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ARTICULO DE REVISION

The immune system and SARS-CoV-2 infection. Are antioxidants a prevention therapy?

El sistema inmune y la infección por SARS-CoV-2. ¿Son los antioxidantes una terapia preventiva?

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ABSTRACT

The novel coronavirus (SARS-CoV-2) causes severe acute respiratory distress syndrome COVID-19. An increased production of oxygen reactive species along with disturbance of antioxidant systems are present in respiratory viral infections, such as COVID-19. We provide an overview about the role of antioxidants in immune system and the effect of ascorbic acid, tocopheroles, carotenoids and retinoids in a viral infection. The immunostimulant effects of vitamin C are related to an increase in cellular and humoral response as well as antinflammatory and antiviral effects. Vitamin C plays an important role for reversing the endothelial damage, hence supporting the use of ascorbate in preventing COVID-19 and its vascular complications in infected subjects. Also, Vitamin C prevents the pro-oxidant activity of vitamin E. Antioxidant protection of immune cells and decreased the pro-inflammatory cytokines are effects attributed to vitamin E. The immune regulatory role of this vitamin could be relevant for reducing the risk of respiratory diseases, such as influenza and pneumonia or COVID-19. Vitamin A is vital for maintaining the integrity of mucosal and epithelia as part of the primary unspecific defense mechanisms, and for cellular and humoral immune response. The incorporation of exogenous antioxidants such as vitamins C, E and A, in well tolerated doses may be useful as supporting therapy during the active period of the disease and the recovery stage.

Keywords: antioxidants; ascorbic acid; tocopherols; tocotrienols; carotenoids; immune system; SARS-CoV-2 infection.

RESUMEN

El nuevo beta coronavirus SARS-CoV-2 es responsable de la COVID-19. Un incremento en las especies reactivas del oxígeno y alteración en los sistemas antioxidantes se producen en las infecciones respiratorias como la COVID-19. Los autores describen el rol de los antioxidantes en el sistema inmune y el efecto del ácido ascórbico, tocoferoles, carotenoides y retinoides en la infección viral. El efecto inmunoestimulante de la vitamina C se relacionan con un incremento de la respuesta celular y humoral, así como con sus propiedades antinflamatorias y antivirales. Esta vitamina desempeña un papel importante para revertir el daño endotelial, de utilidad en la prevención de la COVID-19 y de sus complicaciones vasculares. La vitamina C previene la actividad pro-oxidante de la vitamina E. La protección antioxidante de las células inmunes y un descenso en las citocinas proinflamatorias son efectos atribuidos a la vitamina E. El papel de esta vitamina podría ser relevante en la reducción del riesgo de enfermedades respiratorias como la influenza, la neumonía o la COVID-19. La vitamina A es vital para mantener la integridad de las mucosas y los epitelios como parte de los mecanismos de defensa inespecíficos, y para la respuesta inmune celular y humoral. La administración de antioxidantes exógenos como las vitaminas C, E y A en dosis adecuadas y bien toleradas, pudiera ser de utilidad como terapia de apoyo durante el período activo de la enfermedad y en la recuperación de los pacientes con diagnóstico de COVID-19.

Palabras claves: antioxidantes; ácido ascórbico; tocoferoles; carotenoides; retinoides; beta coronavirus SARS-CoV-2; infección por SARS-CoV-2

INTRODUCTION

At the end of 2019, a pneumonia and a severe acute respiratory distress syndrome caused by a novel beta coronavirus (SARS-CoV-2) were identified in the region of Wuhan, China. The infection has expanded to a great number of countries; hence, COVID-19 was declared a Pandemic, by the World Health Organization (Li *et al*, 2020).

Although a specific and definitive antiviral therapy is not yet available, various pharmacological alternatives have been proposed. Lythgoe *et al* reviewed and registered interventional clinical trials for the treatment and prevention of COVID-19 (Lythgoe & Middleton, 2020). The World Health Organization reports several approved vaccines as well as many vaccine candidates in clinical trials phases, worldwide.

Mortality rates seem particularly high when patients suffer from different comorbidities. In some COVID-19 infections, there is a greater-than-expected release of cytokines by the immune cells. Such signal molecules trigger a pro-inflammatory environment, a condition related to a *redox* metabolism imbalance, with oxidative damage, including lipid peroxidation and DNA oxidation as well as the decrease in antioxidant defenses. Modifications in cell signaling, *redox* control and gene expression are originated as consequence of *redox* imbalance, followed by the progressive and accelerated systemic inflammatory response, tissue damage and multi-organ failure (Song *et al*, 2020).

The function of antioxidant systems could allow the prevention or correction of damaging by reactive oxygen species. Some authors suggested that supplementation with antioxidants attenuates the severity of the acute respiratory distress syndrome, due to their influence on the immune system and via antioxidant action itself (Pauling, 1971; Hemila & Chalker, 2020; Sansone *et al*, 2020). Thus, it can be described a relationship among viral replication, cytokines proinflammatory production, inflammation and *redox* imbalance. Although, the reactive oxygen species are involved in the pathophysiology of these processes, a successful response to exogenous antioxidants has not been achieved, yet. For COVID-19, there is insufficient evidence thus far.

The administration of antioxidants as adjuvant intervention strategies, in the early stages of infection, could play an important role in preventing the disease evolution. In Wuhan, China, a high-dose of intravenous ascorbic acid was administered to patients, for facilitating the immune response development and reducing the COVID cytokine storm (Boretti & Banik, 2020). Moreover, the role of antioxidants in the prevention and treatment of sepsis and pneumonia has been studied for years (Carr & Rowe, 2020).

This article is aimed at analyzing the role of antioxidants vitamins in the immune system and its current potential effect approaches for COVID-19.

SARS-CoV-2, immune system and inflammatory response

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new betacoronavirus that possess an non-segmented, single-stranded, positive-sense RNA genome encircled with an enveloped viral nucleocapsid. The genome of the virus codes four structural proteins identified as protein S (spike), protein E (envelope), protein M (membrane) and protein N (nucleocapsid). Angiotensin-converting enzyme 2 (ACE2) was identified as the entry receptor for SARS-CoV-2. This receptor is broadly distributed in lungs, heart, kidneys, liver, intestine, and brain (Dhama *et al*, 2020).

As part of the host immune - inflammatory response, alveolar macrophages and dendritic cells are infected by the virus. The cells present SARS-CoV-2 antigens to T cells, leading to T cell activation (Zabetakis *et al*, 2020). The cells also release a variety of substances and inflammatory mediators including eicosanoids, proteases, oxygen reactive species and proinflammatory cytokines, with loss of the normal regulatory control of their production. These substances lead to the accelerated progression of the systemic inflammatory response and the severity SARS-CoV-2 infection (Song *et al*, 2020; Ye *et al*, 2020).

Consequently, COVID-19 is characterized by an increase in the release of pro-inflammatory cytokines such as granulocyte macrophage colony stimulating factor (GM-CSF), interleukin 6, monocyte chemoattractant protein 1 (MCP-1) and tumor necrosis factor alpha (TNFα), among others (Ye *et al*, 2020). The molecules exert their activity upon other immune cells, to continue recruiting them to the lesion site. Therefore, changes in oxidative metabolism are produced, with enhanced production of reactive oxygen species, depletion of antioxidant mechanisms, a disruption of *redox* control,

cellular signaling and genetic expression – changes which are associated with the severe evolution of the disease (Khomich *et al*, 2018; Delgado & Mesta, 2020).

Reactive oxygen species and *redox* balance inside cells

The science of free radicals started more than fifty years ago, when Harman suggested that oxygen radicals could be formed *in vivo* by a variety of metabolic reactions (Tan *et al*, 2018). A free radical is considered to be any chemical species that presents at least one unpaired electron in the external orbit; hence, generating free radicals very chemically unstable and very reactive. Free radicals can abstract electrons from other compounds to attain stability. Thus, the attacked molecule loses its electron and becomes a free radical itself, beginning a chain reaction cascade, which finally damages the living cell. Superoxide and hydroxyl radicals together with singlet oxygen and hydrogen peroxide are identified as reactive oxygen species (ROS). ROS have a short half-life, easy dissemination within the body, and diverse subcellular expressions (Phaniendra *et al*, 2015).

Reactive species can act as signal molecules and mediate specific physiological processes at low concentrations, such as in immune system. ROS stimulates intracellular signaling pathways and activate transcription factors. In conditions of *redox* imbalance, nuclear factor □B (NF□B), hypoxia inducible factor 1 (HIF-1) and activator protein 1 (AP-1) are activated. These transcription factors induce the expression of genes that encode inflammatory cytokines and adhesion molecules (Delgado & Mesta, 2020; Sies & Jones, 2020).

An adaptive response to imbalance is achieved with the activation of transcription factor *Nrf2* (nuclear erythroid factor 2). This transcription factor binds to the antioxidant response element, a sequence of nitrogenous bases found in the promoter region of genes that encode antioxidant enzymes, among others (Tebay *et al*, 2015; McCord *et al*, 2020). Some authors recognized the role of *Nrf2* as part of regulatory mechanisms that susceptibility govern to viral respiratory infections and in the preservation of lung architecture (Liu *et al*, 2019). Komaravelli showed that syncytial respiratory virus infection increases ROS and induces a decrease of the *Nrf2* with the consequent reduction of the antioxidant enzyme expression (Komaravelli *et al*, 2015). This result is consistent with the relationship between viral infection, *redox* imbalance and inflammation.

Protective antioxidant pathways are required in response to ROS in cells and body systems, including the immune system.

Reactive species and cells of the immune system

The response to the appearance of a pathogen into the body depends on the immune system. It has two major components: innate and adaptive immunity. The first line of defense (innate immune system) includes monocytes/macrophages, neutrophils, natural killer (NK) and dendritic cells, cells which role is to both directly attack pathogens and activate the acquired immune system. The latter is comprised of T and B cells. This system recognizes foreign pathogens presented by antigen presenting cells, and produces a specific and efficient response along with the development of immunological memory (Brambilla *et al*, 2008).

The protective function of the immune system, against pathogens, is a source of free radicals. The binding of ligands (such as a virus) to phagocytes, triggers signals that result in a respiratory burst. The nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) complex, which reduces molecular oxygen to microbicidal reactive oxygen species, allows the formation of superoxide anion (Harijith *et al*, 2017). Superoxide anion induces to hydrogen peroxide (H_2O_2). H_2O_2 is a reactive specie that mediates cell signaling, and diffuses through cells to initiate effects such as the proliferation and recruitment of immune cells (Sies, 2017).

Catalase (CAT), peroxiredoxin or glutathione peroxidase enzymes permit the transformation of H_2O_2 in water. In addition, the H_2O_2 forms hypochlorous acid, a reactive oxidant that is released from neutrophils and monocytes (Morita *et al*, 2016). In the presence of iron or copper, via the Fenton and Haber Weiss reactions, hydroxyl radicals are formed from the H_2O_2, generating this radical a powerful oxidant (Luczaj *et al*, 2017).

The reactivity of reactive species leads to structural alterations in the biomolecules of cells. The presence of unsaturated fatty acids in the membranes of immune system cells

favors lipid peroxidation. Although, these cells have a higher antioxidant content in regards to other cells, their defense mechanisms may become depleted depending on the exposure to oxidative forces, and in particular in the presence of a cytokine storm (Carr & Maggini, 2017; Kassi *et al*, 2020).
Several studies are aimed at investigating the oxidative damage of the different components of cells, the functioning of antioxidant enzymes and, more recently, the biological effects derived from the activation of signaling mechanisms expressed in the response to oxidant species (Panieri & Santoro, 2015; Schönrich *et al*, 2020). In this context, it has been identified an association between oxidative stress indicators and the degree of severity of lung damage in patients infected with respiratory syncytial virus (Moreno *et al*, 2015).
Due to the involvement of ROS in the functions of the immune system and inflammation, it has been suggested that antioxidants could be used to diminish the negative effects of some disorders in which, there is immune compromise, such as in COVID-19.

Antioxidants

The response to oxidizing action depends on antioxidant mechanisms. Halliwell (2012) defined an antioxidant as any substance that, in low concentrations compared to the oxidizable substrate, significantly reduces or inhibits the oxidation of this substrate. Antioxidants are represented by enzymes that remove ROS, and compounds of low molecular weight that prevent the formation of reactive oxygen species and mitigate their deleterious effects. (Sies, 2017).
Endogenous antioxidants comprise enzymatic and no enzymatic systems. Enzyme systems are represented by superoxide dismutase, catalase, and thiol oxidoreductases enzymes which transform reactive species, as already mentioned. The non-enzymatic system includes water-soluble and fat-soluble antioxidants. Fat-soluble antioxidants are vital in the protection of the membranes from oxidative damage, while water-soluble antioxidants help reducing the effects or avoid oxidative changes in the cytosol and in the extracellular environment. The interconnected mode of action of antioxidants of both systems could produce a greater synergistic effect than that from each antioxidant itself (Tan *et al*, 2018).
A set of low molecular weight molecules like bilirubin, urate, glutathione and ubiquinone is recognized within the non-enzymatic systems. Vitamin E (tocopherols and tocotrienols), vitamin C (ascorbate), □-carotene and vitamin A, lipoic acid and selenium are included in the exogenous antioxidants. In addition, a set of compounds, derived from phytochemicals, and including polyphenols in the form of flavonoids, play an important role in the control of mechanisms related to ROS (Sies, 2017; Ursini *et al*, 2016).

Antioxidant vitamins, reactive species and the immune system

The activation of cells of the immune system generates reactive oxygen species and an inflammatory response in □-coronavirus pneumonia. An association between oxidative stress biomarkers and the severity of lung damage in patients with respiratory infection has been described (Moreno *et al*, 2015). Consequently, ascorbic acid, tocopherols and retinoids could be used as reinforcement for COVID-19 intervention strategies.

Ascorbic acid

Ascorbic acid is a water-soluble vitamin with antioxidant properties and pro-oxidant effects at high concentrations. In humans, the synthesis of this vitamin is limited due to the lack of L-gulono -γ-lactone oxidase enzyme, required in the biosynthetic pathway (Nelson & Cox, 2008). Ascorbate captures hydroxyl and superoxide radicals, participates in the neutralization of the singlet oxygen, blocks lipid peroxidation and protects DNA from oxidation (Oudemans, 2014). Ascorbic acid restores the antioxidant form of vitamin E. Oxidized ascorbate can be reduced by glutathione dependent systems. The actions of vitamin C help conserving the redox homeostasis, gene transcription and epigenetic pathways (Carr & Maggini, 2017; Brabson *et al*, 2021).
Evidence to support the action of vitamin C in the immune system has been demonstrated in numerous experimental studies *in vitro* and *in vivo*. In this context, Tan and collaborators showed activation of NF□B in *Gulo knockout* mice. This effect was reversed with the addition of vitamin C (Tan et *al*, 2005).

The administration of ascorbate, previous to viral exposure, decreased the release of pro-inflammatory cytokines in the lungs of animals exposed to the H1N1 virus (Li & Beck, 2006).

Vitamin C deficiency results in impaired immunity and of high susceptibility to potentially fatal infections such as pneumonia, particularly in the elderly (Carr & Maggini, 2017). It has been reported, in COVID-19 patients, low levels of vitamin C; that is why, some authors have advice their supply during treatment (Xing *et al*, 2021).

Moreover, some authors have described the immunostimulant effects of vitamin C related to an increase in cellular and humoral response as well as antinflammatory and antiviral effects (van Gorkom *et al*, 2018; Colunga *et al*, 2020). Van Gorkom *et al*. debated about the effects of ascorbic acid in the development and function of T and B lymphocytes and concluded that vitamin C is required for T cell proliferation and function. Contradictory results were found, though, in the role of this vitamin for B lymphocytes (van Gorkom *et al*, 2018).

Fowler and colleagues conducted a clinical trial in 167 patients hospitalized at intensive care unit and with a diagnosis of sepsis and respiratory distress syndrome. These patients received a 96-hour infusion of vitamin C. The authors did not find significantly improved organ dysfunction scores or altered markers of inflammation and vascular injury damage after the supplementation (Fowler *et al*, 2019). On the contrary, Hiedra et al.(2020) observed in COVID-19 patients, a decrease of the inflammatory biomarkers, in which oxygen and intravenous vitamin C were used as part of the treatment.

In China, it has been administered high doses of intravenous vitamin C to the patients with COVID-19. The response of the immune system has been promising in the reduction of the cytokine storm or increase of the antiviral activity (Boretti & Banik, 2020). Continuing clinical trials with vitamin C, as an additive antioxidant approach for COVID-19, is also recommended (Carr & Rowe, 2020; Liu *et al*, 2020; Gao *et al*, 2021). Other testings evaluate the potential of supplementation with vitamin C, A, B, and E to decrease severity status and mortality of COVID-19 patients in the intensive care units (Beigmohammadi *et al*, 2020).

The role of vitamin C in the endothelium, in patients with SARS-CoV-2 infection, has also been analyzed and reported. Endothelial damage has shown to be a basic element in infection, either by a mechanism known as endothelitis (Vargas *et al*, 2020) and/or by production of antibodies against endothelial cells (Yang *et al*, 2005). Scioli et al. demonstrated that pretreatment with vitamin C decreases the expression of vascular and intercellular cell adhesion molecules (VCAM/ICAM) in experimental conditions. This antioxidant seems to play an important role in reversing the endothelial damage, hence supporting the use of ascorbate in preventing COVID-19 and its vascular complications in infected subjects (Scioli *et al*, 2019).

Tocopherols and tocotrienols

Vitamin E comprises eight lipophilic isomers, including four tocopherols and four tocotrienols, with an aromatic chromanol ring in their structure, in which phenolic group can provide hydrogen. The □-tocopherol is the most abundant compound in tissues, although the □-tocopherol, a demethylated form, also exists in significant amounts. These molecules capture the peroxyl radicals formed during the oxidation of unsaturated fatty acids and enriched in membranes of immune cells (Jiang, 2014). Recent studies showed that vitamin E modulate cellular responses such as cell signaling, gene expression and apoptosis (Zingg, 2019).

The tocopheryl radical (□-TO□) is generated from the reaction of alpha tocopherol. This radical can be reduced by ascorbate, ubiquinone and bilirubin, or may act as a pro-oxidant (Hensley *et al*, 2004). Also, □- and δ-tocopherol are scavengers of nitrogen reactive species and decrease signaling mediated by NFκB, with the consequent anti-inflammatory effect (Jiang, 2014; Pein *et al*, 2018).

Some studies have exposed that vitamin E is associated with the immune system. De la Fuente *et al.* observed that chemotaxis and phagocytic capacities of neutrophils were increased after antioxidant treatment in animal and human studies (De la Fuente *et al*, 1998; De la Fuente *et al*, 2008). Vitamin E can also improve both humoral (antibody production) and cell-mediated (particularly that of T cells) immune functions. It has been also reported enhanced mitogenic lymphocyte responses, immunoglobulin levels, antibody responses, natural killer (NK) cell activity, increased IL-2 cytokine secretion, and decreased the risk of infection with vitamin E supplementation (Lewis *et al*, 2019; Shakoor *et al*, 2021).

The antioxidant role and beneficial effects on the immune response of the tocotrienols are also recognized when considering these experimental results. The anti-inflammatory and immunomodulatory effects of □-tocotrienol and δ-tocotrienol have been documented, likewise. In a study conducted by Radhakrishnan and his group, administration of these forms of vitamin E improved the production of antibodies against tetanus toxoid via immunizations in mice, along with an increase in IFN-□ in stimulated spleen cells (Radhakrishnan *et al*, 2013).

Antioxidant protection of immune cells and decreased proinflammatory cytokines are effects attributed to vitamin E. The immune regulatory role of this vitamin could be relevant in reducing the risk of respiratory diseases, such as influenza and pneumonia or COVID-19.

Carotenoids and retinoids

Carotenoids are a group of pigments synthesized in plants and microorganisms. They are a numerous group of isoprenoid lipophilic compounds. Hydrocarbon forms of carotenoids are known as "carotenes" while oxygenated forms are termed "xanthophylls" (Toti *et al*, 2018; Bahtt & Patel, 2020).

Some carotenoids such as □-carotene are metabolically converted to vitamin A or retinol in the body. Retinol gets oxidized into retinal and further to retinoic acid. These metabolites are identified as retinoid. These molecules act as ligands for nuclear receptors, regulating gene expression that is sensitive to *redox* states (Oliveira *et al*, 2018).

The carotenoids act as antioxidants. Due to the presence of conjugated double bonds in their structure, these molecules interact with singlet oxygen, a reaction that can occur in cells of the immune system (Edge & Truscott, 2018). Likewise, some of these species have a high potential to eliminate or transform peroxyl radicals, an activity that is relevant in biological membranes. The presence of polyunsaturated fatty acids in the membranes of immune cells becomes them more susceptible to this mechanism of free radical damage. With oxidative changes, the native structure of the membranes is modified, and therefore the functions that derive from it (Kaulmann & Bohn, 2014).

In studies *in vitro*, astaxanthin, a xanthophyll carotenoid, can capture peroxinitrite and nitrogen dioxide with decreased tyrosine nitration. Tyrosine nitration is a biomarker of oxidative damage (Bartesaghi & Radi, 2018). Similar results have been observed with the use of □-carotene and lutein. Astaxanthin can also interact with hydroxyl radicals and superoxide anion (Nishino *et al*, 2017; Maoka, 2019). These processes are related to the antioxidant role of carotenoids, though this function is highly debated.

Carotenoids and retinoids have immunomodulatory function (Toti *et al*, 2018, Asson & Rochetti, 2016; Huang *et al*, 2018). The retinoic acid binds to RAR receptors, which are relevant in the regulation of differentiation, maturation and cell function in the innate immune system (Oliveira *et al*, 2018).

In an interesting work by Surman et al, immune factors and epithelial barriers were examined in mice with deficiency of vitamin A, vitamin D and both combined. Mice received various insults, including a nasal inoculation with a respiratory pathogen of the species. The authors observed squamous metaplasia and bacterial infections in the kidneys of animals with vitamin A deficiency. Changes in immunoglobulin isotypes and cytokine patterns were also observed (Surman et al, 2020).

An association between basal vitamin A levels and the antibody response in healthy children was reported by Patel et al (Patel *et al*, 2019). There have been observed hystopathological changes in lung tissue in adults with vitamin A deficiency. These disorders lead to dysfunction and increased susceptibility to respiratory disease, a matter of great importance in COVID-19 infection (Timoneda *et al*, 2018).

Therefore, vitamin A is vital for maintaining the integrity of mucosal and epithelia as part of the primary unspecific defense mechanisms, and for cellular and humoral immune response.

Bioinformatic and computational studies related to pharmacology approach, are in correspondence with the anti-viral, anti-inflammatory and immunomodulatory actions of vitamin A (Li *et al*, 2020).

Alternatives assays are performed using other molecules with antioxidant properties for COVID-19. Some cited molecules include melatonin (Shneider *et al*, 2020) and polyphenols (Filardo *et al*, 2020, Margină *et al*, 2020). Opportunities for the exploration of *Nrf2* activators are also suggested as possible treatment options, as proposed by McCord *et al*., who found lower gene expression of proinflammatory cytokines in presence of an *Nrf2* activator (McCord *et al*, 2020).

CONCLUSIONS

The authors conclude that: (1) Vitamin C plays a relevant role in the reversion of the endothelial damage, hence supporting the use of ascorbate for the prevention of COVID-19 and its vascular complications, in infected subjects. Vitamin C prevents the pro-oxidant activity of vitamin E. Combined treatment with vitamin C and vitamin E decrease oxidative stress; (2) Antioxidant protection of immune cells and decreased pro-inflammatory cytokines are effects attributed to vitamin E. The immune regulatory role of this vitamin could be relevant in reducing the risk of respiratory diseases, such as influenza and pneumonia or COVID-19; (3) Vitamin A is vital for maintaining the integrity of mucosal and epithelia as part of the primary unspecific defense mechanisms, and for cellular and humoral immune response.

Ascorbate, tocopherols, carotenoids and retinoids have immunomodulatory functions and potential efficacy as supporting therapy during the early active period and recovery stage of the disease.

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