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# VITAMIN C IN HEALTH AND DISEASE

VITAMINA C EN LA SALUD Y EN LA ENFERMEDAD

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## ABSTRACT

Vitamin C has been widely studied in medicine and although the importance of its deficiency with scurvy was recognized, the optimization of its use as a therapeutic resource has not been included in protocols or clinical practice guidelines. The pharmacokinetics and biology of vitamin C indicates the systemic effects it has, and based on it, research has been developed in recent years that supports its parenteral use in some diseases. The available evidence indicates that the benefit of its use does not extend to several diseases but to some such as cancer, whose preliminary report is promising, with adequate tolerability at high doses, but still needs to complete the prospective follow-up of the intervention.

**Key words:** Vitamin C; Cancer; High doses. (source: MeSH NLM)

## RESUMEN

La vitamina C ha sido ampliamente estudiada en medicina y si bien se reconoció la importancia de su deficiencia con el escorbuto, la optimización de su uso como recurso terapéutico no ha sido incluida en protocolos o guías de práctica clínica. La farmacocinética y biología de la vitamina C demuestran los efectos sistémicos que posee, y fundamentado en ello, se vienen desarrollado en los últimos años investigaciones que sustenten su uso parenteral en algunas enfermedades. La evidencia disponible señala que el beneficio de su uso no se extiende a varias enfermedades sino a algunas como el cáncer, cuyo reporte preliminar es promisorio, con adecuada tolerabilidad a altas dosis, pero que aún precisa de completar el seguimiento prospectivo de la intervención.

**Palabras clave:** Vitamina C; Cáncer; Alta dosis. (fuente: DeCS BIREME)

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## INTRODUCTION

EOxygen as an oxidizing molecule is involved in the production of energy, however, it also generates reactive intermediates or free radicals that, depending on their oxidizing degree, can damage biological molecules such as proteins, lipids and nucleic acids. This process of oxidative stress leads to the production of reactive oxygen species such as free radicals and which, under physiological conditions, does not occur in more than 5% due to endogenous antioxidant regulation[1]. This minimum oxidative level has functional importance; for example, in the immune effect of neutrophils, for the activity of the myeloperoxidase enzyme.

The environment is a source of reactive oxygen species. In general, the exogenous sources are constituted by different xenobiotic substances, which are inorganic elements as chemical products. Of which 4 million of these xenobiotic substances are known, 63 thousand are in common use and 11 thousand can be ingested directly as drugs or additives in food. There are another 50 thousand pollutants in the environment[2]. For example, chemicals derived from cigarette smoke, where radioactive substances such as polonium 210, which is linked to lung cancer, have been described. As to radiation, a smoker of 1 and a half packages per day over a year means radiation

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equivalent to 300 chest x-rays[3], which is equivalent to 30 millisieverts (mSv), which exceeds the Commission's recommendations Radiation Protection International, which for the general public, sets a maximum value of 1 mSv per year[4].

The response to oxidative stress occurs by different endogenous substances of antioxidant capacity such as glutathione, superoxide dismutase, catalase, among others, but we also have sources of exogenous antioxidants from the diet, which include phenolic compounds such as flavonoids, carotenoids and vitamins like C, D and E.



## VITAMIN C BIOLOGY

Vitamin C, evolutionarily appears with the ability to synthesize ascorbic acid in terrestrial vertebrates at the end of the Paleozoic era, in response to the dramatic increase in atmospheric oxygen. This toxic and unusual crisis led to the mass extinction of organisms in the pernicum period, and only those tetrapods that developed an antioxidant system survived. This is where the enzyme gulonolactone oxidase arises, which synthesizes vitamin C. However, man, monkey, some species of pigs and several species of birds, lose the ability to produce this enzyme[5].

There are two important biological forms of vitamin C, the reduced form or ascorbic acid, and the oxidized form, DHA (dehydroascorbic acid). The highest concentration of vitamin C is found at the tissue level, so its transport is important. The reduced form or ascorbic acid is transported intracellularly through the SVCTs (Sodium dependent vitamin C transporters) transporters. Dehydroascorbic acid is transported by GLUT (glucose transporter) because of the chemical similarity between glucose (C6H12O6) and vitamin C (C6H8O6). The oxidized form of vitamin C (DHA), once it reaches the intracellular one, undergoes a spontaneous reversion to its reduced form or ascorbic acid by the action of glutathione. If this process were not given, inactive compounds such as 2,3-diketogulonic acid and subsequent oxalate metabolism[6,7,8,9] would be formed. In patients with primary hyperoxaluria, vitamin C consumption is restricted due to the possible formation of oxalate, especially if the consumption is excessive[8].

When dehydroascorbic acid enters the mitochondrial level, its reduction to ascorbic acid is important because antioxidant mechanisms are required in response to mitochondrial oxidative phosphorylation. The damage at the level of mitochondrial DNA (deoxyribonucleic acid) against this oxidative stress is 3 to 10 times greater than the damage of nuclear DNA[10].

An antioxidant, by definition, is one that has the ability to donate electrons to the free radical that is unstable in order to prevent oxidation of other compounds. When an antioxidant donates its electrons, it becomes a free radical, but it does not have the ability to be reactive. In this sense, vitamin C, after donating an electron, becomes the radical ascorbic (or semi-dehydroascorbic acid), but it is relatively stable and not very reactive. After the loss of its second electron, it is when dehydroascorbic acid is formed. The reduction to ascorbic acid will be the most stable[8].

Vitamin C donates electrons to 8 different types of enzymes, of which 3 participate in the hydroxylation of collagen (adds hydroxyl groups to proline and lysine amino acids of the collagen molecule) increasing its stability. It is because, scurvy symptoms are associated with alterations of connective tissue, such as capillary fragility, bruise, gingival and peripheral bleeding and inadequate wound healing[11,8].

Two other enzymes that are regulated by vitamin C, through two dioxygenases, are involved in the synthesis of carnitine, allowing the transport of fatty acids for oxidation. Three remaining enzymes participate in the formation of norepinephrine from dopamine, in adding amide groups to peptide hormones and in the metabolism of tyrosine[8].

Vitamin C can reduce various substances such as:

1. compounds derived from reactive oxygen species (SRO), such as superoxide or hydroxyl radical, and reactive nitrogen species (SRN), such as nitric oxide, nitrogen dioxide and peroxynitrite.
2. compounds such as the alpha-tocopheryl radical, which occurs when a free radical interacts with alpha tocopherol and LDL (low density lipoprotein). This radical can be reduced again to alpha tocopherol thanks to the action of ascorbate, allowing its metabolic reuse as an antioxidant.
3. Elements such as iron ferrous to ferrous, which favors its intestinal absorption[12,8].
4. compounds that are reactive, but that are not free radicals, such as hypochlorous acid, nitrosamines and ozone. The mutagenic effect of nitrosamine derivatives on gastric cancer has been demonstrated and that the concentration of vitamin C in gastric juice is 3 times higher than that of plasma in healthy people.

Experimentally, elevated concentrations of vitamin C induce apoptosis in gastric tumor cells mediated by p38 MAP-kinase (mitogen-activated protein kinase)[13], however, no clinical intervention trials evaluating this aspect. There are retrospective studies that demonstrate a risk association between low vitamin C consumption and gastric cancer (OR 0.40, 95% CI 0.19-0.83)[14], but only recently has a preliminary report of a clinical trial in gastric cancer been published that It combines a chemotherapy regimen with intravenous vitamin C, whose results are favorable, but it is not a comparative study[15].

On the other hand, vitamin C can favor oxidation reactions such as Fenton, which occurs between the free form of metals such as iron or copper and ascorbate. These metals, when bound to hydrogen peroxide, will form highly reactive hydroxyl radicals, and therefore, these metals are not in their free form because they are captured by transferrin or ferritin for iron, or ceruloplasmin for copper. Ascorbate can induce the release of iron from ferritin, being a therapeutic strategy used, for example, in the treatment of refractory anemia in hemodialysis patients who have high iron saturation, although the evidence is still weak due to limited clinical trials[16].

Vitamin C, at the tissue level, is distributed up to 52% in skeletal muscle and 11% at the brain level[17]. In neuronal cells, vitamin C in its biological form of dehydroascorbic acid can cross the blood-brain barrier through GLUT 1 receptors. Experimentally it has been shown that, in cerebral infarction, intravenous administration of DHA produced rapid absorption at the cerebral level with subsequent conversion to ascorbic acid with neuroprotective properties by reducing the volume of the infarction[18,19,20].

## Dose

Currently, the RDA (recommended dietary allowance) or recommended dose of vitamin C is 90 mg / day in adult men and 75 mg / day in adult women[21]. Establishing the RDA of a vitamin requires determining its serum and tissue concentration against different doses, knowing its bioavailability, absorption, urinary excretion and its potential toxicity. Vitamin C dose recommendations were established in 1943, describing that a dose of 60 mg was twice that necessary to prevent scurvy and was the threshold at which vitamin C was excreted in urine. Subsequent studies of pharmacokinetics showed a low incidence of urinary excretion at a dose of 100 mg, a bioavailability of 100% at a dose of 200 mg and a complete saturation when the dose reaches 1000 mg / day. Consequently, the RDA was increased to 90 mg / day, although pharmacokinetics support an RDA of 200 mg / day[22]. It should be considered that it is not about establishing the MDA "minimum dietary allowance" or minimum preventive dose of the deficiency, but about establishing the optimal dose that can vary according to the clinical condition of each patient.

## Applications

a. Immune response. At the level of leukocytes, vitamin C can be stored up to 100 times more during infectious episodes, compared to blood levels[22]. On the other hand, it is involved in the chemotaxis of neutrophils and monocytes, proliferation of lymphocytes and in the activity of killer natural cells[23,24]. Clinically, there has been no evidence of a consistent effect in the prevention of the common cold according to the latest Cochrane report[25]; In the case of pneumonia, Cochrane reports that the evidence is still weak[26], so the research support should migrate to other clinical contexts but related to the immune response.

b. Cancer. Since 1976, the use of high doses of intravenous vitamin C in cancer management had been reported as favorable[27]. Blood concentrations can reach 21,000 µM / L at a dose of 60g / day, unlike the concentrations that are reached orally with the maximum tolerated dose of 3 gr / day that does not exceed 220 µM / L per limit of intestinal absorption. This difference of up to 95 times has been related to a pro-oxidant effect characterized by the formation of hydrogen peroxide, affecting tumor cells, which is observed from a vitamin C concentration of 1000 to 5000 umol / L[28.29]. Therefore, a dual selective tumor pro-oxidant effect is proposed in high doses and a systemic antioxidant effect, according to in vitro observations[30,31]. Hydrogen peroxide is found at the level of tumor cells, but not in blood, due to the antioxidant load of molecules such as glutathione or red blood cell catalase, but that is not found in tumors[32,33]. The increased glycolytic metabolism of tumors favors the uptake of ascorbate by the structure of the transporter already mentioned and once inside, the SRO cluster induces death of tumor cells[9,34,35,36]. There is no systematic review on the intravenous intervention of vitamin C since no clinical trials had been developed for decades because of a publication that dismissed its usefulness in 1985, research that used oral supplementation, and today it is known that no presents therapeutic utility for this group of patients[37]. In recent years, clinical trials have been developed. A phase I trial in patients with metastatic

gastric or colorectal cancer studied that a dose of 1.5g / Kg reported no toxicity and that the effects related to rapid infusion or high osmotic load, such as headache, stunning, mouth dry or gastrointestinal discomfort are unusual, likewise, there was no adverse interaction with chemotherapy. Likewise, its preliminary efficacy is promising with a partial response of 58.3% and a disease control of 95.8% with a follow-up of 8.8 months[15]. Another phase I and II clinical trial reported the adequate tolerance of vitamin C in cancer patients treated with chemotherapy using a dose of 43 grams without significant adverse effects and in some cases symptomatic improvement, for example, increased functional capacity[38].

c. Epigenetically, vitamin C potentiates DNA methyltransferase inhibitors, so it has a hypomethylating action, being important for aberrant methylation of DNA and histones in cancer, it is also proposed that vitamin C, by promoting the immune response , it may favor that endogenous retroviruses, which normally form 9% of the genome, induce demethylation of DNA, thereby opening research in chemoimmunotherapy[36].

Regarding primary prevention, previously reported studies used the oral route for cancer prevention without demonstrating any consistent benefit in solid tumors such as breast, lung, colon or cervix[39-43].

d. Circulation. Considering that in smokers a dose of vitamin C of 2000 mg / day reduces the presence of oxidative stress markers[44], its possible effect on vascular tone is considered[17], however, no controlled studies have been developed for the primary or secondary prevention of diseases cardiovascular[45].

e. Diabetes. In diabetes mellitus, in addition to the pathogenic mechanisms linked to glucotoxicity and lipotoxicity, we have those related to oxidative stress. It is recognized that glucose inhibits ascorbate uptake[46], so a hyperglycemic state could be associated with an ascorbate deficit[47]. Under normal conditions, glucose uptake, at the tissue level, is preferred over ascorbate. To maintain antioxidant capacity in the blood, red blood cells synthesize a membrane protein, stomatin, which allows the GLUT 1 transporter to prefer the transport of DHA over glucose. It would then be reduced to its ascorbic acid form to generate its respective antioxidant effect[48]. In the case of diabetic retinopathy, well-designed studies according to Cochrane are not available[49].

## DIET AND VITAMIN C

When the initial recommendation of 60 mg / day of vitamin C was established, only its anti-scurvy effect was assessed and not the antioxidant effect whose need may vary depending on the vitamin C turn-over, such as during pregnancy or physical stress . In stress, vitamin C is involved in adrenal steroid hydroxylation, and therefore an increase in the urinary excretion of ascorbic acid is observed. In fact, ascorbic acid was isolated in 1928 by Szent-Gyorgyi from the adrenal tissue as hexuronic acid or antiscorbutic factor[24]. The highest levels per gram of vitamin C tissue are found in the pituitary and adrenal gland. In the United States, 25% of men and women consume less than 60 mg / day of vitamin C. 10% of adults consume less than 10%. The primary source of vitamin C in the diet is shown in Table 1, the rich source being from citrus fruits, kiwi, guayaba, camu-camu, papaya, melon, strawberry, mango, tomato, orange fruit juice and grapes ; and vegetables such as cauliflower, broccoli, cabbage, watercress, spinach, pepper and potatoes. A consumption of five pieces of fruits and vegetables, provides a concentration of more than 200 mg / day of vitamin C. The consumption of this source of nutrients also lies in the presence of other antioxidants such as flavonol glycosides and anthocyanins. Smoking patients who ingested camu-camu (Myrciaria dubia) equivalent to a dose of 1050 mg of vitamin C had a greater antioxidant and anti-inflammatory capacity than, if they received the equivalent dose of vitamin C in tablets[50], which is important for the participation of Other biochemical components.

**Table1.** The primary source of vitamin C in the diet.

| Source (portion) | Vitamin C (mg) | Source (portion) | Vitamin C (mg) |
|---|---|---|---|
| Camu-camu (100 g) | 2780 | Juice | |
| Guayaba | 273 | Grapefruit (½ cup) | 35 |
| Melón (¼) | 60 | Orange (½ cup) | 50 |
| Grapefruit | 40 | Grapes (½ cup) | 120 |
| Kiwi (1) | 75 | Vegetables | |
| Mango (1 cup, sliced) | 45 | Broccoli (fresh, ½ cup) | 158 |
| Orange (1) | 70 | Cauliflower (cooked, ½ cup) | 25 |
| Papaya (1 cup, sliced) | 85 | Cabbage (cooked, ½ cup) | 25 |
| Strawberry (1 cup) | 95 | Paprika (cooked, ½ cup) | 50 |
| Tangerina (1) | 25 | Potato (1, cooked) | 25 |
| Mango | 57 | Tomato (raw, ½ cup) | 15 |

Sources of vitamin C[11,17,8].

ARTÍCULO DE REVISIÓN

## CONCLUSION

While the evidence does not support any benefit in some diseases such as some infectious processes, the evidence is not consistent enough due to lack of well-designed studies in other morbid processes such as cancer in terms of parenteral use. It is reported its tolerability at high doses intravenously and there are reports that indicate a symptomatic health benefit. The development of clinical trials should maintain scientific plausibility based on the biology of vitamin C, tissue distribution and the type of cell transport it possesses. The consumption of fruits and vegetables represents a healthy recommendation and the understanding of the various biological effects of vitamin C indicates the importance of its consumption.

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