



REVIEW ARTICLE

Oxidative Stress Associated with SARS-Cov-2 (COVID-19) Increases the Severity of the Lung Disease - A Systematic Review

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Abstract

COVID-19 patients have a higher risk of developing inflammatory responses associated with serious and even fatal respiratory diseases. This review focuses on the relationship between oxidative stress and COVID-19. Coronaviruses are a family of common RNA viruses that can cause serious lower respiratory tract infections, followed by bronchitis and pneumonia. Pulmonary inflammation, fever and fibrosis are symptoms of COVID-19 mediated by cytokine pro-inflammatory. Oxidative stress affect repair mechanisms and the immune control system, which is one of the main events of the inflammatory response which allows us also to conclude that oxidative stress is a major factor increasing the severity of COVID-19 especially during chronic diseases associated with the fragility of the antioxidant system, suggesting to recommend antioxidants supplementation in therapeutic strategies against COVID-19.

Keywords

Inflammatory response, Oxidative stress, Antioxidant therapy, SARS-CoV-2

Background

SARS-CoV-2, the virus responsible for COVID-2019 for (Coronavirus disease 2019) is a new coronavirus discovered in the city of Wuhan in Hubei province in China in December 2019 ref. COVID-19 has been described as a pandemic by the WHO from the date March 11, 2020, the first triggered by a coronavirus [1]. Coronaviruses are enveloped RNA viruses belonging to the

family of Coronaviridae, genus betacoronavirus [2]. In humans, SARS-CoV-2 (COVID-19) has identified as the seventh now pathogenic Coronavirus for humans after other coronavirus species which are: seasonal HCoV, SARS-CoV, MERS-CoV [3]. Whereas coronavirus 2 (SARS-CoV-2) causes a severe acute respiratory syndrome that spreads worldwide [4]. According to the guidelines of the World Health Organization (WHO), the communicability, severity and impact of the disease are the criteria for assessing the severity of pandemic influenza [5]. Communicability reflects the movement of the virus, which is influenced by the dynamics of spread [6]. The lungs are the preferred target of COVID-19 by the large area exposed to viruses, they are among the most oxygenated organs in the human body [7]. Multiple lung disease including apnea causes alveolar hypoventilation, vasoconstriction of the pulmonary artery and cyclic changes in hypoxemia contribute to increased production of reactive oxygen species (ROS) characteristic of the condition oxidative stress [8]. Oxidative stress is an important factor causing metabolic and physiological alterations and various diseases in the body [9]. COVID-19 attack triggers inflammatory reaction which releases pro-inflammatory cytokines characteristic of acute lung damage [10]. A great association between the pro-inflammatory elements and the reactive oxygen species (ROS) in the different lung disease including Coronavirus infection which is associated with inflammation and

oxidative stress [11]. The current review focuses on the relationship between COVID-19 infection and inflammation on one side and between oxidative stress and inflammation on the other to identify the possible effect of oxidative stress on the progression of the state of health of the COVID-19 host.

Oxidative Stress and Lung Disease

In lung tissue and during pulmonary ischemia, alveolar oxygen helps maintain aerobic metabolism, delaying hypoxia [12] which results in decreased levels of adenosine triphosphate (ATP) and more intense breakdown of ATP, resulting in increased production of hypoxanthine [13]. When oxygen is reintroduced into the environment by ventilation, the superoxide radical is formed under the action of the enzyme xanthine oxidase on hypoxanthine [14]. In the absence of blood circulation in the lungs there is lipid peroxidation and oxidative damage due to the presence of oxygen [15]. Furthermore, NADP oxidase and NO oxidase in the endothelium seem to be one of the main causes of oxidation in pulmonary ischemia. Also immune cells such as macrophages and neutrophils can contribute to oxidative damage in the lungs by the same enzymatic mechanism (NADP Oxidase) [16].

Oxidative stress and chronic obstructive pulmonary disease

Oxidative stress plays a central role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Exposure to the environment is the main source of oxidative stress, such as cigarette smoke (CS) and air pollutants, which may be example for the role of cigarette smoke [17]. The study of Sundar, et al. showed that chronic smokers release more free radicals from leukocytes, have high levels of lipid peroxidation products with a decrease in antioxidants (vitamin E) in the distal respiratory tract compared to non-smoking controls [18]. This can cause inflammation and higher release of protease. Also it has been shown that in smokers there is a lack of vitamin A depletion which protects lipids against peroxidation caused by free radicals under the effect of benzopyrene, a component of cigarette smoke [19]. In addition, leukocytes and macrophages are involved in the inflammatory process in the lungs of subjects with chronic obstructive pulmonary disease, which increases the ROS [20]. The latter are capable of causing oxidative damage to DNA, lipids, carbohydrates and proteins, which contribute to the development and progression of COPD [21]. Reactive oxygen species also activate epithelial cells and alveolar macrophages, to generate chemotactic molecules that recruit neutrophils, monocytes and lymphocytes into the lung [22], which develops persistent inflammation and chronic oxidative stress in the lungs, and also develops defects in tissue repair mechanisms, accelerated apoptosis and increased autophagy in lung cells, all of which have

been linked to the severity and progression of chronic obstructive pulmonary disease [23].

Oxidative stress and obstructive sleep apnea and asthma

During obstructive sleep apnea, circulating neutrophils increases free radical release, lipid peroxidation and reduce nitric oxide, which is an endothelial vasodilator [24]. In addition, reactive oxygen species cause an increase in platelet aggregation and can increase the expression of various endothelial genes, such as those responsible for the synthesis of adhesion molecules, endothelin and vascular endothelial growth factor [25]. On the other hand, Asthma is a disease characterized by chronic inflammation of the airways. Several pathophysiological changes in asthma are associated with the production of free radicals by inflammatory cells [26]. In asthma, an increased oxidative charge can lead to the release of nitric oxide which interact with the superoxide anions to form peroxynitrite (ONOO⁻), which has considerable oxidative capacity [27].

Oxidative stress and acute respiratory distress syndrome

Acute lung injury (ALI) and its most serious form, acute respiratory distress syndrome (ARDS) are common complications in critically ill patients and are responsible for significant morbidity and mortality [28]. Following a bacterial or virus infection, the pulmonary macrophages and the endothelium are activated and regulate the surface expression of the adhesion molecules [29]. This leads to the activation of neutrophils and to the subsequent transmigration of the intravascular space into the socket [30]. This produces a plethora of inflammatory mediators that include reactive oxygen species (ROS) such as hydroxyl radical and nitric oxide (NO), cytokines and chemokines which are the source of oxidative stress associated with acute lung injury [31].

COVID-19 Induced Inflammatory Reaction

Covid19 and host targets in lung cells

The large volume and area of the lung is an important factor in susceptibility to inhaled viruses, but there are also other biological factors [32]. More recently, the first and complete sequence of the COVID-19 genome has been deposited in NCBI (GenBank: MN908947.3) [33] which makes it possible to identify the key to the potential structure, the viral protein binding model and the model of interaction with target proteins of host cells (such as ACE2, cyclophilins and other cell adhesion factors) which important for cell adhesion and virulence [34]. The identification of COVID-19 structure makes it possible to know the nature of interaction protein with respect to the structure of SARS virus which shows an identity of 91% in the region of domain S2, but it lacks similarity in three other regions [35]. A greater sequence difference (55% identity) was found in the S1 domain

which is known for its target host cell interaction underlying cell adhesion and virulence [36]. This suggests that COVID-19 may interact with some of the host targets previously described (ACE2, cyclophilins), but via slightly varied molecular interactions [37]. In the lower respiratory tract, angiotensin 2 converting enzyme (ACE2) has been shown to be the major receptor for glycoprotein S of SARS-CoV suggest that COVID-19 may also infect cells of the lower respiratory tract via the same ACE2 enzyme [38]. It has been shown that 83% of ACE2 is expressed in epithelial cells alveolar type II suggesting that these cells can serve as a reservoir for the virus and that these cells expressing ACE2 facilitates invasion coronavirale entry and replication, as well as serious lung damage [39]. On the other hand, Extracellular cyclophilins (eCyPs), one of the interactive targets of COVID-19 in lung cells, are also pro-inflammatory factors playing an important role in the pathogenesis of a number of inflammatory diseases through interaction with the CD147 receptor and the initiation of a poorly characterized signal transduction process leading to chemotaxis and the production of pro-inflammatory factors [40].

Covid19 and pro-inflammatory production

The data so far available seem to indicate that the COVID-19 infection is capable of producing an excessive immune reaction in the host [41]. In the study by Dan Zhang, et al. 2020, performed on patients with COVID-19 they illustrated larger than normal monocytes, easily identifiable by forward scattering, with the presence of a distinct population monocytes with strong forward diffusion (FSC-high) [42]. On a more detailed analysis, these elevated FSC monocytes are CD11b+, CD14+, CD16+, CD68+, CD80+, CD163+, CD206+ and secrete IL-6, IL-10 and TNF-alpha, consistent with an inflammatory phenotype [43]. Infection with COVID-19 leads to excessive activation of monocytes/macrophages with the development of a cytokine storm and consequently, leading to the appearance of acute respiratory distress syndrome (ARDS) [44]. Pulmonary inflammation, fever and fibrosis are symptoms of COVID-19 mediated by the production of active IL1 under the action of toll like receptors (TLR) when it interacts with cytokine pro-inflammatories, including IL-1b and IL-6 via COVID-19 induced [45]. In addition, an increase in the interferon gamma of type 1 helper T lymphocytes (Th1) (IFN- γ), inflammatory cytokines IL-1 β , IL-6 and IL-12 have been reported in patients with SARS-Cov in for at least two weeks after the onset of the disease [46]. IL-6 is produced by activated leukocytes, acts on a large number of cells and tissues, promotes the differentiation of B lymphocytes, the growth of certain categories of cells and inhibits the growth of others [47]. IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer [48]. An increase in pro-inflammatory cytokines linked by inflammatory reactions and acute lung dam-

age induced by Protein N of SARS-CoV which proves the induction of pulmonary inflammation during COVID19 attack [49]. On the other hand, Extracellular cyclophilins (eCyPs), one of the interactive targets of SARS-Cov in lung cells, are also pro-inflammatory factors playing an important role in the pathogenesis of a number of inflammatory diseases [50] through interaction with the CD147 receptor and the initiation of a poorly characterized signal transduction process leading to chemotaxis and the production of pro-inflammatory factors [51].

Oxidative Stress and Inflammation of Lung Cell

Inflammatory response markers in the lungs

The cooperation between the functions of cytokines, chemokines and adhesion molecules controls the inflammatory response in the lungs [52]. Pulmonary edema, infiltration of inflammatory cells and thickening of the alveolar interval have been shown to promote pulmonary edema and the spread of hypoxia gradually worsens inflammation of the lung tissue [53]. The induction of cytokines such as TNF- α and IL-6 is involved in transcriptional reprogramming induced by CIH [54].

Oxidative stress and inflammatory response

Inflammation of the airways and oxidative stress have been implicated in the pathogenesis of COPD [55]. A high number of neutrophils, macrophages and lymphocytes (TCD8+) have been shown in the bronchoalveolar lavage fluid during inflammation, and an elevated level of TNF- α and IL-8 has been detected in the plasma of patients with of COPD, in the case of IL-8 which is a powerful chemoattractant of neutrophils, it initiates degranulation and the production of reactive oxygen species (ROS) which induce oxidative stress. This last plays a primary role in the pathogenesis of COPD [56]. Oxidative stress is a condition caused by an imbalance between oxidants and antioxidants. Oxidative stress may affect extra-cellular matrix remodeling, mitochondrial respiration, cell proliferation and lung defense mechanisms [57]. Neutrophils and macrophages are inflammatory cells responsible for producing the majority of oxidants in the lungs of COPD patients by releasing cytokines and regulating cell adhesion molecules [58]. Moreover, oxidative stress affect repair mechanisms and the immune control system, which is one of the main events of the inflammatory response [59].

Strategies to Improve Oxidative Stress in COVID-19 and Lung Disease

Categories of antioxidants approaches

Several clinical approaches have been tested in order to repair the state of oxidative stress. These strategic approaches can generally be classified according to the therapeutic target as agents blocking the production of NO• in the case of excess NO• [60]; increase

or supplement deficient antioxidants, in particular GSH and non-enzymatic antioxidants, including vitamins and trace elements; or trap the ROS directly [61]. Each of these categories of therapeutic approaches, most of which have ultimately had little or no success in treating pulmonary or pulmonary vascular disease [62]. But in parallel with the recommendation of one of these approaches there are problems concerning the chosen dose, with the half-life of the antioxidants supplemented; targeting of the appropriate tissue, organ or cells; type of patient and disease and according to the type of physiological disturbance of the oxidants [63]. Oxidative stress plays an important role in the development and progress of lung disease either by increasing the production of oxidants or by reducing antioxidant resources [64]. Numerous laboratory studies demonstrate the protection of pulmonary vascular diseases when the production of ROS is suppressed, so this is another strategy that has also been considered in the field of clinical research [65].

Glutathione and its biosynthesis in lung cells

Glutathione (GSH) plays an important protective role in the air and intracellular spaces in epithelial cells and also plays a role in maintaining the integrity of the epithelial barrier of the pulmonary air space [66]. Harju and colleagues (2002) found in the airways of smokers a decrease in the immunoreactivity of glutamate cysteine ligase (GCL), the speed-limiting enzyme in GSH synthesis compared to non-smokers, which suggests that cigarette smoke predisposes lung cells to oxidant during stress [67]. Protection against chronic inflammation and oxidative-mediated lesions during respiratory disease through induction of the enzyme glutamate cysteine ligase by therapy to increase cellular levels of GSH is also very important and promising [68]. Therefore the direct increase in GSH levels in lung cells would be a logical approach to protection against chronic inflammation and oxidant-mediated injury in lung disease [69].

Dietary polyphenols supplementation

Phytochemicals in the diet can exert on different targets that can relieve multiple pathological processes, including oxidative damage, epigenetic alterations, chronic inflammation, active stimulators, inhibitors and growth terminators and prevention of various diseases associated with oxidative stress [70]. A typical example of the action of polyphenols is Curcumin, an active ingredient in the perennial herb *Curcuma longa* [71]. It inhibits the expression/activation of NF- κ B, the release of IL-8, cyclooxygenase (COX) -2, heme oxygenase-1, cytokines and the recruitment of neutrophils in the lungs [72]. Moreover, it acts as a scavenger of oxygen and hydroxyl radicals and induces the activation of GCL and therefore increases the glutathione level [73]. On the other hand, an effective flavonoid, resveratrol, in-

hibits macrophages from producing inflammatory cytokines in infected lungs. Polyphenols can induce phase II detoxifying genes by mechanisms dependent on Nrf-2 [74]. The catechins present in green tea (epigallocatechin-3-gallate) in addition to theophylline have antioxidant and anti-inflammatory character [75] and also possibly effective in the increase of glucocorticoids in lungs diseases [76].

Prevention strategy

Preventive measures are the current effective strategy to limit the spread of COVID-19. The most important strategy for people is to wash their hands frequently and use a portable hand sanitizer and avoid contact with the face and mouth after interacting with a potentially contaminated environment. For the health sector, preventive strategies focus on isolating patients and carefully controlling infections, including appropriate measures to be taken during diagnosis and the provision of clinical care to an COVID-19 infected patient.

Conclusion

The rapidly progressing COVID-19 pandemic has led to difficult decision-making regarding the treatment of critically ill patients with the new viral infection. This systematic review seeks to provide guidance based on the relationship between the inflammatory responses induced by COVID-19 and the release of ROS, which generates a state of oxidative stress, which suggests recommending antioxidants in therapeutic strategies against COVID-19.

Conflicts of Interest

No funding was provided for this manuscript. Author has no conflicts of interest to report.

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