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Biochemical Effects and Therapeutic Application of Vitamin C (C6H8O6) on COVID-19 Infection

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***Abstract**: The current pandemic of COVID-19 infection worries the world, due to high morbidity and mortality. Various strategies for infection control, including nutritional interventions, have been considered, given the extremely rapid spread of the disease, the lack of specific effective and safe antiviral treatment and the difficulty of having a vaccine in the near future. Vitamin C, long known for its antioxidant and anti-infective effects, has been analyzed from the perspective of biochemical mechanisms with potential benefits in patients with severe COVID-19 infection. Favorable clinical results have been reported after intravenous administration of high doses of Vitamin C, but confirmation of these data requires extensive studies.*

***Keywords**: ascorbic acid, COVID-19, reactive oxygen sources , antioxidant, immune cells*

1.Introduction

Ascorbic acid is known as vitamin C, which is an essential micronutrient for the functioning of the human body. The effects of ascorbic acid deficiency have been known since antiquity, but the systematic description of the disease called scurvy was given by James Lind in the monograph *A Treatise on the Scurvy*, published in the seventeenth century. The structure of ascorbic acid was identified in 1932 by Albert Szent-Györgyi, who was awarded the Nobel Prize for this scientific contribution [1].

The plasma level of vitamin C in healthy people is 70 μmol / L, requiring a daily intake of 0.2 g/ day, but the needs may increase in certain pathological circumstances that increase the metabolism of ascorbic acid [2].

Today, scurvy is a rare disease, but time has shown that vitamin C has a huge potential, which continues to surprise us. To date, vitamin C has been shown to be a co-factor for at least 15 enzymes, involved in the processes of collagen and L-carnitine biosynthesis, tyrosine metabolism and dopamine to norepinephrine conversion, peptide degradation and hypoxic factor. Vitamin C has a detoxifying and antioxidant capacity, it acts on cell growth and differentiation and on immune regulation. Numerous studies have investigated the role of vitamin C in the treatment of neoplastic and infectious diseases [3]. In viral infections that do not have a specific treatment, nutritional interventions are often considered, by administering supplements, of which vitamins A, B, C, D, E, zinc and iron are well known. Currently, several clinical trials are evaluating the benefits of vitamin C administration for the evolution of COVID-19 infection [4].

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2.Materials and methods

This is a systematic review on the highest interest scientific topic of the day, related to pandemic COVID-19. The study is based on the theoretical correlation of biochemistry of vitamin C as a therapeutic application for the patients with COVID-19 infection. We have analyzed the medical and chemistry science published material since 2015 until the present day to identify the arguments for the benefits of vitamin C for the pathologic mechanisms of this viral disease.

Biochemistry of Vitamin C

Natural vitamin C has a crystalline, water-soluble structure with a melting temperature of 190°C. The chemical composition is C6H8O6, the four stereoisomers of the L-ascorbic-acid form is biological active, and the other three are inactive [5].

Many species of plants and animals can synthesize vitamin C from glucose, but the human species has lost this ability, being dependent on external intake, food or drug supplements.

Vitamin C helps the digestive absorption of iron and helps maintain the reduced form of iron and copper, which catalyzes many biochemical processes in the body.

The role of vitamin C in the regulation of collagen biosynthesis, maintaining the tissue structure and functionality, many processes have consequences for vascular disease, bone and joint, muscle, dermis, heart valve or of the lens level [3].

Vitamin C is easily damaged by oxidation after exposure to oxygen, alkanes, iron, copper or heat.

Vitamin C can reach most cells in the body in the form of L-ascorbic acid, transported specifically by *sodium-ascorbate cotransporter (SVC Ts)*, but especially in the oxidized form of dehydroascorbic acid (DHA), transported nonspecifically by *glucose transporters (GLUTs).* ***)*** and reduced to the level of the mitochondrial enzyme L-ascorbic acid (Figure 1) [3,6].

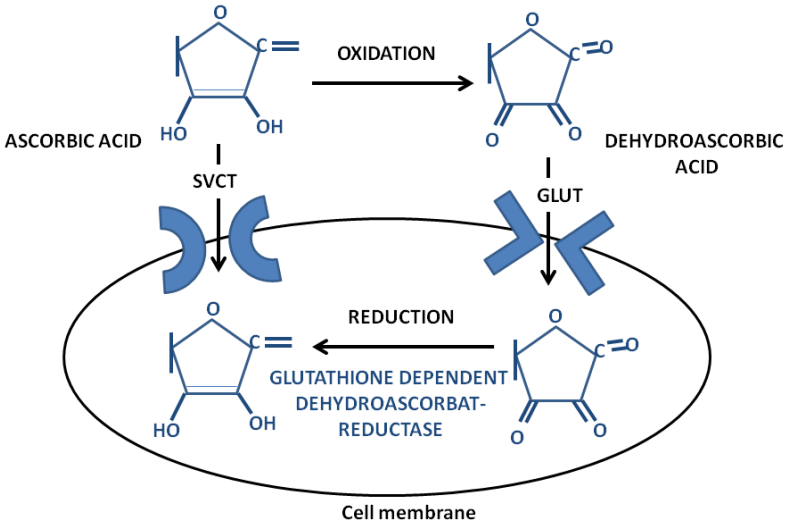

Figure 1. Chemical structure of ascorbic acid and dehydroascorbic acid and distinct mechanisms of transmembranar transport

Legend: SVCT: sodium-ascorbate cotransporter; GLUT: glucose transporters. Adapted on: ROOMI, M.W., SHANKER, N., NIEDZWIECKI, A., RATH, M. Vitamin C in Health: Scientific focus on its anti-cancer efficacy. Journal of Cellular Medicine and Natural Health, 15 June 2015:1-16. https://www.jcmnh.org/vitamin-c-in-health-scientific-focus-on-its-anti-cancer-efficacy/

Dehydroascorbic acid is unstable under physiological *p*H conditions, the excess remaining after reduction being irreversibly hydrolyzed [5].

Vitamin C is the most powerful and less toxic water-soluble antioxidant that can protect mol is collected by the DNA, lipids, proteins, and enzymes from the damaging action of ***reactive oxygen species (ROS)*** produced from normal or pathological cellular metabolism. The antioxidant role of vitamin C is supplemented by the recycling of other antioxidants, such as vitamin E and glutathione

[2].

Vitamin C has a protective role against some degenerative diseases such as cancer, aging, heart disease, cataracts. On the other hand, the influence of vitamin C in human pathology was considered for diabetes, hypertension, gout, asthma, allergies, infertility, schizophrenia, depression [5].

Vitamin C supplementation can lead to iron overload of the body or excess sodium after parenteral administration, with congestive heart failure or kidney failure. Haemolytic anemia may occur after high doses of vitamin C in people with glucose-6phosphat dehydrogenază (G6PD) [3].

The Role of Vitamin C on Infections

The involvement of vitamin C in the pathology of bacterial and viral infections is well known, but the benefits of additional vitamin C administration during infections remain controversial.

Activation of phagocytes during infections causes the release of ROS, with a role in inactivating viruses and destroying bacteria, but which can also destroy host cells, contributing to infectious pathogenic mechanisms [7].

The concentration of vitamin C in leukocytes is more than 10 to 100 times higher than in plasma, accumulated against the concentration gradient, suggesting that in addition to the anti-inflammatory role it intervenes in the proliferation and differentiation of these cells. In addition, vitamin C is the co-factor that ensures the normal functioning of hydroxylases, which enzymatically regulates the activity of *hypoxia-inducible factors (HIF),* gene transcription and immune cell signaling [2, 8].

The effects of vitamin C proven in vitro target the functioning of all populations of the immune system.

Vitamin C protects the integrity of the neutrophil wall, improves chemotactism, migration, microbial phagocytosis and ROS release. At the level of monocytes / macrophages decreases the secretion of cytokines, especially IL-6 and TNF-α, stimulates phagocytosis and clearance of macrophages.

Vitamin C stimulates the proliferation and activation of T lymphocytes, but high doses decrease cell viability and the secretion of pro and anti-inflammatory cytokines. Activation of T lymphocytes is accompanied by increased SCTV2 expression, which allows intracellular uptake of ascorbic acid, with antioxidant effect [9].

Vitamin C intervenes in regulating the proliferation and functionality of B lymphocytes, the main component of adaptive immunity, influencing the serum concentration of IgA and IgM.

Natural killer cells (NK) in the immune response play an important role in viral infections, accelerating the proliferation observed in the presence of vitamin C, without being influenced by the cytotoxic capacity [7, 10].

The use of vitamin C in viral infections can be based on two hypotheses: decreased circulating levels through metabolic consumption in acute viral infections and immunomodulation of α / β interferon production and *downregulating* of pro-inflammatory cytokines.

Although numerous studies have been conducted on the benefits of curative or preventive administration of vitamin C in influenza epidemics, contradictory results have been reported [11].

Given experimental data, increased ROS during the infectious immune response leads to decreased levels of vitamin C in plasma, leukocytes, urine, or bronchoalveolar secretions, and the hypothesis that vitamin C administration in severe infections may attenuate systemic inflammation, sepsis-induced clotting may be supported and vascular lesions, too. Numerous clinical trials have demonstrated the safety of intravenous administration of high doses of vitamin C and have given encouraging conclusions on the decrease in mortality in patients with sepsis, but these data are to be validated by extensive randomized trials [1 2].

Vitamin C related to COVID-19 Infections

COVID-19 infection is the cause of the most devastating pandemics in the last century, whose etiology is virus SARS-COV-2, the entire world learn to know and live with him. Although it spreads easily, the impact on the population varies. Three clinical stages of the infection have been described:

asymptomatic stage I, stage II with mild and moderate symptoms, accompanied by the presence of the virus and stage III with severe respiratory symptoms, sepsis or multiple organ failure [13].

The anatomically-pathologically observed lung lesions in severe respiratory forms of COVID-19, even in patients with viral clearance and without opportunistic infections, were diffuse alveolar destructions, alveolar epithelial hyperplasia and the presence of activated alveolar and interstitial macrophages. Alveolar alteration is the consequence of inflammation due to the excessive immune response from the host, in conditions of very rapid viral replication and a delayed response of type I IFN, accompanied by the accumulation of a large number of macrophages-monocytes attracted by inflammation mediators. Thus, a vicious circle is formed that aggravates severe respiratory dysfunction. In addition, disorder of the type I IFN response contributes to increased apoptosis of T lymphocytes, decreasing viral clearance [14].

Type I interferons are synthesized by most cells as an antiviral defense mechanism. In alveolar epithelial cells of type II, their production is triggered by the signals transmitted by the recognition of the virus at the level of specific receptors.

Macrophages react quickly by intensifying inflammatory activity and consecutive burns [15].

The "Warburg effect" is installed in macrophages and effector T lymphocytes due to changes in metabolism by increasing glycolysis and glucose consumption in the presence of oxygen, associated with cellular processes such as angiogenesis, hypoxia, macrophage polarization and T lymphocyte activation [16].

At the level of activated macrophages, an increased amount of lactate is produced, which is transferred to alveolar epithelial cells of type II, where it is used to produce ATP inhibits the mitochondrial signaling loci of viral proteins. Macrophage-released lactate can attenuate the nonspecific immunity of the host by decreasing the production of type I IFN, decreasing viral clearance (Figure 2) [14,17].

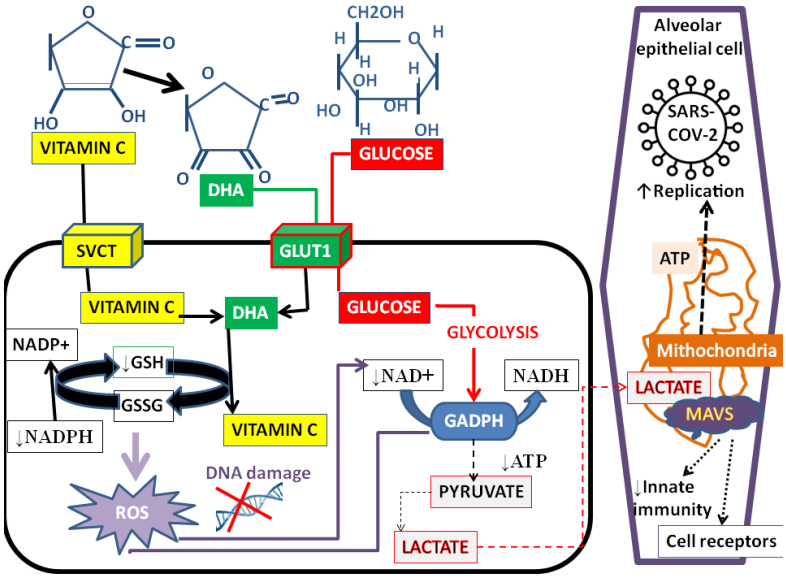

Figure 2. Possible effect of Vitamin C on Glucose Metabolism related to SARS-COV-2 Infection point to immune activated effectors cells and epithelial alveolar cells

***Legend**: ATP: adenosine triphosphate; DHA: dehydroascorbate; GADPH: glyceraldehyde-3-phosphate dehydrogenase; GSH: glutathione; GSSH: glutathione disulfide; GLUT: Glucose transporter; MAVS: mitochondrial antiviral-signaling protein; NADH: reduced nicotinamide adenine dinucleotide; NAD: nicotinamide adenine dinucleotide; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: reduced nicotinamide adenine dinucleotide phosphate; SVCT: sodium vitamin C co-transporter. Adapted on: EROL, A. High-dose intravenous vitamin C treatment for COVID-19. (a mechanistic approach). Preprint 2020 Feb. (https://www.researchgate.net/publication/339511104). https://doi.org/10.31219/osf.io/p7ex8*

In activated immune cells, the production of reactive oxygen species (ROS) increases, and dehydroascorbic acid is transported intracellularly, where it is reduced to vitamin C, with the price of GSH, thioredoxin and nicotinamide adenine dinucleotide phosphate (NADPH). The accumulation of

ROS is the consequence of the increased production, but also of the decrease of the elimination, by involving the redox couples NADPH / NADP + and GSH / GSSG (glutathione disufide). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is an enzyme of the redox system, inhibited by ROS growth, which can alter DNA and RNA polymerase**.** *Nicotinamide adenine dinucleotide* (NAD +) is an enzymatic co-factor of enzymatic activation of GAPDH. Decreased NAD + inhibits GADPH, with decreased ATP and pyruvate production, leading to an energy crisis and cell death [9, 17].

Intravenous administration of high doses of vitamin C in sepsis and septic shock acts as a pro-oxidant for immune cells, dependent on glycolysis for bioenergetic function, but as an antioxidant for lung epithelial cells, which produce ATP by oxidative phosphorylation at the mitochondrial level. Furthermore, vitamin C can inhibit the production of lactate in the act of immune cells and wool protecting alveolar type II epithelial cells. Intravenous administration of high doses of vitamin C may be beneficial for the patient with COVID-19 if the decision is made at the right time, as early as possible after the report of respiratory distress, based on clinical scores and biomarkers of inflammation and oxidative stress.

The recommended effective doses are 200mg / kgc / day for 4 days. The risks of this procedure are related to alveolar inflammation secondary to the destruction of immune cells by osmotic mechanism, but not apoptotic. The combination of intravenous glucocorticoids is useful for attenuating this alveolar inflammation [14, 17, 18].

Conclusions

Severe lung damage from COVID-19 infection is the consequence of uncontrolled inflammation, lesion activity of oxygen free radicals and alteration of the alveolo-capillary barrier. Documentation of the antioxidant action of vitamin C at the cellular and tissue level justifies the benefit of use in severe viral infections, accompanied by excess cytokines and oxidative stress. Favorable clinical data reported to date are favorable for the intravenous use of high doses of vitamin C in severe COVID-19-associated pneumonia, but further studies are needed in this area, at least until specific vaccines and antiviral drugs are available.

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