

REVIEW ARTICLE**Oxidative Stress, Antioxidant Defenses, COVID-19 and Pollution****Author**

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Abstract

Patients with degenerative diseases present a chronic oxidative stress state, which puts them at a disadvantage when facing viral infections such as COVID-19. This is because there is a close relationship between redox signaling and this inflammatory response. Therefore, chronic changes in the redox balance cause alterations in the regulation of the immune system. An inflammatory response that must be reparative and self-limited loses its function and remains over time. In a chronic state of oxidative stress, there is a deficiency of antioxidants. This results in low levels of hormones, vitamins and trace elements, which are essential for the regulation of these systems.

Furthermore, low levels of antioxidants imply a diminished capacity for a regulated inflammatory responses are much more vulnerable to a cytokine storm that mainly attacks the lungs, since they present a vicious circle between the null or diminished response of the antioxidant systems and the loss of regulation of the inflammatory process. Therefore, these patients are at a disadvantage in counteracting the response of defense systems to infection from SAR-COV19. A plausible option may be to restore the levels of Vitamins A, B, C, D, E and of essential trace elements such as manganese, selenium, zinc, in the body, which are key to either preventing or reducing the severity of the response of the immune system to the disease caused by SAR-CoV2.

For the present review, we searched the specific sites of the Cochrane library database, PubMed and Medscape. The inclusion criteria were documents written in English or Spanish, published during the last 10 years.

Keywords: SARS-CoV2 virus, oxidative stress, dysregulation of the immune response, pollution

1. Oxidative stress and COVID-19

There is a correlation between oxidative stress and SARS-CoV2 infection. This virus, which mainly attacks the respiratory tract, generates a pro-oxidant response.^{1,2,3,4} Patients with comorbidities associated to a chronic oxidative stress state tend to be severe cases of COVID-19, what can lead to death.¹

1.1. Virus induced oxidative stress

As part of the general innate immune response, the presence of respiratory burst inside phagocytes' endosomes, mainly neutrophils, is expected. Its purpose is to destroy pathogens with reactive oxygen species (ROS). This process, induced by the nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), has to be regulated in order to avoid cell death due to an elevated ROS synthesis.⁵ With respect to virus properties, the molecular mechanisms, by which respiratory viruses (such as influenza virus, respiratory syncytial virus and rhinovirus) cause a redox state alteration, have not been completely elucidated, for example, when it comes to HIV and hepatitis virus. Nevertheless, for influenza virus, which is part of the same family as SARS-CoV 2 (Orthomyxoviridae), there are studies that report elevation of oxidative biomarkers in blood and urine in patients with influenza. 8-hydroxideoxiguanosine, malondialdehyde (MDA) and F2-isoprostane are some examples of the markers that have been reported. The above is due to the virus capacity to induce ROS-producing enzymes, such as NADPH oxidases, especially Nox2 and

xanthine oxidase, alveolar macrophages, neutrophils and, in less quantity, in epithelial cells. The elevated cell recruitment in the site of infection causes a cytokine storm and cell death due to the virus, presence in pulmonary tissue.^{1,4,6}

Regarding SARS-CoV2 properties, they could favour an epithelial deregulation by reducing the presence of angiotensin converting enzyme 2 (ACE2) receptors at the epithelial cell membrane. This can be done by two mechanisms (Figure 1): 1) internalization, after SARS-CoV2 S protein binds to ACE2; or 2) inhibition, mostly by the disintegrin and metalloprotease, ADAM-17, also known as Tumour Necrosis Factor alpha converting enzyme (TACE). The presence of viral mediators and proinflammatory cytokines inside epithelial cells entails upregulation of ADAM-17 expression, an enzyme with diverse functions, one of them being shedding membranal ACE2.^{7,8} Epithelial dysregulation is characterized by a low production of Ang (1-7), which leads to an increase of ROS production by low nitric oxide (NO) and an enhanced peroxynitrite synthesis (ONOO⁻).⁹ High levels of hydrogen peroxide (H₂O₂) can inhibit the JAK-STAT pathway, resulting in an interferon alpha (IFN- α) decrease,¹⁰ an importer viral response element. Moreover, low expression of Nrf2 has been found in COVID-19 patients.¹¹ In an ROS-rich environment, NRF2 binds to the antioxidant response element (ARE) in the promotor region of genes that codify for enzymes such as superoxide dismutase, catalase, peroxidase, glutathione peroxidase, etc.¹²

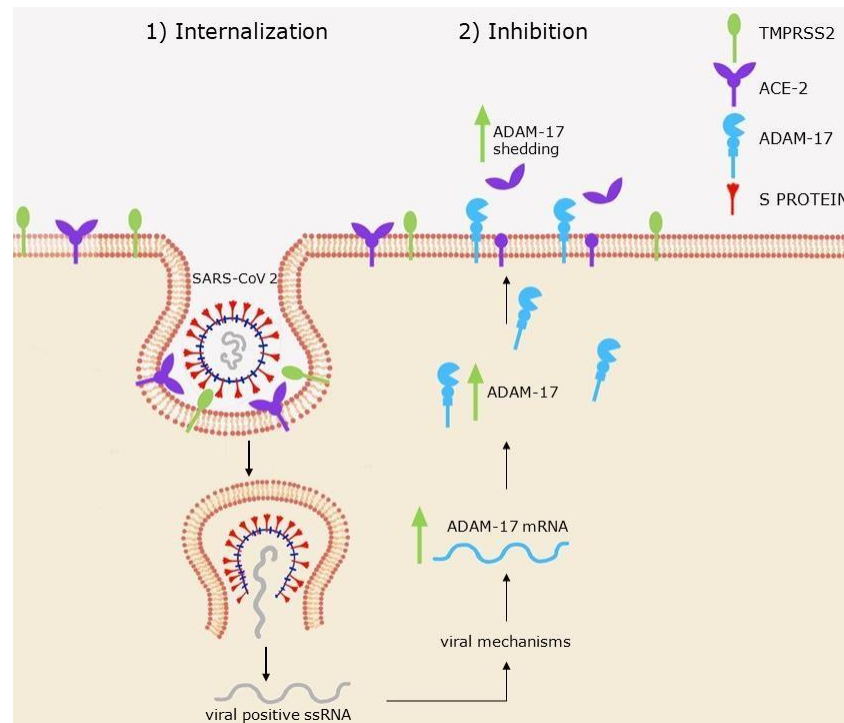


Figure 1. SARS-CoV2 mechanisms to decrease ACE-2 presence in the cellular membrane.

1) After the transmembrane protease, serine 2 (TMPRSS2) primes the S protein of SARS-CoV2, the latter binds to the receptor ACE-2 and internalizes into the cell as membrane proteins. 2) The presence of the positive single-stranded RNA induces upregulation of ADAM-17 transcription, thereby increasing its presence on the cellular surface. One of the functions of ADAM-17 is ACE-2 shedding, inhibiting its activity.

Another finding that allows us to see the relationship between case severity and ROS presence is the difference between ROS/Glutathione rates, which is high in intermediate and severe cases, and low in mild cases.¹²

In addition, cytokines and endotoxins stimulate one of the endothelial nitric oxide synthase (eNOS) isoforms, the inducible one (iNOS); this enzyme stimulates the production of NO, which reacts with the superoxide ion, forming the oxidant radical peroxynitrate (ONOO⁻)¹³. The generation of "cytokine storms" is a phenomenon that has occurred in patients with COVID-19, which includes uncontrolled production of IL-2, IL-6, IL-7, and tumour necrosis factor alpha (TNF- α), accompanied by hyperinflammation, cytopenia and hyperferritinemia, and is mainly caused by the presence of ROS, which can be generated from the Fenton reaction (Figure 2).

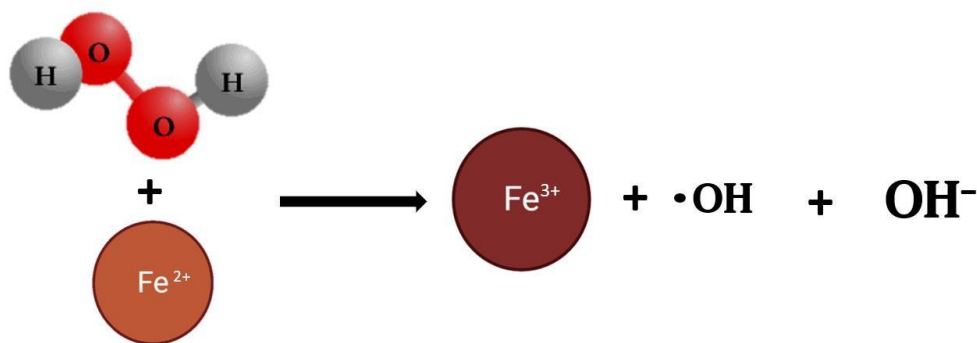


Figure 2: Fenton reaction, whose products are: ferric ion, hydroxyl radical and hydroxide.

Oxidative stress can result in cell death and decomposition of proteins, generating “oxidation specific epitopes”, which act as damage-associated molecular patterns (DAMP’s) capable of unleashing innate immune responses through their expression in the extracellular matrix, due to biomolecular damage that exceeds repair capacity. Also, excessive oxidation products can facilitate the activation of toll-like receptors (TLR’s) in cells, leading to a progressive amplification of the initial inflammatory response.¹⁴

1.2. Comorbidities and chronic oxidative stress

Some of the principal comorbidities among the severe COVID-19 cases are: Diabetes Mellitus 2 (DM2), obesity, hypertension and chronic obstructive pulmonary disease (COPD).¹⁵ These metabolic and cardiovascular pathologies entail chronic oxidative stress, which plays a role in the pathogenesis and its progression. Furthermore, this state is favored by endothelial dysfunction.¹⁶ Therefore, it is logical to expect a worse outcome in an infection that promotes the pre-existent dysfunction.

Some of the mechanisms that drive an increased production of ROS in the comorbidities mentioned earlier are:

- Hyperinsulinemia and insulin resistance lead to decreased activation of eNOS.
- Hyperactivity of the Renin-Angiotensin-Aldosterone System (RAAS) reduces NO bioavailability and increments macrophage activation.
- Increasing leptin levels also reduce NO bioavailability and increment monocyte chemoattractant protein-1 (MCP-1) or chemokine CCL2.
- Rising levels of perivascular adipose tissue (PVAT) products elevate the presence of TNF- α , IL-6, ROS and lower NO.
- Low density lipoproteins diminish the endothelial eNOS expression.¹⁷
- Elevated asymmetric dimethylarginine (ADMA) serum levels in diabetes, obesity and smokers is a competitive endogenous inhibitor of eNOS.¹⁸

Although there are several factors that alter the normal function of eNOS, hyperactivity of the inducible NOS (iNOS) has been described, principally in muscle and adipose tissue.¹⁸ Other diseases that present chronic oxidative stress, and are considered risk factors for severe infections,¹⁹ are autoimmune diseases. These are characterized by constant activation of the innate and adaptive immune response, provoked by self-antigens, leading to chronic inflammation,

either systemic or localized, depending on the antigen location. The continuous cell exposure to ROS generates a constant alteration of DNA, lipids and proteins, promoting the progression of the illness. Therefore, autoimmune diseases and COVID-19 share an altered and exacerbated immune response, with a pro-oxidant environment.

Dexamethasone is a glucocorticoid with an immunomodulatory effect, used in the treatment of inflammatory disorders, such as multiple sclerosis acute exacerbation, rheumatoid arthritis, etc. According to the preliminary result reported by the Nuffield Department of Medicine, treatment with dexamethasone, appears to diminish the mortality rate in COVID-19 patients needing mechanic ventilation or oxygen.²⁰ However, there are specifications, pros and cons, and profound analysis yet to consider, especially since the adverse effects of its administration are diverse.

2. Immune response dysregulation

Redox balance is primordial in order to have an adequate immune response, since this determines the maintenance of the membrane, proteins and nucleic acids integrity and functionality. In the immunologic cells, it is normal to find elevated ROS levels, seeing that they are one the main defense mechanisms against pathogens; thus, there is also a greater need of antioxidants. In the case of diabetes, continuous antioxidant supplementation reduces lipid peroxidation and the consecutive cell damage.^{21,22} Recent investigation suggests that the onset of severe pulmonary injury in COVID-19 depends on oxidative stress machinery activation and the innate immune response, causing the activation of transcription factors, such as nuclear factor NF- κ B, exacerbating the proinflammatory disease and oxidative

damage. The effects of ROS and reactive nitrogen species (RNS), especially lipidic peroxidation and membrane proteins oxidation, contribute to the transformation and hyalinization of the alveolar membranes, causing lethal respiratory difficulty.¹³

An alternative for countering the pro-oxidant state in COVID-19 patients is the supplementation of antioxidant elements and vitamins, such as: zinc, which reduces the formation of hydroxyl radical, avoids protein sulfhydryl group oxidation, and stimulates the immune system; some other examples are selenium, vitamin E, vitamin A, and others.²³

3. The role of antioxidants in viral infection by SARS-CoV2:

3.1. Vitamins A, B, C, D and E

3.1.1. Vitamin A.

In the human body, vitamin A is found as retinol, retinal, and retinoic acid. Its deficiency has been linked to infectious diseases such as measles and diarrhea.²⁴ In the lung, keratinization, loss of ciliated cells, mucus and goblet cells in the respiratory epithelium can be found, which cause lower respiratory tract infections.²⁵ In general, it triggers inflammation and aggravates previous inflammatory conditions. Immunologically, its deficit also conditions a progression and worsening of tuberculosis (TB) and human immunodeficiency virus (HIV), due to a decrease in TCD3+, TCD4+, and TCD28+ lymphocytes, as well as malaria. A dietary restriction deficiency compromises immunoglobulin (Ig) G1 responses, suppressing Th2 responses. It also compromises the effectiveness of inactivated bovine coronavirus vaccines.²⁵

On the other hand, when the vitamin is supplemented, a reduction in morbidity

and mortality has been seen in the aforementioned infectious pathologies.²⁶

Vitamin A and retinoids inhibit measles replication by upregulating elements of the innate immune response. This mechanism reveals the role it plays in the maintenance and function of innate and adaptive responses.²⁷ Two mechanisms have been proposed by which vitamin A exerts its effects on immune function, both by direct and indirect routes.

1) Direct pathways: vitamin A has a role in lymphocytic proliferation, through the activation of the retinoic acid receptor (RAR)-alpha.²⁸ In vitamin A-deficient subjects, excessive IFN-gamma production has been seen along with limited growth and differentiation of Th-2 cells, which subsequently promote Th-1 type responses and contribute to impaired immunity.²⁹

2) Indirect pathways: vitamin A exerts a control in the differentiation of epithelial

cells, by regulating keratin.³⁰ Hence, its deficiency results in an alteration of the epithelial structure (squamous metaplasia) and a reduction in the number of mucosa-secreting cells.³¹ The accelerated division of the epithelium on the mucosal surfaces of the intestines and lungs are especially susceptible to deficiency, resulting in a loss of gap junctions between epithelial cells,³² thus increasing the risk of bacterial translocation.³² Additionally, a reduction in the replication rate of basal and mucosal cells and in the proportions of hair cells has been seen, which is related to an increase in susceptibility to infections.³³

Vitamin A supplementation has been studied mainly in children with vitamin A deficiency, in the form of retinol, as capsules composed of 200,000 IU of retinol acetate in oil, taken orally every 6 months to replace retinol deficits (<0.70 µmol/L).³⁴

EFFECTS OF VITAMIN A ON INFECTIOUS DISEASES.

DISEASE	IMMUNE RESPONSE	CLINIC.	IMMUNE EFFECT.
Measles.	Th2-like response.	Decreased mortality and morbidity.	The replication of the virus decreases. Increased IgG response against measles. Increased lymphocyte count.
Diarrheal disease.	Important response through sIgA; variable immunity.	Decreased mortality and morbidity.	Unknown.
Respiratory disease.	Ciliary motility; alveolar macrophages.	Decreased mortality and morbidity of measles-associated pneumonia.	Unknown.
Malaria.	Cell and antibody mediated immune responses. Protective immunity is poorly defined.	Decreased morbidity.	Unknown.
HIV / AIDS.	Cell and antibody mediated immune responses.	Decreased mortality and morbidity.	Increase in the cell count of CD4+ and NK.

Table 1: Effects of vitamin A on infectious diseases and Th2, Type 2 Helper Cells. sIgA: secretory immunoglobulin A; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; NK: Natural Killer.

3.1.2. Vitamin B

Vitamin B plays a fundamental role in the energy metabolism of all cells. In studies using it (specifically Riboflavin [B2]) in conjunction with ultraviolet light, a reduction in the MERS-CoV titer has been seen in human plasma products.³⁵ On the other hand, nicotinamide (B3) is involved in the inhibition of neutrophil infiltration in the lungs. It has a strong anti-inflammatory effect during ventilation-induced injury (VILI); this injury increases alveolar permeability, promotes neutrophilic influx in the lung, inhibits neutrophil apoptosis, and increases oxidative stress. Initially, it inhibits neutrophilic infiltration into the lungs, but, paradoxically, it leads to a state of exacerbated hypoxemia.³⁶ The contribution of vitamins to the energy metabolism of the mitochondria is understood thanks to the citric acid cycle (Tricarboxylic / Krebs Cycle).

3.1.3. Vitamin C

Vitamin C is also known as "ascorbic acid" (which prevents scurvy). It has a fundamental role in the synthesis of collagen in the connective tissue and acts as an antioxidant.³⁷ It improves the functions of the immune system and protects against coronavirus infection.³⁸ This has a positive impact on phagocytic function, T lymphocyte transformation, and interferon production.³⁹

It is a weak antihistamine agent, providing relief from typical cold symptoms

(sneezing, runny nose, and inflammation of the sinuses). A lower incidence of pneumonia has been reported in those who use vitamin C supplements. In general terms, it generates a decrease in the susceptibility of the lower respiratory tract.^{37,39} Antiviral resistance and anticarcinogenic effects are increased by daily intake of vitamin C. It has been shown that 1 g. of Vitamin C along with 200 mg. of Vitamin E daily, for 16 weeks, significantly increases lymphoproliferative capacity and phagocytic functions in neutrophils located in peripheral blood (adherence to the vascular endothelium, chemotaxis, and production of superoxide anion),³⁷ and promotes the down-regulation of the expression of pro-inflammatory cytokines (IL-1, TNF-alpha) dependent on ROS, via inhibition of NF-kB transcription.

3.1.4. Vitamin D

The vitamin D receptor (VDR) is related to functions of the immune system. It is expressed in cells of the innate and adaptive immune system (T and B lymphocytes, neutrophils, monocytes, macrophages, and dendritic cells). Some of them are even capable of expressing CYP27B1, resulting in the endogenous production of 1,25 (OH) 2 D.⁴⁰ VDR forms part of the family of steroid receptors, including retinoic acid, thyroid hormone, suprarrenal steroid and sexual hormone receptors. 1,25 (OH) (2) D is a ligand of nuclear receptor VDR, which acts as a transcription factor.⁴¹

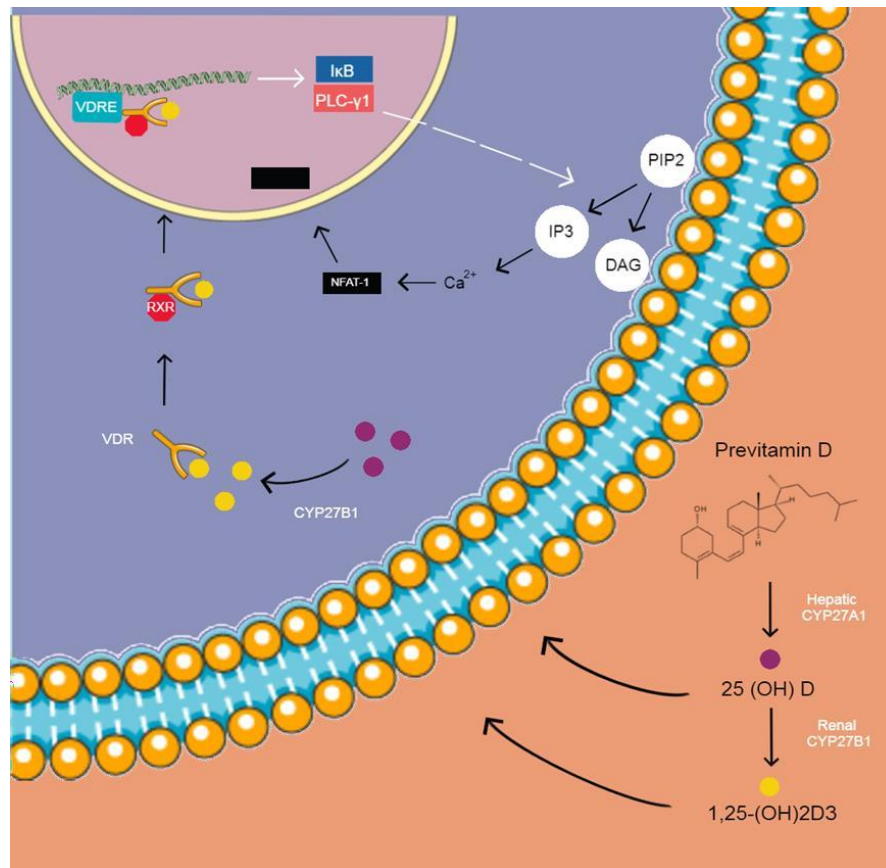


Figure 3: Vitamin D metabolism and signaling 1,25 (OH) 2 D 3 favors the endothelial production of nitric oxide. Said production occurs through a cascade of phosphorylation dependent on VDR, which is considered a transcriptional regulator that favors expression of the eNOS gene.

The functionality of VDR is given by the association with other transcription factors, including retinoid X receptor (RXR). VDR and RXR have the ability to form heterodimers. When they are formed, they are translocated to the nucleus, where they bind to DNA sequences in the target genes, also known as vitamin D response element (VDRE), promoting the genes that VDRE regulates,⁴² including phospholipase C-γ1 (PLC-γ1), which is a signaling protein of the T cell receptor (TCR) pathway. PLC-γ1 signaling activates T lymphocytes. PLC-γ1 hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to generate the secondary messengers inositol 1,4,5-triphosphate (IP3) and diacylglycerol

(DAG). IP3 increases cytoplasmic calcium levels, resulting in the nuclear import of nuclear factor of activated T cells (NFAT-1).

Transcription factor NFAT-1 moves to the nucleus and mediates the transcription of the cytokines involved in the response of T lymphocytes. The role of NFAT is paradoxical, since it is a transcription factor that promotes the expression of genes necessary for activation of T lymphocytes, and in turn, promotes anergy and depletion of CD8⁺ T lymphocytes by binding to sites that do not require cooperation with activator protein-1 (AP-1), whose function could be to limit the immune response. 1,25 (OH) 2 D 3

directly and indirectly regulates the immune system through differentiation of the T lymphocytes favoring phenotype Th2, while at the same time inhibiting the development of Th1. Said regulation inhibits the proliferation and activation of T lymphocytes, which results in a reduction in the production of IL-2 and IFN- γ in TH1 lymphocytes.⁴³

Inhibition of T lymphocyte proliferation is associated with a decrease in cytokine production. In COVID-19 disease, a phenomenon called "cytokine storm" occurs and is considered the main cause of the manifestation of acute respiratory distress syndrome (ARDS). The cytokine storm is characterized by an excessive inflammatory response, as a consequence of a local and systemic lack of control of its production. Patients infected with SARS-CoV2 present extensive infiltration of neutrophils and monocytes in the lungs.^{44,45}

The main uptake mechanisms identified include divalent cation transporter 1 (DMT1) also called the macrophage protein associated with natural resistance 2 (NRAMP 2) and transferrin / transferrin receptor (Tf-TfR) mediated endocytosis. DMT1 is encoded by the SLC11A2 gene, and is expressed in the basal ganglia of the brain, including the globus pallidus, hypothalamic nucleus and striatum. Its level of expression may increase with age;

it has a higher transport affinity for Mn and transports it to the brain across the blood-brain barrier, especially under low iron (Fe) conditions, also transporting Mn from endosomes to the cytosol in a TfR-dependent manner.⁴⁶

The role of 1,25 (OH) 2 D 3 in dendritic cells is to inhibit the expression of IL-12 through nuclear factor - κ B (NF- κ B). The activity of NF- κ B lies in its location. NF- κ B is active in the nucleus, while in the cytoplasm it is inactive due to the action of the inhibitor of κ B (I κ B). The NF- κ B-I κ B α complexes move between the cytoplasm and the nucleus, allowing their regulation.^{47,48,49} The role of 1,25 (OH) 2 D 3 is related to the regulation of I κ B α levels by increasing the stability of mRNA and decreasing the phosphorylation of I κ B α resulting in an increase in I κ B α levels, which in turn decreases the nuclear translocation of NF κ B and thus decreases its activity.⁵⁰

Vitamin E.

Vitamin E includes tocopherols and tocotrienols. It has an important role in reducing oxidative stress, through binding to free radicals.⁵¹ Its depletion (along with vitamin C) can cause greater susceptibility to bovine coronavirus infection.⁵² In general, vitamin E, in interaction with other vitamins, protects membranes from ROS damage and increases T cells.³⁷

EFFECTS OF VITAMIN E ON IMMUNE FUNCTION	
FUNCTION	PROPOSED MECHANISMS
Antioxidant Reduces immunosuppression	Prevents lipid peroxidation and damage to cell membranes Reduces PGE2 formation by modulating the arachidonic acid cascade initiated by lipoxygenase and/or cyclooxygenase (COX).
Lymphocyte maturation	Stabilizes membranes, thus increases proportion of CD4+ CD8- T cells through enhanced binding of antigen presenting cells to immature T cells via increased expression of ICAM-1.

Table 2: Effects of Vitamin E on immune function

4. Essential trace element

4.1 Manganese

Manganese (Mn) is an essential trace element component of metalloenzymes such as manganese-dependent superoxide dismutase (MnSOD), pyruvate carboxylase and arginase, which also acts as an enzyme activator, participates in the endocrine regulation of carbohydrate metabolism, lipids and in the synthesis and secretion of insulin.^{53,54} Mn is a necessary component for MnSOD, which is responsible for the removal of reactive oxygen species (ROS) in the mitochondria. Mn deficiency in the diet, as well as excessive exposure to it, could increase the generation of ROS and cause greater oxidative stress.⁵³ Mn excess can disrupt normal mitochondrial function by

increasing mitochondrial ROS, inhibiting ATP production, and altering membrane permeability, resulting in mitochondrial dysfunction or disorder. Excessive ROS and oxidative stress would lead to metabolic diseases and likewise, metabolic diseases will increase ROS production and oxidative stress accelerating mitochondrial dysfunction or disorder. Mn deficiency will cause growth problems, poor bone formation and skeletal defects, reduced fertility and birth defects, abnormal glucose tolerance, and impaired lipid and carbohydrate metabolism in both animals and humans

^{53,54} The maintenance of Mn homeostasis involves a complex network of proteins that mediate the import or export of Mn.

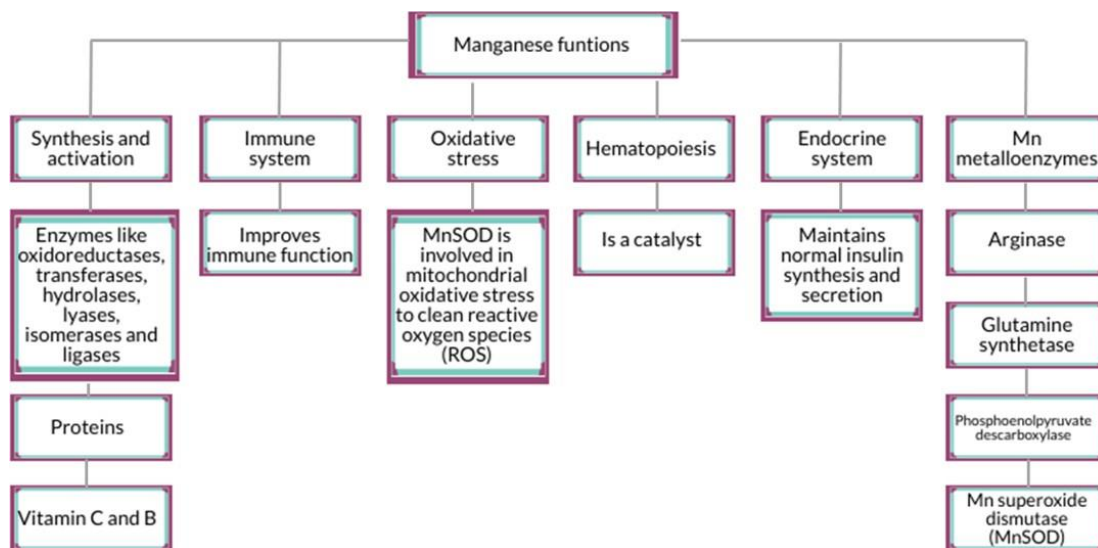


Figure 4. Physiological role of Mn

Likewise, Tf/TfR transports 20% of the total Mn in blood, Tf is synthesized in the liver and secreted in plasma, where it binds to Mn³⁺, and TfR is expressed in most cells. Mn bound to Tf in blood is transported by TfR to cells through ligand- receptor endocytosis. Endosomal Mn³⁺ is reduced to Mn²⁺ by ferrireductase and

Mn²⁺ is transported to the cytosol by endosomal DMT1.⁵⁴

The main uptake mechanisms identified include divalent cation transporter 1 (DMT1), also called the macrophage protein, associated with natural resistance 2 (NRAMP 2) and transferrin / transferrin receptor (Tf-TfR) mediated endocytosis.

DMT1 is encoded by the SLC11A2 gene, and is expressed in the basal ganglia of the brain, including the globus pallidus, hypothalamic nucleus and striatum, and its level of expression may increase with age. It has a higher transport affinity for Mn and transports it to the brain across the blood-brain barrier, especially under low iron (Fe) conditions, also transporting Mn from endosomes to the cytosol in a TfR-dependent manner. Other proteins that play a role in Mn uptake are calcium channels (Ca^{2+}), choline transporters, citrate transporters and the ZIP family of zinc (Zn) transporters; however, they are not specific transporters for Mn because they also transport other metals and substrates.^{53,54}

4.2 Selenium.

Selenium is an essential trace element for the redox state. Its nutritional deficit

impacts the immune response and viral pathogenesis, including: diet deficiency and causing oxidative stress.⁵⁵ In the presence of a state of oxidative stress in the host, viruses that are benign or moderately pathogenic become highly virulent.⁵⁶ Selenium deficiency generates a very rapid mutation of benign RNA virus variants. Selenoproteins such as glutathione peroxidase (GPX) and thioredoxin reductase (TXNRD) play important roles in viral replication models. They are produced by phagocytic cells by ROS, which initiate intracellular signaling pathways both to activate the immune response and to activate antioxidant responses. Unlike other trace elements, selenium is covalently bound to organic molecules. Together with Vitamin E, it prevents the formation of free radicals and oxidative damage to cells and tissues.⁵⁶

EFFECTS OF SELENIUM ON IMMUNE FUNCTION

FUNCTION	PROPOSED MECHANISMS.
Antioxidant	Co-factor for glutathione peroxidase. The selenoenzyme thioredoxin reductase can break down hydroperoxide and lipid peroxides in the presence of NADPH.
Anti-viral	Deficiency results in enhanced mutation rate and pathogenesis of several viruses.
Anti-inflammatory	Deficiency is associated with increased neutrophil adherence (increased expression of E-selectin and ICAM-1). Thioredoxin reductase is a selenoenzyme that acts alone or in conjunction with its substrate, thioredoxin, to affect the redox regulation of a variety of key enzymes, transcription factors and receptors, including the anti-inflammatory proteins AP-1 and NF κ B.
Lymphocyte and NK function.	Enhances the expression of the alpha and/or beta subunits of the IL-2R on activated lymphocytes and NK cells.
Effector cells.	Increased IL-2R expression and thus increases ability of CTL & macrophages to destroy tumor cells, reverses decreased proliferative potential of T cells

Table 3: effects of selenium on immune function and proposed mechanisms through which it acts.

4.3 Zinc

Zinc (Zn) is a dietary micronutrient which plays a fundamental role in human physiology. It participates in regulatory, signaling, catalytic and antiviral functions. It acts as a structural component of approximately 3000 metalloenzymes, of which the following stand out: superoxide dismutase, DNA polymerase, and carbonic anhydrase.^{57,58} The cellular homeostasis of Zn, as well as its transport through the cell membrane, is mediated by two families of specialized proteins: 14 Zrt-, Irt-like protein (ZIP) transporters, which belong to the SLC39A gene family and are responsible for transporting zinc ions from the extracellular space to the cytosol, and 10 transporters belonging to the SLC30A (ZNT) gene family responsible for transporting Zn ions from the cytosol to the extracellular space.^{59,60}

This metal collaborates in the modulation of inflammatory responses by regulating the expression of pro-inflammatory cytokines. Furthermore, it reduces oxidative stress, as it is a cofactor for the antioxidant enzyme Cu-Zn-superoxide dismutase (SOD 1) and inhibits the production of ROS.⁶¹ Another elementary function is the decrease in apoptosis by inhibiting enzymes such as caspases.⁶² Part of the immune response depends on rigorous regulation and appropriate Zn homeostasis. By having an adequate homeostasis, the immune system will be in balance, because this metal contributes to the development and maturation of T and B lymphocytes. Its deficiency results in great susceptibility to inflammatory and infectious diseases.⁵⁸

4.3.1 Zinc and COVID-19

Recent studies consider Zn as an adjunctive treatment for COVID-19 infection, in which it has been shown that the combination of Zn²⁺ with Zn ionophores such as pyrithione (PT), at low concentrations, inhibits the replication of SARS-coronavirus (SARS-CoV2) by inhibiting the activity of RNA-dependent RNA polymerase (RdRp), which is the enzyme responsible for replication and transcription.⁶³

Zn has anti-inflammatory activity, since it has the ability to inhibit the activation of NF-κB, by driving signal transduction to through the A20 and PPAR (Peroxisome Proliferator Activated Receptor) signaling pathways (Figure 6). Similarly, the modulation of T cell functions by Zn can also limit the inflammatory response, favoring mucociliary clearance from the respiratory epithelium.^{64,65,66}

Zinc deficiency

Zn participates in the metabolism of lipids and glucose, improving its regulation at the serum level;⁶¹ however, it has been shown that obese patients with a decreased dietary intake of Zn have a low concentration of intracellular and plasma Zn, as well as a low response to oxidative stress. Alterations in the lipid profile and an increased inflammatory state (due to an increase in the expression of pro-inflammatory cytokines) are observed, compared to obese patients with a normal dietary intake of Zn.⁶⁷ As for the elderly, it is known that they have micronutrient deficiencies in their diet, and with it in their bodies, which makes them prone to a poor response of the immune system, affecting the innate and adaptive immune system.⁶⁸

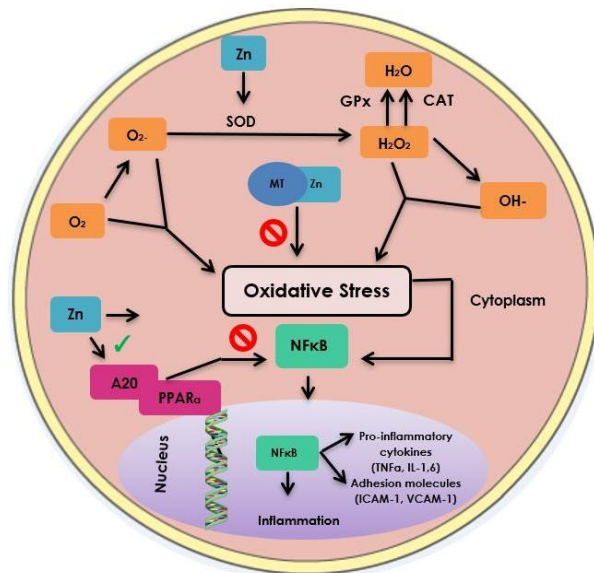


Figure 6. Zinc participation in oxidative stress and inflammation. Zn prevents the formation of Reactive Oxygen Species (ROS) and thus the production of oxidative stress, through different routes. Zinc, being a cofactor of superoxide dismutase (Zn-SOD), catalyzes the conversion of superoxide anion (O_2^-) to hydrogen peroxide (H_2O_2). In turn, catalase (CAT) and glutathione peroxidase (GPx) reduce H_2O_2 to water (H_2O). As the synthesis of metallothionein (MT) is induced in response to oxidative stress, it functions as a protector against oxidative damage.

To date, there is no treatment for COVID-19 infection; however, studies are underway with antimalarial and immunomodulatory drugs such as chloroquine and hydroxychloroquine, which involve Zn. Chloroquine has been shown to be a Zn ionophore,⁶⁹ which increases the flux of Zn^{2+} into the cell, and could interfere with the synthesis of RNA-dependent RNA polymerase (RdRp).⁷⁰

In patients with type 2 Diabetes Mellitus, it has been observed that Zn is associated with insulin levels, since people suffering from this chronic-degenerative disease present a decrease in this metal at the pancreatic level, specifically in the β cells. It can be said that Zn^{2+} ions are an important element for the development of insulin, by prolonging its half-life.⁷¹

Multiple investigations that have been carried out report that the populations most

susceptible to morbidity and mortality from COVID-19 are: diabetics, the elderly, patients with chronic-degenerative diseases and the immunosuppressed. All of them have a deficient immune system which is associated with Zn deficiency, which could be considered as an aggravating factor of the disease in these patients.^{58,61}

The expression of Zn-induced A20 and PPAR α (peroxisome proliferator activated receptor alpha) signaling pathways inhibit NF κ B activation, and, as a consequence, there is a down-regulation of the expression of pro-inflammatory cytokines and adhesion molecules.

5. Endogenous antioxidant system

Within the endogenous antioxidant systems, we will refer exclusively to those

antioxidant systems that are peptides or enzymes which are genetically encoded and vary from one individual to another. These enzymes and the enzymes that participate in the synthesis pathways are key factors in maintaining the body's redox balance. However, their synthesis depends on trace elements which are essential in redox reactions, such as copper, zinc, selenium, etc. Among these systems, we will mention the glutathione, thioredoxin, superoxide-dismutase, etc.⁷²

5.1 Superoxide dismutase

Superoxide dismutase (SOD) is an enzyme that catalyzes the reduction of the superoxide anion, which is produced in the organism as a product of cellular metabolism.⁷³ The mechanism activated during this process is to transform superoxide anion into a product such as hydrogen peroxide, which is easily metabolized in water for peroxidase glutathione (GPx) and catalase (CAT). Within a process of inflammation, it is known that the elimination of superoxide impacts the inflammatory cascade by three main pathways: 1) inhibition of the formation of peroxynitrite and preservation of nitric oxide;⁷⁴ 2) inhibition of the infiltration of neutrophils to the site of inflammation;⁷⁵ and 3) through the inhibition of the release of proinflammatory cytokines.⁷⁶ On the other hand, it is known that the reaction of SOD with oxygen reactive species is found in some diseases related with ischemia, inflammation, and others.⁷⁷ However, these modifications have a reversible effect, making them a target for study of the redox signaling processes in the cells.⁷⁸

5.2 Glutathione and thioredoxin system

Among the antioxidant biomolecules indicating a state of cellular redox are the

glutathione system (GSH/GSSG) and the thioredoxin system (TrX/TrxR); both systems are thiolic proteins determining the cellular redox state. In a state of oxidative stress, the cells modify the activity of TrX, which generates downstream activation in response to the presence of free radicals present in cytoplasm.⁷⁹ The thioredoxin system offers electrons to the enzymes that participate in DNA synthesis and defense against certain oxidants. This system is composed of NADPH, thioredoxin reductase (TrxR) and thioredoxin (Trx). This system participates as an antioxidant in the defense against oxidative stress. Mammal cells have two Trx systems, cytosolic Trx 1 and mitochondrial Trx 2. Together with the GSH system, they allow regulation. It is known that elevated serum Trx in various diseases associates with an increase in cellular oxidative stress, which gives rise to activation of those systems. On the other hand, various authors have demonstrated that administering Trx prevents the appearance and progression of acute respiratory difficulty syndrome. Trx may suppress the accumulation of eosinophils in the respiratory vias and in respiratory hyperactivity through the inhibition of the production of Th2 cytokines by Th1 cytokines induced by Trx.⁸⁰

GSH interacts with other antioxidant defense systems such as vitamin C and vitamin E,^{81,82} which play an important role in maintaining adequate function of immune cells such as lymphocytes,^{83,84} There are various physiological and pathological factors that may alter the glutathione system, including age, chronic-degenerative diseases and acute diseases such as those produced by virus.

6. COVID-19 and pollution

Repeated exposure to environmental pollution caused by low doses of ozone in vulnerable individuals causes a state of chronic oxidative stress and subclinical inflammation⁸⁵ that makes them more vulnerable to infection by SARS-CoV2, but a second route of action is the presence of the virus in the air, which can infect by different mechanisms.⁸⁶

It is clear that contamination acts as a cofactor in the infection caused by SARS-CoV2, and there are conditions in which the time in which microorganisms can be viable increases, such as the case of several types of coronavirus found in bio-aerosol, which increases the rate of contagion of various diseases, while these conditions affect the population, making them more susceptible to diseases.⁸⁷

Until now, studies have been able to link up to 100 different pathologies with pollution, from bronchial problems, chronic obstructive disease, asthma, lung cancer, stroke, hypertension, atherosclerosis, neurodegenerative diseases such as Parkinson's, Alzheimer's, cardiovascular diseases. According to data, 80% of environmental pollution impacts on cardiovascular health (angina, heart attacks, respiratory failure among others).⁸⁸

Pollution is directly responsible for 3.3 million deaths from cardiorespiratory diseases; 2.1 million from CVD and 1.1 million from ischemic and/or hemorrhagic stroke. This represents the leading cause of morbidity and mortality, ahead of traditional cardiovascular risk factors such as tobacco, obesity, diabetes, or high cholesterol.⁸⁹

In the case of COVID-19, it is known that all the pathologies described above are considered comorbidities, and aggravate the illness caused by the SARS-CoV2 virus, which suggests that a large percentage of the population that developed severe COVID-19 symptoms could be related to a high pollution index in their living areas.⁹⁰ Very recent studies that correlate air pollution as a risk factor for respiratory infection when transporting microorganisms affect the immunity of the body support this theory. There is a relationship between the environment and the infection caused by the new coronavirus. The studies collected contemplating the daily confirmed cases, the concentrations of air pollutants and the meteorological variables in 120 cities were obtained from January 23, 2020 to February 29, 2020 in China, using a generalized model for pollutants PM 2.5, PM 10, SO₂, CO, NO₂ and O₃ with confirmed COVID-19 cases; an increase of 10 mg/m³ in any of these pollutants was associated with a range of 2.24% to a 4.76% increase in daily confirmed case counts, respectively.⁹¹

Airborne transmission can occur in two different modes that do not require direct contact. The first mode is through large droplets (> 5µm in diameter) loaded with virus released by infected individuals through coughing or sneezing; the second mode is when a susceptible individual inhales small virus-laden aerosol released during respiration or vocalism⁹² or the residual solid component after evaporation of the droplets.⁹³ Large droplets, emitted by coughing or sneezing, are quickly stopped by air resistance and eliminated by dry deposition, mainly through gravitational settlement, generally at a distance of less than 1 to 1.5 m from the emission. Smaller virus-laden particles (<5µm in diameter) associated with

respiratory emissions from infected individuals could remain in the air for hours and could be carried and dispersed by turbulent winds and eddies. Therefore, it is this mechanism that contributes to contagion.^{86,92}

7. Conclusions

For all the above, we can establish that patients suffering from chronic degenerative diseases, which are in a state of oxidative stress and with loss of regulation of the inflammatory response, are much more vulnerable to a cytokine storm that mainly attacks the lungs, since they present a vicious circle between the null or diminished response of the antioxidant systems and the loss of regulation of the inflammatory process.

Therefore, these patients are at a disadvantage in counteracting the response of defense systems to infection from SAR-CoV19. Patients with chronic

degenerative diseases have low levels of antioxidants. If we consider the interaction between redox signals and the inflammatory response, it is clear that there is a reciprocal modulation between the two. Furthermore, low levels of antioxidants imply a diminished capacity for a regulated inflammatory response.

A plausible option may be to restore the levels of Vitamins A, B, C, D, E and of essential trace elements such as manganese, selenium, zinc, in the body, which are key to either preventing or reducing the severity of the response of the immune system to the disease caused by SAR-CoV2.

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