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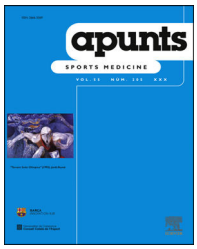

LETTER TO THE EDITOR

A study of possible role of exercise and some antioxidant supplements against coronavirus disease 2019 (COVID-19): A cytokines related perspective

Coronavirus disease (COVID-19) is an infectious disease induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most of the patients with COVID-19 have mild to moderate symptoms, approximately 15% progress to severe pneumonia, and finally, about 5% develop acute respiratory distress syndrome (ARDS). ARDS is a condition caused by reactive oxygen species (ROS) and oxidative stress, septic shock, and/or multiple organ failure.[1]

Serum levels of pro-inflammatory cytokines - characterized as cytokine release syndrome (CRS), or also known as cytokine storm- are evaluated in most of the patients with COVID-19, *i.e.* interleukin 6 (IL-6), interleukin 1 beta (IL-1β), interleukin-2 (IL-2), interleukin-8 (IL-8), interleukin-17 (IL-17), granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)-1α, tumor necrosis factor-alpha (TNF-α).[2] Cytokine storm has been described as an acute systemic inflammatory syndrome or an extreme immune response that can cause oxidative stress, tissue destruction, dehydration, and circulatory shock. Cytokine storm affects several tissues, mainly the lungs, leading to acute lung injury with variable degrees.[3] Cytokine storm is a reason for some patients who progress rapidly with acute respiratory distress syndrome and septic shock, followed by multiple organ failure and death. Oxidative stress has been implicated in the pathophysiology of acute lung injury and sepsis-induced multiorgan failure, two of the most common causes of morbidity and mortality in critical illness.[4] Thus, oxidative stress has been an attractive therapeutic target in critical illness, and antioxidants have been tested in critically ill patients for decades. ROS play a key role in inflammatory responses, while exercise with different intensities has a different effect on ROS production. On the other hand, antioxidants exert anti-inflammatory effects which may also be effective for the treatment of cytokine storm.[5]

The present study investigates the role of exercise and antioxidant supplements against oxidative stress and inflammatory factors related to illness condition.

Exercise and supplements

Exercise

Cerqueira et al. in a systematic review investigated the inflammatory effects in response to different exercise intensities.[6] They concluded that, an elevation of pro-inflammatory cytokines (IL-6 and IL-10) was more evident after intense exercise bouts. Also, creatine kinase (CK) increased only after intensive and long exercising. They suggested that long intense exercise can lead, in general, to higher levels of inflammatory mediators, and thus might increase the risk of injury and chronic inflammation. On the other hand, moderate exercise or vigorous exercise with appropriate resting periods can achieve maximum benefit.[6] Rahmati-Ahmadabad et al. recommend moderate-intensity exercise (and not high-intensity physical activity) as a non-pharmacological, inexpensive, and viable way to cope with COVID-19 virus.[7,8] They suggested a conservative approach based on indirect evidence which means that high intensity exercises probably due to the production of ROS weakness of the immune system may be dangerous and help to exacerbate the COVID-19 virus.[7] They also noted that COVID-19 disease may be asymptomatic in several days. Thus, severe high- intensity exercise may be more dangerous. They also suggested two mechanisms that may justify their suggestion. Based on the 'open window' theory, suppression of the immune system may occur following high intensity exercise.[9] This window of opportunity may allow for an increase in susceptibility to upper respiratory illness.[9] 'J curve' concept explains that individuals that regularly perform moderate intensity exercise improve their immune system, while excessive bouts of prolonged training can impair immune function.[10]

Glutathione

Glutathione plays a critical role in many of the mechanisms of viral pathophysiology including an imbalance of the redox balance of the cell in favor of oxidative stress.[11] Glutathione is synthesized from three amino acids cysteine,

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glutamic acid, and glycine. It is one of the body mechanisms against ROS. Glutathione exists in reduced (GSH) and oxidized (GSSG) states. In healthy cells and tissue, more than 90% of the total glutathione pool is in the reduced form (GSH), with the remainder in the disulfide form (GSSG). An increased GSSG-to-GSH ratio is indicative of oxidative stress. The overall cellular redox homeostasis is aimed at maintaining harmful reactive oxygen and nitrogen species and GSSG at very low levels and GSH at a high level. Researchers suggest that GSH is poorly absorbed by oral route mainly due to the action of an intestinal enzyme, the γ-glutamyl transpeptidase (GGT) which degrades GSH. GSH has been shown to alter cytokine expression specifically by enhancing through N-acetylcysteine (NAC).[12] Oral administration of NAC (1 g/d for 7 days) has been demonstrated to increase intracellular GSH.[13] *In vitro* infection of the whole blood cultures derived from HIV positive individuals with M. tb resulted in an increased production of pro-inflammatory cytokines such as IL-1, TNF-α, IL-6. However, levels of the pro-inflammatory cytokines (IL-1, TNF-α, and IL-6) were reduced when the whole blood cultures were treated with the GSH precursor, NAC. *In vitro* studies have demonstrated that increased intracellular GSH decreases pro-inflammatory cytokine (IL-1, IL-17, transforming growth factor-TGF- beta) production and up-regulates the expression of GSH synthetic enzymes.

Glutamine

L-Glutamine is probably the most widely recognized immuno-nutrient since it can be used as an oxidizable fuel and a component of GSH-mediated antioxidant defense. Glutathione synthesis is dependent on the supply of L-glutamate from L-glutamine, which is, in turn, the most abundant free amino acid in the human body, especially in the plasma and skeletal muscles under normal conditions. Oxidative stress and inflammation are always a hallmark of human sepsis and may lead to an imbalance in the L-glutamine-glutathione axis.[14] Wang et al. investigate the effects of glutamine on cytokines 1L-1, TNF-α and prognosis of patients with lobectomy in the process of postoperative rehabilitation. Their results indicated that glutamine can regulate the levels of IL-1, TNF-α, and improve lung function.[15] Coëffier et al. evaluate the effects of glutamine on IL-1beta-induced cytokine production by human gut.[16] Glutamine was shown in human intestinal mucosa to reduce the production of the pro-inflammatory cytokines IL-6 and IL-8, and enhance the production of the anti-inflammatory cytokine, IL-10.[16]

Intravenous high-dose vitamin C

The effects of vitamin C on the immune system have been argued for many years. Vitamin C is known to be an important antioxidant in the immune system. The results of meta-analyses have demonstrated that intravenous (IV) high-dose vitamin C treatment has significant benefits in the treatment of sepsis and septic shock. The beneficial effects of intravenous high-dose vitamin C in sepsis and septic shock are most likely due to its immunosuppressive effects.[17] Christoph et al. investigate the impact of vitamin C on intracytoplasmic production of pro-inflammatory cytokines in monocytes and lymphocytes by flow cytometry after human whole blood assay. Their results showed that vitamin C (20 mM) inhibited the LPS-induced number of monocytes producing IL-6 and TNF-α.[18] Nieman et al. showed that runners completing the 90-km ultramarathon comrades experienced strong increases in concentrations of plasma IL-6, IL-10, IL-IRA, and IL-8. These increases were attenuated in runners ingesting 1500 mg vitamin C supplements for 1 week prior to the race and on the race day.[19]

Melatonin

Melatonin is one of the hormones that play an antioxidant role in the body. Previous research has documented the positive effects of melatonin in alleviating acute respiratory stress induced by virus, bacteria, radiation, *etc.*[20,21] Melatonin is not viricidal but it has indirect anti-viral actions due to its anti-inflammation, anti-oxidation, and immune-enhancing features.[22] A recent meta-analysis of a total of 22 randomized controlled trials suggested that a supplementary use of melatonin is associated with a significant reduction of TNF-α and IL-6 level.[23] This clinical evidence suggests that the use of melatonin as a supplement may effectively reduce the levels of circulating cytokines, and may potentially also lower pro-inflammatory cytokine levels in COVID-19 patients.[24]

Selenium

It is a crucial element which is needed for the progression of both natural and acquired immune system. Glutathione peroxidase which is catalyzing hydrogen peroxide is selenium-dependent. It ensures the integrity of the cell membrane and prevents DNA damage. It reduces the fatality rate in sepsis treatment. Selenium support enhances the antibody level in blood. Zeng et al. showed that pancreatic mRNA expressions of proinflammatory cytokines IL-1β, TNF-α and IFN-γ reduced responses to selenium treatment.[25] Gao et al. showed that selenium deficiency induced high expression levels of prostagland E synthase (PTGE), cyclooxygenase-2 (COX-2), TNF-α, and nuclear transfer factor κB (NF-κB) in the gastrointestinal tract tissues.[26]

Some related considerations

The imbalance between reactive oxygen species (ROS) production and effective removal by antioxidants and ROS scavengers has been proposed to contribute to many pathological conditions, including critical illnesses such as acute respiratory distress syndrome (ARDS) and sepsis. Although antioxidant supplementation may at first be considered as beneficial, the consequent reduction of ROS/RNS could actually have negative effects. It seems that the use of antioxidants may be beneficial during periods of exaggerated inflammatory responses but may be detrimental during periods of relative immunosuppression. Thus, the effectiveness of antioxidants may depend on the inflammatory response of individuals and the time and duration of antioxidant use.

Conclusion

There are several antioxidant supplements that have effects on inflammatory cytokine. They may be used to strength the body defense against COVID-19. So we must consider whether administering antioxidants could have beneficial and/or detrimental effects within the same patient at different time points. Also, the use of moderate-intensity exercise is recommended to strength the body defense against COVID-19.

Authors' contribution

MS and HSH wrote the first draft of the manuscript. SRA revised and improved the quality of the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interests

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