestinal discomfort and acidification of urine. There is a purported risk of kidney stones, but this hypothesis has been based mainly on increased oxalate excretion rather than actual occurrence of kidney stones; large scale studies in humans have shown no association between vitamin C and increased prevalence of kidney stones.[42-44] While there is potential for vitamin C to interact with metals and increase mutagenic activity, clinical trials have shown that vitamin C decreases overall mutagenic activity.[42,45]

Some people have a genetic defect in the glucose-6-phosphate dehydrogenase (G6PD) gene that may result in haemolysis if high levels of vitamin C are taken. All patients starting high dose intravenous therapy should first be checked for G6PD deficiency.[46]

Vitamin C increases iron absorption so people with iron overload disorders such as haemochromatosis should be cautioned before taking large doses of oral vitamin C.[47] However, intravenous ascorbic acid may be indicated in some circumstances.[48]

Other side effects that have been described are: headaches, nausea, vomiting, trembling and fatigue. Symptoms are normally acute, lasting less than 24-hours. Vitamin C can be a diuretic and can cause mild dehydration so plenty of water should be consumed when having large doses.[49]

Table 2. Important dietary sources of vitamin C[33]

Fruit	Vegetables
Oranges	Broccoli
Lemons	Brussels sprouts
Strawberries	Asparagus
Kiwifruit	Cauliflower
Pineapple	Cabbage
Blackcurrants	Red capsicum
Grapefruit	Potatoes

Table 3. Variations in ascorbic acid content of some common fruit grown in New Zealand

Fruit (reference)	Range (mg/100g)
Tomato (37)	165–252
Orange (38)	<1–116
Kiwifruit, green (39)	29–80

Clinical Applications

Prophylaxis

Numerous epidemiological studies have shown that high daily intake and high blood plasma levels of vitamin C are associated with reduced risk for many diseases. For example, increasing vitamin C levels reduces the risk of arthritis, asthma, cancer, cataracts, cardiovascular disease, obstructive airway disease, periodontal disease and stroke.[50-60] In several of the studies relating to these medical conditions, long-term vitamin C supplementation was associated with higher vitamin C plasma levels and reduced incidence of disease. A regular intake of an appropriate dose of vitamin C would ensure that the body has a sufficient supply to facilitate all the chemical reactions and antioxidant activities vitamin C is involved with in the body.

Immune support

Vitamin C has long been a means for enhancing the immune system and supporting the body during periods of infection or disease. It has been used in many conditions, including viral infections (e.g. colds, herpes, shingles, hepatitis, HIV), bacterial infections (e.g. Helicobacter pylori, E. coli), allergies, asthma, arthritis, pneumonia, chronic fatigue, glandular fever and tuberculosis.[3,6,61]

Vitamin C deficiency is a common factor in many chronic and acute illnesses. It is important for promoting the function of immune cells and protecting them from oxidation.[62] Clinical trials support the positive role of vitamin C on the immune system: for example, vitamin C supplementation may reduce the severity and duration of common cold symptoms.[63]

Vitamin C has an anti-bacterial and anti-viral effect due to interaction with metal transition ions (particularly copper) creating a selectively pro-oxidant environment that kills or inactivates pathogens through the production of hydrogen peroxide, without causing significant toxicity to healthy cells.[64-66]

Cancer

Vitamin C is implicated in preventing cancer due to its ability in scavenging free radicals and carcinogens, maintaining the integrity of connective tissue and improving immunocompetence and resistance to cancer.[67] Most adults have cancer cells in their body but the immune and circulatory systems normally eliminate them and prevent them from becoming established. Adequate vitamin C intake is important to prevent nutrient deficiencies and maintain antioxidant levels so the anti-tumour defence system keeps working effectively.[68]

If cancer does become established, evidence suggests that vitamin C may selectively kill cancer cells via production of hydrogen peroxide,[69] encapsulate tumours with a collagen wall to prevent metastasis,[67] promote macrophage function and removal of cancer cells,[70,71] prevent or reduce side effects from conventional treatments,[72,73] relieve pain and improve quality of life.[74]

In vitro studies by Riordan and colleagues have shown that extracellular vitamin C concentrations of more than 20 000μmol/L (350mg/dL) are toxic to most cancer cells, but not to normal cells.[14] This concentration has been measured in vivo in human blood plasma following intravenous administration.

Intravenous vitamin C may have a palliative care role, particularly for terminal cancer patients. A study of cancer patients assessed with a quality of life survey before and after intravenous vitamin C showed an improvement in physical, emotional and cognitive function as well as a reduction in fatigue, nausea, vomiting, pain and loss of appetite.[74]

Cardiovascular diseases

Vitamin C is important for maintaining a healthy heart and blood vessels by reducing oxidative stress and promoting vasodilation increasing nitric oxide bioavailability.[75] This helps reduce endothelial dysfunction, one of the key features of cardiovascular disease. Research suggests vitamin C may be supportive in the following conditions: hypertension, coronary artery disease, angina, reperfusion injury, atherosclerosis, heart failure, acute myocardial infarction, obstructive sleep apnoea, Behçet's syndrome, and Kawasaki disease.[76-85] Clinical trials investigating these conditions consistently found that vitamin C improved flow-mediated vasodilation (FMD). Several of the studies also found that vitamin C infusions given during major surgery, such as a cardiopulmonary bypass, resulted in fewer post-operative complications.[79]

Diabetes

Dehydroascorbic acid (the oxidized form of vitamin C) competes with glucose for uptake into cells using a glucose transporter.[86] As a result, many diabetics with hyperglycaemia have low tissue concentrations of vitamin C.[87] Vitamin C can support diabetics by preventing vitamin C deficiency, helping regulate glucose and sorbitol levels, acting as an antioxidant to protect organs from free radicals and protecting the function of the cardiovascular system.

Oxidative stress and the accumulation of sorbitol in cells are major contributing factors to diabetic complications such as endothelial dysfunction, retinopathy and nephropathy.[88,89] Vitamin C is an aldose reductase inhibitor and has been shown to normalise sorbitol levels in red blood cells.[90] As an antioxidant, vitamin C may help prevent the oxidative damage to organs such as the eyes and kidneys that frequently occur in type 2 diabetes.[91,92] It may also reduce the risk of cardiovascular complications by several mechanisms including lowering blood pressure and preventing haemodynamic changes induced by hyperglycaemia.[93,94]

Wound healing

Vitamin C promotes the healing of wounds and injuries through increasing production of collagen, antioxidant activity and enhancing immune cell function.[95] It has been shown to assist recovery from fractures, ulcers and pressure sores, burns, trauma and surgery.

Clinical studies found that vitamin C reduced the incidence of complex regional pain syndrome following wrist fractures.[96] Collagen and vitamin C are essential for new bone formation and repair. High serum vitamin C levels have been associated with higher bone mineral density and lower incidence of bone fractures.[97] It may also accelerate the healing of ulcers and pressure sores. In a clinical trial with surgical patients, after one month the group given extra vitamin C had an 84% reduction in size of pressure sores while the placebo group had a 42% reduction.[98]

High dose intravenous vitamin C given within 24 hours of receiving severe burns or trauma can reduce lipid peroxidation, resuscitation volume, oedema formation and respiratory dysfunction.[99] Following surgery or major trauma, vitamin C levels are very low. Vitamin C administration can correct the deficiency and reduce the incidence of organ failure, duration of mechanical ventilation, intracranial hypertension and time spent in the ICU (intensive care unit).[100,101]

Haemodialysis

The typical treatment for anaemic haemodialysis patients is erythropoietin; however, some patients do not respond well to this treatment. Vitamin C has been shown to increase responsiveness, relieve anaemia, improve functional iron stores and correct vitamin C deficiency.[102,103]

Neurological disorders

Vitamin C is an important cofactor and antioxidant in the brain and central nervous system. Many neurological diseases involve oxidative stress and reduced concentrations of vitamin C in the cerebrospinal fluid. Some evidence suggests vitamin C may have therapeutic value in Alzheimer's disease,[104] Charcot-Marie-Tooth disease,[105] Parkinson's disease,[106] and stroke.[107]

Smoking

Smokers have low serum levels of vitamin C.[108] The recommended daily allowance of vitamin C for smokers is higher than for non-smokers because they are exposed to increased oxidative stress. Vitamin C may be beneficial for smokers because it reduces endothelial dysfunction and inflammation caused by cigarette smoke,[109,110] it reduces blood lead levels (when daily intake is at least 1000mg/day),[111] and may prevent white blood cells adhering to blood vessels, thus potentially preventing the development of atherosclerosis or emphysema.[112]

Conclusion

Vitamin C has a critical role to play in the prevention and intervention of many medical conditions. There is scientific evidence supporting the use of vitamin C during acute and chronic illnesses, for injuries, and for reducing the risk of disease. The safety of vitamin C over a wide range of doses has been demonstrated in a number of clinical trials; reports of serious adverse events are very rare. As a safe, natural, low-cost nutrient, the potential immune-supporting and antioxidant benefits of vitamin C should be considered when developing treatment plans.

Competing interests

All of the authors are involved, via direct or indirect employment, with Centre for Advanced Medicine Ltd, a medical clinic offering intravenous vitamin C for patients with a range of medical conditions.

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