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Are Antioxidants a Therapeutic Option in COVID-19?

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Abstract

There is a growing body of evidence that the poor outcome of novel coronavirus infection (COVID-19) is related not only to pneumonia but also to thrombotic complications. Among the putative mechanisms accounting for vascular disease, the overproduction of reactive oxygen species (ROS) could play a role. Thus, ROS formation is involved in the process of platelet and clotting activation and could be implicated in the thrombotic process of COVID-19. Studies performed in COVID-19 patients showed over-activation of NOX2 in cells deputed to ROS formation and implicated in thrombosis such as leucocytes and platelets. Furthermore, several types of antioxidants such as albumin and vitamins C and E are lowered in COVID-19 suggesting an imbalance between ROS over-production and low antioxidant status as a mechanism eliciting changes of redox status. However, interventional studies with antioxidants provided inconclusive results, therefore further study is necessary to assess the efficacy of this treatment in COVID-19.

Keywords: SARS-CoV-2; Oxidative stress; Inflammation; Antioxidants

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Introduction

COVID-19 is a pandemic characterized by severe acute respiratory syndrome (SARS-CoV-2) needing mechanical ventilation and intensive care unit (ICU) treatment. Among the factors predisposing to poor survival, thrombotic complications have been suggested to have an important role [1,2]. Accordingly, clinical studies in COVID-19 showed a high incidence of venous and arterial thromboembolism, which were dependent upon a hyper coagulation state, as depicted by elevated plasma levels of D-dimer [3,4].

There is a growing body of evidence that this tendency to thrombosis may depend upon several mechanisms including activation of platelets or endothelial damage that ultimately favour thrombus growth. Reactive oxygen species (ROS) play a role in the activation of cells implicated in the thrombotic process and there is evidence that pro-oxidant enzymes such as NOX2 are upregulated in SARS-CoV-2 and correlated with thrombosis [5]. As it would be conceivable, therefore, that antioxidants could have a place in the treatment of SARS-CoV-2, the aim of the review is to explore the "pro and contra" of using antioxidants in SARS-CoV-2.

Role of ROS in platelet and endothelial activation

ROS derive from molecular oxygen and are formed by redox reactions or by electronic excitation. ROS, such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO^\bullet$), are implicated in the cellular response to xenobiotics, cytokines, and bacterial invasion. When ROS levels increase, oxidative stress occurs. Oxidative stress represents the imbalance due to excess ROS production over the antioxidant response capability of the cell [6].

Oxidative stress is considered a common pathophysiological mechanism associated with many pathological conditions such as cancer, diabetes, cardiovascular and neurodegenerative diseases [7]. Furthermore, oxidative stress is recognized as an important mediator of atherothrombotic events in cardiovascular disease [8]. Indeed, cardiovascular risk factors, such as obesity, hyperglycemia, insulin resistance, hypertension, and dyslipidemia are associated with increased ROS production [9]. Moreover, the higher risk of developing thrombotic events is due to platelet hyperactivation, which is a crucial event in thrombus formation. Of note, both ROS and enzymes that regulate ROS generation are implicated in platelet activation in health and disease [10].

Platelets can generate ROS through several intracellular sources such as NADPH oxidase, cyclooxygenase, uncoupled endothelial nitric oxide synthase (eNOS), xanthine oxidase (XO), and mitochondrial respiration [11] and this seems to be important during recruitment,

adhesion, and aggregation [12]. In human platelets, both NOX1 and NOX2, two different isoforms of NADPH oxidase, significantly contribute to ROS production and is considered responsible for the regulation of platelet responsiveness [7].

NOX2 activity has been correlated to platelet responsiveness in physiological and pathological conditions. Impaired platelet activation has been described in patients with genetically determined NOX2 deficiency. Particularly, platelet activation was studied in X-linked chronic granulomatous disease (X-linked CGD), a rare primary immunodeficiency, commonly associated with severe infectious diseases. Patients with X-linked CGD, genetically deficient in NOX2, showed impaired platelet ROS generation and CD40 ligand (CD40-L) expression upon thrombin, collagen, and arachidonic acid stimulation [13]. Similar results were obtained in patients with hereditary deficiency of p47phox, the cytosolic subunits of NOX2 [14].

The intact endothelium plays an important role in vascular tone, regulating thrombosis and thrombolysis, platelet adherence, and activation to maintain an undisturbed blood flow under physiologic conditions. Adhesion of platelets to the endothelium is prevented by numerous mechanisms, including endothelial cell production of prostacyclin and nitric oxide (NO) [15]. Thus, changes in endothelial activity can promote a pathologic condition called endothelial dysfunction, which is characterized by impaired vasodilatation, vascular remodelling, pro-coagulant, and pro-inflammatory activity that strongly expose the organism to vascular damages and cardiovascular disorders such as atherosclerosis, plaque instability, and thrombosis [16]. The presence of superficial endothelial injury, caused by plaque rupture or erosion, induces the adhesion of platelets to endothelial cells by binding to collagen or vWF. Local platelet activation further stimulates thrombus growth via additional platelet recruitment and in turn thrombin formation and releasing potent platelet agonists such as adenosine diphosphate (ADP), serotonin, and thromboxane A2 [17,18]. Oxidative processes may also have deleterious effects on the vascular system through complex interactions with endothelial and inflammatory cells, playing a major role in the initiation and progression of the thrombotic process. Indeed, when platelets enter in an activation state, release inflammatory mediators and growth factors such as chemokines, adhesion proteins, and coagulation factors, and other mediators to activate the endothelial cells. When activated, endothelial cells generate ROS by several enzymatic sources including NOX2, which was the first NOX isoform to be identified in endothelial cells and is likely to be the most important in the context of vascular pathology. Indeed, NOX2-derived ROS induce inactivation of NO so promoting endothelial dysfunction and increasing atherosclerosis burden. Moreover, ROS induce peroxynitrite ($ONOO^-$) overproduction that causes irreversible damage to macromolecules including proteins, lipids, and DNA, and react with the key eNOS cofactor, tetrahydrobiopterin. In the absence of tetrahydrobiopterin, eNOS generates, in fact, superoxide, thus exacerbating oxidative stress within the cell. Moreover, NOX2-derived ROS act as intermediates in the signalling pathways regulating pro-inflammatory transcription factors thus triggering vascular inflammation that is a relevant process in human atherosclerosis [19]. Based on these data, an interesting approach to reduce platelet activation and endothelial dysfunction would be downregulating the above reported pro-oxidant systems. Cells have developed many protection mechanisms against oxidative damage including enzymatic systems, such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GpX), and non-enzymatic scavenger that can neutralize ROS such as glutathione and vitamins E and C [20]. Therefore, inhibition of oxidative stress by antioxidant supplementation may be a tool to lower platelet and endothelial activation in case of ROS-related vascular disease such as COVID-19.

Oxidative Stress in COVID-19 Patients: A Possible Role for Antioxidant Supplementation

Several pathophysiological mechanisms related to oxidative stress have been implicated in the pathogenesis of COVID-19 (Figure 1).

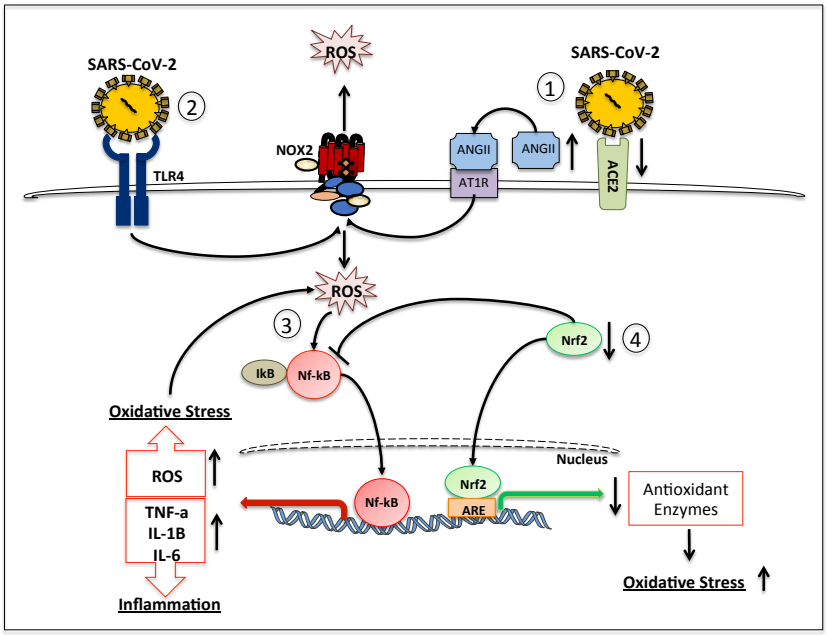

Figure 1: Mechanisms of SARS-CoV2-mediated oxidative stress. SARS-CoV2 can elicit oxidative stress by several mechanisms: 1) the spike protein of the virus binds ACE2 for cell entry and down-regulates the enzyme, Angiotensin II increases and binds the angiotensin type 1 receptor (AT1R), which stimulates NADPH (NOX) activity; 2) SARS-CoV2 binds and activates Toll-like receptor (TLR) 4 that is implicated in the generation of NOX-2 derived ROS; 3) ROS activate NF-kappa B (NF-κB) increasing cytokines and inflammatory markers levels; 3) lower expression of Nfr2 increases NF-κB-mediated inflammation and reduces the transcription of components of the antioxidant systems.

In SARS-CoV-2 patients, the Spike protein of the virus binds ACE2 for cell entry and, in doing so, down-regulates such enzyme, which usually degrades angiotensin II to angiotensin 1-7 [21]. The consequence of this binding is the increase of angiotensin II levels, which are known to exert pro-oxidant activity [22]. Thus, when ACE2 is no longer available to convert Angiotensin II to Angiotensin 1–7, Angiotensin II binds the angiotensin type 1 receptor (AT1R), which stimulates NADPH (NOX) activity [23]. Such increased NOXs activity leads to ROS generation, which in turn influences many downstream signalling targets [24] inducing oxidative stress and inflammatory responses, contributing to the severity of COVID-19. The generation of proinflammatory cytokines and ROS could be mediated by other receptors such as the toll-like receptors (TLRs) [25]. Interestingly, one study hypothesized that TLR4 may be involved in recognizing molecular patterns from the Spike protein of the virus [26]. Thus, SARS-CoV-2 binding to TLR4 may have a deleterious effect for its implication in inflammation and oxidative stress process via up-regulation of NOX2 resulting in H_2O_2 generation [27].

An uncontrolled systemic inflammatory response, the so-called cytokines storm, which provokes the expression of pro-inflammatory cytokines and chemokines by the effector cells, could be another mechanism of increased oxidative stress in COVID-19. The link between pro-inflammatory cytokine signalling and oxidative stress is being actively explored suggesting that inflammation and oxidative stress are co-dependent and strongly interrelated processes [28]. Pro-inflammatory cytokines induce a release of ROS, which act as signalling mediators for a variety of signal transduction pathways such as NF-kB [29]. NF-κB is a family of inducible transcription factors that upon stimulation bind to their cognate DNA and activates transcription of cytokines, chemokines, and adhesion molecules. Moreover, it is sensitive to many different oxidative stress stimuli [30] but is also a key factor in controlling the expression of NOX2 creating a positive feedback loop [31]. It has been demonstrated that in patients with COVID-19 the genes involved in the NF-κB signalling pathway were upregulated coincidentally with increased levels of cytokines and inflammatory markers [32]. Cyclically, these pro-inflammatory cytokines activate macrophages, neutrophils, endothelium cells via NADPH oxidase to produce more superoxide and H_2O_2 [33]. Such pro-inflammatory process is counteracted by the nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) which is a cytoprotective factor that regulates cellular resistance to oxidants, controls the basal and induced expression of an array of antioxidant response element–dependent genes to regulate the physiological and pathophysiological outcomes of oxidant exposure [34]. Moreover, Nrf2 inhibits the NF-kB and the expression of inflammatory cytokines. The transcriptome analysis of lung biopsies from COVID-19 patients demonstrated that the genes linked with inflammatory and antiviral pathways were enriched in COVID-19 patient samples, whereas genes associated with the Nrf2 dependent antioxidant response were suppressed [35].

COVID-19 patients displayed dysregulated oxidative status, as defined by the imbalance between oxidant and antioxidant status. Several blood biomarkers of oxidative stress and antioxidant status were analyzed. In summary, the studies consistently showed elevated biomarkers reflecting ROS over-production such as serum lipid peroxides or isoprostanes and lower levels of natural antioxidants vitamin C, a-tocopherol, b-carotene, and glutathione (GSH) [36,37].

Two studies examined the role of selenium, which is an essential trace element incorporated into antioxidant selenoproteins, confirmed that COVID-19 patients showed a pronounced deficit in total serum selenium and selenoprotein P [38,39]. Interestingly, the selenium status was significantly higher in samples from survivor versus non-survivor COVID-19 patients [39].

The mechanism accounting for oxidative stress has been investigated by our group by measuring the activity of NOX2 in patients affected by COVID-19 patients; we found higher activation in patients versus controls and in severe versus non-severe COVID-19; moreover, patients with thrombotic events had higher NOX2 activation than thrombotic event-free ones [40].

Clinical trials using antioxidant therapies based on the use of N-acetylcysteine (NAC) [41], or melatonin [42], are currently underway. To date, however, very few studies evaluated the effect of antioxidant supplementation in COVID-19 patients (Table 1). In a retrospective analysis of twelve severe or critical COVID-19 patients, the beneficial effect of high intravenous doses of Vitamin C was evaluated (162 mg/kg/day or 178.6 mg/kg/day) within 24 hours after disease aggravation; both dosages significantly decreased C-reactive protein (CRP), improved PaO_2/FiO_2 and organ failure assessment score [43]. Chavarría AP, et al. (2021) evaluated the effect of antioxidant treatment with Vitamin C or Vitamin E or N-acetylcysteine (NAC) or Melatonin (MT) plus pentoxifylline (Px), a methyl-xanthine derivative with anti-inflammatory effects, in COVID-19 patients with moderate and severe pneumonia; they found improved survival scores and lower oxidative stress as indicated by decreased levels of lipid peroxidation (LPO) and by increased total antioxidant capacity [44].

Table 1: Antioxidant supplementation in COVID-19.

Author (year)	Study type (setting)	Type of supplementation	Outcome(s)/Variable of interest	Main results
Zhao B, et al. (2021) [43]	Retrospective case series study 12 COVID-19 patients	Vitamin C 162.7 mg/kg/day 178.6 mg/kg/day Intravenous	Inflammatory response, immune and organ dysfunction	CRP decreased, Lymphocyte and $CD4^+$ T cell counts in severe patients reached to normal level, PaO_2/FiO_2 improved.
Chavarria AP, et al. (2021) [44]	Open, analytical, prospective and longitudinal study 110 COVID-19 patients	Vitamin C, 1 g every 12h for 5 days, oral route Vitamin E, 800mg, every 12h for 5 days, oral route NAC, 600mg, every 50mg, every 12h for 5 days, oral route	Oxidative stress and inflammation	Antioxidant therapy improves the survival scores including SOFA, Apache II, SAPS II, COVIDGRAM, GCS by lowering the lipid peroxidation, IL-6, CRP, PCT and increasing systemic TAC and NO_2^-.
Thomas S, et al. (2021) [45]	Multicenter, randomized clinical factorial open-label trial 214 COVID-19 patients	Zinc gluconate, 50 mg/10 days Vitamin C, 8000 mg/10 days, Zinc gluconate 50 mg + Vitamin C 8000 mg/10 days	Days to reach 50% reduction in symptoms and days to reach a total symptom severity score of 0	High-dose zinc gluconate, Vitamin C, or a combination of the 2 supplements did not significantly decrease the duration of symptoms compared with standard of care.
Violi F, et al. (2020) [4]	Observational cohort study 10 COVID-19 patients	Albumin 80 g/day in the first 3 days and 40 g/day thereafter for a maximum of 7 days Intravenous	Hypercoagulation	After albumin treatment D-dimer levels significantly decreased.

CRP: C-reactive protein; GCS: Glasgow Coma Scale; NAC: N-Acetil-L-Cisteina; NO: nitric oxide; PTC: procalcitonin; SAPS score: Simplified Acute Physiology Score; SOFA score: Sequential Organ Failure Assessment Score; TAC: total antioxidant capacity.

In a randomized clinical factorial open-label trial of 214 adult patients with a diagnosis of SARS-CoV-2 infection, patients were randomized to receive for 10 days zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents, or standard of care. No significant differences in severity or duration of symptoms were found after the treatment with the two supplements, alone or in combination, compared with the standard of care [45].

Finally, our group supplemented COVID-9 patients with intravenous infusion of albumin at the dosage of 80 g/day in the first 3 days and 40 g/day thereafter for a maximum of 7 days; at the end of treatment, a significant reduction of D-dimer coincidentally with albumin serum increase was detected compared to the control group [4].

Conclusion

In conclusion, there is evidence that COVID-19 patients display an imbalance between ROS formation and antioxidant status, which could favour oxidative stress and eventually thrombosis and death. However, data regarding the impact of antioxidants on COVID-9 outcomes should be considered very preliminary for several pitfalls including study methodology, sample size and end- point analysis. Thus, RCTs are mandatory to assess if changes of redox status are actually relevant in deteriorating the outcome of COVID-19 patients.

Conflict of Interest

The author has no conflict of interest to disclose.

Consent for Publication

All authors have read and agreed to the published version of the manuscript.

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