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Research Paper

The Role of Exercise and Physical Activity in Protecting Against the Inflammatory Responses Triggered by COVID-19: An Integrative Review of the Current Literature

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. The disease is still out of control despite unprecedented social distancing and other constraints. Mortality, mutations, economic and health effects are increasing worldwide. This novel virus is caused by over-release and uncontrolled and impaired regulation of pro-inflammatory cytokines that leads to cytokine storm. Cytokine storm is considered to be one of the major causes of severe acute respiratory syndrome and multiple organ failure that plays an important role in the worsening process of COVID-19. Several studies have shown the effect of physical activity and exercise as an efficient therapy for the treatment and prevention of chronic diseases. The sub-mechanisms between regular physical activity and exercise, and health are numerous. Physical activity and exercise influence on the immune system and its antiviral defenses. The adaptations caused by regular exercise increase the effectiveness of the immune system, which actual levels can affect the severity of SARS-CoV-2 infection. Besides, exercise may provide protection against COVID-19 by increasing performance of some physiological systems, so that endurance training causes numerous biochemical changes in the diaphragm muscle, resulting in the production of a phenotype that is protected against several challenges, including long mechanical ventilation. Therefore, people who exercise continuously and regularly may develop higher antibody titers to the SARS-CoV-2 strain found in the vaccine compared to those who do not exercise. This insight can help to properly design physical activity and exercise programs as a preventative and/or therapeutic approach against the COVID-19 pandemic.

Keywords: Coronavirus, Cytokine Storm, Anti- Inflammatory, Exercise, Physical Activity

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The disease has been described by the World Health Organization as a pandemic and was first identified in Wuhan, China [1]. Despite unprecedented social distancing and prolonged quarantine periods, the status quo is still out of control and the mortality and morbidity rate of COVID-19 is increasing, mutant forms of it have emerged and its negative economic and health impacts have affected people around the world. According to the recent case studies, COVID-19 is manifested by severe pneumonia with alveolar damage, which leads to severe acute respiratory distress syndrome (ARDS) (up to 20% of COVID-19 cases), multiple organ failure and in worse cases even death [2]. In such cases, this novel virus is caused by over-release and uncontrolled and impaired regulation of pro-inflammatory cytokines leading to cytokine storm or cytokine release syndrome (CRS) [2]. Cytokine storm is considered to be one of the major causes of severe ARDS and multiple organ failure [3] that plays an important role in the worsening process of COVID-19 [4]. Cytokine storm is the primary mechanism of ARDS resulting in uncontrolled systemic inflammation caused by pro-inflammatory cytokines, including IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, IL-33, and tumor necrosis factor (TNF-α), and chemokines including, CCL2, CCL-5, IP-10 and CCL3 [5]. Studies show that inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7, TNF-α, macrophage inflammatory protein 1, C-reactive protein (CRP), granulocyte colony-stimulating factor, D-dimer and ferritin are significantly elevated in those patients with more severe disease [5,6]. The plasma level of IL-6 considered as a significant cytokine contributing to macrophage activation syndrome (MAS), increased in patients with severe COVID-19 infection [6].

Many clinical and therapeutic efforts have been made to treat the coronavirus, but pharmacological approaches are not the only therapeutic solution, and exploring other preventive and therapeutic strategies against coronavirus are also of great importance. Several studies have shown the effect of physical activity and exercise as an efficient therapy for the treatment and prevention of chronic diseases [7,8]. Planned and structured, regular and targeted physical activity and exercise have been shown to be an effective treatment for most chronic diseases, with preventive or therapeutic benefits and with regard to primary immunological mediators involved [9]. Physical activity and exercise influence on the immune system and its antiviral defenses [10]. However, there is limited information on how physical activity or exercise interacts with the immune system to influence SARS-CoV-2 infection and susceptibility to COVID-19 pandemic. Therefore, this review essentially examines currently available scientific data related to the anti-inflammatory and mitigating SARS-CoV-2 infection effects of physical activity and exercise.

Developing an Anti-Inflammatory Environment

Inflammation is the predisposing factor for several clinical problems [11]. Many studies have shown that the COVID-19 pandemic is an inflammatory disease [1-6] and therefore providing an anti-inflammatory environment can help manage and reduce the severity and clinical symptoms of the pandemic. Anti-inflammatory activity of physical activity and exercise has been well demonstrated [7,10,12]. Therefore, using the potential of physical activity and exercise in this field can be useful and provide an interesting research field in this regard.

Research data show that higher fitness levels improve immune responses to vaccination, reduce low-grade inflammation, and improve various immune markers in several disease states including cancer, acquired human immunodeficiency syndrome, cardiovascular disease, diabetes, cognitive disorders and obesity [13]. During and after exercise, the level of IL-6 blood circulation increases and skeletal muscle contraction plays a role in this increase and seems to be related to the duration and intensity of the training session [14]. A temporary increase in muscle-derived IL-6 is associated with activation of the anti-inflammatory response, resulting in higher levels of IL-10 and IL-1 receptor antagonist in the blood [15]. In vitro, IL-6 suppressed the production of LPS-induced TNF-α and IL-1β by PBMcs [16]. However, while creating an anti-inflammatory environment following continuous prolonged exercise is very obvious, anti-inflammatory effects have also been observed after short-term low to moderate-intensity exercise, which does not cause IL-6 secretion [12]. The latter suggests that in addition to the production of IL-6 muscle, there should be other mechanisms to reduce inflammation after exercise.

Following from exercise, high levels of IL-6 in circulation are followed by an increase in IL-1ra and IL-10, and two latter anti-inflammatory cytokines can be caused by IL-6 [17]. Therefore, IL-6 creates an anti-inflammatory environment by inducing the production of IL-1ra and IL-10, but as suggested by laboratory [18] and animal studies [19], it also inhibits the production of TNF-α. Other potential effects of exercise that can help control COVID-19 have been described, such as reducing the inflammatory response [20], modulating oxidative stress [21] and increasing nitric oxide (NO) synthesis [22]. Therefore, exercise may provide protection against COVID-19 by increasing the performance of some physiological systems. This insight can help to properly design physical activity and exercise programs as a preventative and/or therapeutic approach against the COVID-19 pandemic.

Physical Activity and Exercise as a Non-Pharmacological Intervention

Physical activity and exercise are one of the most common treatments in health and diseases [23]. The concept of a useful relationship between exercise and

health dates back to Hippocrates writings (5th century BC) [24]. Eventually, years of scientific interest and research followed, and the role of regular exercise in determining health became more important, so that in the late 1990s, it was proposed as a treatment [25] and ten years later it was called a real treatment and "Exercise is medicine" was launched [26]. The advantages of regular exercise are evident both in the secondary stage (preventing the recurrence of clinical events in patients with obvious clinical diseases), both at the beginning (preventing the occurrence of the first clinical event among those at risk) and elementary (avoiding the creation of risk factors in the first place) prevents [27] of many diseases [28]. In addition, regular exercise is associated with longevity [29], reduced risk of physical disability and dependence [30], cognitive function in youth [31] and adulthood [32] and stress reduction [25,33].

The underlying mechanisms of the relationship between regular physical activity and exercise and wellness are many, and new evidence suggests that new benefits are constantly emerging. In connection with upper respiratory tract infections (URTI) caused by pathogens such as COVID-19, physical activity may improve pathological outcomes by increasing the secretion of stress hormones responsible for reducing local excessive inflammation in the respiratory tract and by releasing anti-inflammatory cytokines, such as IL-4 and IL-10, in order to prevent the long-term activity of type 1 helper T cell (Th1) against pathogen, which leads to cell damage and necrosis [34,35].

Many patients with COVID-19 develop respiratory failure and need mechanical ventilation (MV) to maintain adequate pulmonary gas exchange. Interestingly, studies show the effects of endurance training on the respiratory system. Endurance training causes numerous biochemical changes in the diaphragm muscle, resulting in the production of a phenotype that is protected against several challenges, including long MV [36]. In fact, during 10 consecutive days of endurance training, it leads to significant protection against diaphragm dysfunction caused by the respiratory tract [37,38]. Therefore, it is predictable that people with COVID-19 and those who need ventilator support will benefit from exercise-induced diaphragm preconditioning. Studies on the mechanisms responsible for endurance preconditioning diaphragm are powerful tools in the pursuit of pharmacological treatments to prevent ventilator-induced diaphragm dysfunction and reduce weaning problems in patients exposed to long-term support for ventilators. In this regard, preclinical research shows that endurance exercise changes the frequency of ~70 proteins of cytosolic and ~25 mitochondrial proteins in the diaphragm [39]. Studies have been performed on which of these proteins helps protect the diaphragm from ventilator-induced diaphragm dysfunction and show that exercise-induced changes in mitochondrial (e.g., superoxide dismutase 2) and cytosolic (e.g., heat shock protein 72) proteins can be helpful to exercise-induced diaphragm preconditioning [37-39]. This important

information is used to develop successful pharmacological treatments to protect the diaphragm against the weakness of the MV-induced diaphragm [38].

The production and presence of vaccine serum antibodies and T cells will increase in response to exercise-induced antigen stimulation [10,40]. Exercise modulates positive flexibility of the immune system [40]. A 10-month study with aerobic training showed that antibody titers to H1N1 and H3N2 strains of influenza A virus increased in older adults vaccinated with trivalent influenza vaccine [41]. Similarly, in different demographic groups, moderate-intensity exercise improved responses against vaccine strains (influenza, diphtheria, pneumococcus, tetanus toxoids and meningococcal). However, this created a significantly inadequate immune response in the non-athlete group [42]. Finally, in a randomized experiment in dangerous groups susceptible to respiratory viral infections, a 24-week moderate cardiovascular aerobic exercise program showed that protecting people who only stretched their muscles after receiving the influenza vaccine significantly increased [43] In this regard, people who exercise continuously and regularly may develop higher antibody titers to the SARS-CoV-2 strain found in the vaccine compared to those who do not exercise.

Anti-Inflammatory Effects of Physical Activity and Exercise

Chronic inflammation is an important risk factor for several clinical diseases. Interest in using lifestyle-related interventions, such as increase physical activity and exercise, is increased in order to reduce chronic inflammation and disease risk. Currently, there is limited information on how physical activity and exercise interact with the immune system to influence SARS-CoV-2 infection and susceptibility to COVID-19 pandemic. However, exercise affects the immune system and its antiviral defenses [10]. Animal experiments using influenza virus and herpes simplex 1 (HSV-1) in the respiratory tract have shown that moderate exercise, performed before or after infection (for several days before the onset of symptoms), improves the complications and mortality from infection. [44,45]. Lack of physical activity and exercise and decreased physical fitness may increase susceptibility to infection and will surely increase the spread of some comorbidities associated with COVID-19 outcomes if this trend is prolonged. So far, no data is available on whether fitness levels affect the progression of SARS-CoCV-2 infections. However, it is well documented that adaptations caused by regular exercise increase the effectiveness of the immune system [46], which actual levels can affect the severity of SARS-CoV-2 infection. Exercise has been shown to create a short-term inflammatory response, while both cross-sectional comparisons and longitudinal exercise studies show a long-term anti-inflammatory effect [47]. Chronic exercise training reduces the production of inflammatory cytokines and increases the production of anti-inflammatory cytokines [48,49]. Therefore, the multifaceted effects of exercise training change the balance of cytokines at rest to an anti-inflammatory state.

Anti-inflammatory cytokines after an acute period of exercise may also play a role in reducing systemic inflammation caused by CRS [50]. IL-6 released from skeletal muscle during exercise (a more powerful mediator of acute phase training response) leads to the next increase in IL-10 and IL-1 receptor antagonists (IL-1ra), which are anti-inflammatory agents [51]. It seems that IL-6 plays an important role in the anti-inflammatory effects of exercise. Contraction of human skeletal muscles produces and releases a significant amount of IL-6 in circulation to stimulate mobilize energy substrates similar to stress hormones [14]. Hormones released during exercise have an anti-inflammatory effect because cortisol acts as an anti-inflammatory mediator and adrenaline regulates the production of inflammatory cytokines IL-1β and TNF-α [40]. In sum, it is believed that exercise training may reduce CRS as changes in these pro-inflammatory cytokines may be moderated by anti-inflammatory cytokines, such as IL-1ra, IL-6 and IL-10, and cytokine inhibitors, such as IL-2, prostaglandin E2, Cortisol and soluble receptors against TNF [40].

Other anti-inflammatory pathways regulate the expression of pro-inflammatory TLRs after completing concurrent exercise programs (aerobic plus strength) [52]. In particular, they reduce the expression of TLR4 at the level of monocytes and macrophages, enabling control inflation states in patients with chronic diseases, such as diabetes or obesity [53]. Another effect that exercise has on macrophage cells is the possibility of stimulating the conversion of inflammatory macrophages (M1) to anti-inflammatory (M2) [54]. This isotype change allows for a reduction in the penetration of macrophages into adipose tissue, which can reduce the synthesis of inflammatory cytokines [54].

In addition, exercise reduces the expression of TLR4 and NF-κB, which shows an anti-inflammatory response. This is most likely due to the blockage of NF-κB transport to the cell nucleus, leading to neuro-inflammatory patterns in mice [55]. In this context, exercise-affected mice (8-12 minutes of moderate aerobic exercise for four consecutive days) infected with influenza virus, significantly increased in TNF receptors soluble in lung cells without changes in TNF-α, which can stimulate inflammation control response [56]. Exercise may be a tool to help reduce the risk of cytokine storms in COVID-19 infection and minimize side effects during inflammatory conditions. In fact, the inflammatory process created by ROS can be more effectively detoxified by antioxidant systems in various organs including the brains of well-trained people from adaptation to exercise [57].

Regular exercise with low and moderate intensity is associated with decreased pro-inflammatory markers in circulation and improved immune function [58]. The main mechanisms by which exercise acts functionally in the immune system and lead to anti-inflammatory effects include: (1) reducing adipose tissue mass (2) creating an anti-inflammatory environment by the release of anti-inflammatory

cytokines; and (3) changes in the expression or activity of TLR in innate immune cells. Exercise has long been proven to have anti-inflammatory effects and can therefore prevent chronic inflammatory diseases [12,58]. A significant increase in circulatory levels of IL-6 following exercise without muscle damage has been a consistent finding [58]. Plasma-IL-6 increases exponentially with exercise and relates to exercise intensity, duration, muscle mass and endurance capacity [59].

Sub-mechanisms of anti-inflammatory responses of physical activity and exercise

Since the effect of physical activity and exercise training on the immune system and antiviral defense of the body has been shown [10], investigating and recognizing the mechanisms that cause anti-inflammatory responses and antiviral defenses caused by physical activity and exercise training can be helpful to understand the positive effects of physical activity and exercise training on the immune system and antiviral defense of the body.

One of the proposed mechanisms underlying the anti-inflammatory effects of exercise is the reduction activation and expression of TLR in innate immune cells [12]. This decrease has been observed after acute periods of exercise and longer exercise studies [60–62], but the molecular mechanisms of regulation of exercise-induced TLR2 or TLR4 are not entirely clear. The first report on CD14 monocytes described a decrease in cell expression of TLR2 and TLR4 after 1.5 hours of endurance training (~65% VO_2max) performed at 34 ℃ in healthy subjects [63]. Likewise, the reduction of TLR4 expression at the cell level of CD14 monocytes was found after 45 minutes of endurance training at 75% VO_2max [61] and reduction of CD14 monocyte TLR4 expression in healthy men after 1.5 hours of endurance exercise at 75% VO2max, while TLR2 expression remained unchanged in a latter study [62]. TLR4 expression returned to baseline values after 4 hours of exercise, which highlights the acute effect of exercise on TLR4 expression [62]. Conversely, an acute resistance exercise (9 exercises, 3 sets, 10 repetitions, 80% 1RM) causes not changes in CD14 monocyte TLR4 cell expression in untrained or trained elderly women [64], suggesting that the type of exercise and/or age-related inflammatory state may induce different TLR regulation. In addition, 12 weeks of combined resistance and endurance training resulted in a decrease in cell expression of CD14 monocyte TLR4 cells [60] and expression of TLR2 and TLR4 [65] in sedentary subjects compared to pre-training values. In addition, intervention leads to a decrease in the ratio of classic monocytes/monocytes "pro-inflammatory" CD16, indicating a change in a higher anti-inflammatory monocyte profile [65]. Eight weeks of resistance training reduced the expression of TLR2 and TLR4 in PBMCs in healthy older adults [66]. This reduction in regulation was associated with an increase in the protein content of HSP70 and a decrease in NF-jB signaling and the production of pro-

inflammatory cytokines [66]. An increase in HSP70 concentrations after exercise was reported in both animals [67] and humans [68] by intensity- and frequency-dependent method [69]. The HSP70 protein reduces the activity of NF-jB [70], thereby reducing the expression of pro-inflammatory cytokines, such as IL-6, TNF-α or IL-1b [71]. MicroRNAs (miRNAs) have been considered as key regulators and an essential part of the networks involved in regulating TLR signaling pathways during and after exercise [72]. Growing evidence suggests an important role for miRNAs in modulating immune functions in response to exercise [73,74].

Regular exercise can reduce IL-6 resting levels and ultimately CRP production due to reduced obesity [75]. In addition to adipose tissue, part of this effect may be caused by modulating cytokine production from other sites, such as skeletal muscle [76]. IL-6 is a pleiotropic cytokine with various physiological activities including regulating inflammatory processes [77]. Overproduction of IL-6 may contribute to systemic inflammatory processes and induce the production of cytokines [78]. Exercise studies have reported vague results (decrease or no change) at baseline levels of IL-6 [79]. However, many longitudinal and cross-sectional studies in healthy and sick people have shown that markers of inflammation are reduced after long-term behavioral changes such as increased physical activity [80], and there are possibly anti-inflammatory effects of regular exercise as well to mediate beneficial health outcomes in exercise. Regular exercise training can reduce the baseline level of IL-6 production as well as the acute response rate of IL-6 to exercise. Accordingly, a decrease in plasma IL-6 concentration at rest, as well as in response to exercise, appears to be a normal adaptation feature in training [81]. In addition, our findings confirm the idea that exercise itself has anti-inflammatory properties and acts through inflammation inhibitor mechanisms and stimulates anti-inflammatory pathways, in which the role of HIIT is more pronounced [48,49]. Further, our findings showed a significant increase in HDL levels [48,49,82,83], which can be one of the most thoughtful points in the findings. In vitro and in vivo experiments have been provided mechanical explanations for the anti-atherosclerotic effects of HDL, including stimulating the removal of cholesterol from the arterial wall, preventing endothelial dysfunction and reducing oxidative stress [84].

In normal physiologic conditions, endothelial cells do not express adhesion molecules [85]. However, damaged endothelium expresses and releases adhesion molecules such as ICAM-1, VCAM-1 and selectins to absorb circulating leukocytes [86]. There are two possible mechanisms behind the effects of exercise training on endothelial cells in reducing chronic inflammation. First, exercise training may increase the number of endothelial progenitor cells, bone marrow-derived stem cells that can be distinguished into endothelial cells [87]. Current findings by several groups support the positive effect of exercise on endothelial

progenitor cells [88]. This may improve vascular capacity to regenerate endothelial cells after injury, potentially reducing inflammation of the vascular wall during obesity and metabolic syndrome. Second, regular exercise increases blood flow and laminar shear stress, and reduces endothelial expression and release of adhesion molecules [89]. This has been supported by the findings of human and animal studies, during which circulatory levels and endothelial expression of VCAM-1 and P-selectin are reduced by exercise training [90-93]. This reduces the effects of leukocyte migration to the vessel wall and reduces local inflammatory responses. It is noteworthy that endothelial cell damage is an important mechanism for initiating the penetration of leukocytes (e.g. macrophages) into various tissues including adipose tissue [94]. Therefore, the effect of exercise training on endothelial cell inflammation is also useful in reducing inflammation of adipose tissue. This effect overlaps with exercise effects on angiogenesis of adipose tissue, blood flow and hypoxia status. In sum, these effects may lead to a decrease in macrophage penetration into adipose tissue and a rapid change in the rate of inflammatory M1 macrophages to the anti-inflammatory M2 type in adipose tissue.

Studies have shown that during exercise, expression and activity of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production are increased in response to shear stress [85]. NO is an important molecule that plays a role in neural transmission, vasodilation and immune responses [22]. NO antimicrobial activity has been described for several bacteria, protozoa and some viruses such as CoV-2 [95]. However, SARS-CoV-2 proteins involved in modulating this type of IFN response host inhibit IFN signaling [96], which alters nitric oxide inducible levels (iNOD) and NO production [97]. Physical exercises lead to increased blood flow and stress, which contributes to the endothelial expression of eNOS. This enzyme is dependent on calcium, continuously expressed and releases NO [22]. Therefore, physical activity and exercise can partially restore the COVID-19 control mechanism by releasing NO.

Conclusion

Humans have long been involved in many communicable and non-communicable health challenges, including various epidemics, silent epidemics of inactivity, obesity, diabetes, heart disease, etc. One of the current health challenges is COVID-19 pandemic, which has had many deaths and negative health and economic consequences. Undoubtedly, confronting such a challenge is of great importance to human beings and the role of physical activity and exercise training in this regard is significant and important, because by doing physical activity and proper exercise, as a pharmacological treatment, in addition to gaining many benefits, the person will not be harmed. The advantages of regular exercise are evident both in the secondary stage (preventing the recurrence of clinical events

in patients with obvious clinical diseases), both at the beginning (preventing the occurrence of the first clinical event among those at risk) and elementary (avoiding the creation of risk factors in the first place) prevents [26,27] of many diseases [28].

Currently, there is limited information on how physical activity and exercise interact with the immune system to influence SARS-CoV-2 infection and susceptibility to COVID-19 pandemic. However, exercise affects the immune system and its antiviral defenses [10]. The adaptations caused by regular exercise increase the effectiveness of the immune system [46], which actual levels can affect the severity of SARS-CoV-2 infection. On the other hand, chronic exercise training reduces the production of inflammatory cytokines and increases the production of anti-inflammatory cytokines [48,49]. Therefore, the multifaceted effects of exercise training change the balance of cytokines at rest to an anti-inflammatory state.

Physical activity and exercise are one of the most common treatments in health and diseases [23], and lack of physical activity and exercise and decreased physical fitness may increase susceptibility to infection and will surely increase the spread of some comorbidities associated with COVID-19 outcomes. Thus, using the potential of physical activity and exercise in this field can be useful and provide an interesting research field in this regard. Exercise may provide protection against COVID-19 by increasing the performance of some physiological systems, so that endurance training causes numerous biochemical changes in the diaphragm muscle, resulting in the production of a phenotype that is protected against several challenges, including long mechanical ventilation [36]. Therefore, it is anticipated that people with COVID-19 and those who need ventilator support will benefit from exercise-induced diaphragm preconditioning. Also, people who exercise continuously and regularly may develop higher antibody titers to the SARS-CoV-2 strain found in the vaccine compared to those who do not exercise. This insight can help to properly design physical activity and exercise programs as a preventative and/or therapeutic approach against the COVID-19 pandemic.

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