

COMMENT

Title: COVID-19 AND EXERCISE-INDUCED IMMUNOMODULATION

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Abstract

A novel coronavirus, so-called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has strong transmissibility and progress rapidly among human beings. COVID-19 has led to pneumonia, lymphopenia and elevated cytokine production. Lockdown without any outdoor activities have been advised. However, sedentary behavior is associated with obesity and cardiovascular disease that can increase the morbidity for COVID-19 patients. Defining the role of regular physical exercise on immunomodulation provides potential target for taking precaution and for clinical management.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the novel coronavirus disease 2019 (COVID-19), is responsible for a large global outbreak. Latest global number of confirmed cases of COVID-19 is more than 1,600,000, including almost 100,000 confirmed deaths in 213 countries (reported by WHO in April, 2020). Most people with COVID-19 experienced mild to moderate illness, but around 15% progress to severe pneumonia and about 5% progress to acute respiratory distress syndrome. The maintenance of social distancing, wash hands frequently and avoid touching eyes, nose and mouth have been strongly advised by WHO. Reports from health authorities worldwide converge for put cities on lockdown, without any outdoor activities, including physical exercise. However, it is important to consider the benefits of regular exercise-induced immunomodulation as potential target for taking precaution and for clinical management. Indeed, the sedentary behaviors such as watching TV, long period of sitting and use of smartphones are associated with increased risk of obesity, hypertension and type 2 diabetes mellitus. This is an important point of discussion once most of the patients on admission in hospital presented comorbidity: diabetes (10 – 20%), hypertension (16.9%), and other metabolic diseases, including obesity and chronic inflammation (53.7%) [1].

The immunopathology of the SARS-CoV-2 infection involves both the innate and adaptive immune system. After SARS-CoV-2 infection, there is an increase of neutrophils counts and a decrease in the number of natural killer cells (NK cells), as well as a leukopenia based on reduced percentage of monocytes, eosinophil and basophils [2]. For the adaptive immune response, it has been observed reduction of TCD4+ and TCD8+ lymphocytes. The upregulation of B lymphocytes induces the detection of high levels of IgG in the plasma from 7 to 10 days after SARS-CoV-2 infection. In addition, there is an elevated production of pro-inflammatory cytokines including TNF- α , IL-6, IL-1 β , IL-8, IL-17 and IL-2 [3]. The abnormal elevated concentration of those cytokines led to crosstalk activation of the neuroendocrine-immune system, with consequent glucocorticoids release, which may impair immune responses [4]. The abnormally elevated cytokine release can induce a multiple organ failure, such as heart, liver, kidney and lungs. Particularly in the lungs, the cytokines-induced infiltration of neutrophils and macrophages can provoke formation of hyaline membranes and shortness of the alveolar wall [3].

Exercise-induced immunomodulation is recognized for more than three decades, with around 5,000 peer-reviewed original and review papers (Medline Pubmed databases). Exercise-induced immunomodulation seems to be dependent of interplay between intensity, duration and frequency of exercise [5]. In both, human and animal models, long-duration and/or intense exercise (> 2hours and/or > 80% of maximal oxygen uptake, VO_{2max}) is associated with markers of immunodepression, such as: 1) increased production of pro-inflammatory cytokines (IL-6, IL-8, TNF- α and IL-1); 2) symptoms of upper respiratory tract infections; 3) reduced NK cells, T- and B-

lymphocyte and neutrophils function; 4) reduced production of salivary IgA, and plasma IgM and IgG; 5) low expression of major histocompatibility complex II (MHC II) in macrophages [6, 7]. These changes can be detected from hours to days after the end of a prolonged and/or intense endurance exercise bout. In addition, the hormones of the hypothalamus-pituitary-adrenal axis, glucocorticoids receptors (GR) and intracellular signalization of NF-kappaB seems to be involved to chronic inflammatory airway disease, all which might be increased after prolonged/intense exercise [5]. Thus, long-duration and/or intense exercise may do humans more susceptible for infection (mainly upper respiratory tract infections), which may increase the risk of infection and aggravation by COVID-19.

Conversely, clinical and translational studies in humans have demonstrated that regular bouts of short-lasting (i.e., up to 45 - 60 minutes), moderate intensity exercise (50 to 70% VO_{2max}), performed at least three times a week is beneficial for host immune defense, particularly in older adults and people with chronic diseases [5]. Moderate intensity exercise seems to be associated with increased leukocyte function [8] and enhanced chemotaxis, degranulation, cytotoxic activity, phagocytosis and oxidative activity of neutrophils and macrophages [9]. A previous study showed an increase in the cytolytic activity of NK cells and NK cell activating lymphokine (LAK) during a 60-min of moderate intensity exercise [8]. Thus, contrary to long-duration/intense exercises, moderate-intensity exercise may carry to increased immune protection. Whether or not individuals habituated to practice moderate intensity exercise experience less serious complications associated with COVID-19 deserve further investigation.

Clinically, the first phase of immune responses induced by SARS-CoV-2 infection is a specific adaptive immune response to eliminate the virus and prevent disease progression. Patients with severe complications derived from COVID-19 infection present lymphocytopenia with a cytokine release syndrome mediated by leukocytes other than T cells. This is important because the reduction of IL-6 and TNF will increase the release of anti-inflammatory cytokines. Anti-inflammatory cytokines can suppress hyperactive immune response, promoting tissue repair, especially for lung damage [2]. Interestingly, there is an increase in the expression of pro-inflammatory cytokines in skeletal muscle (TNF- α and IL-1 β) during moderate-intensity exercise; however, there is no alteration in the circulating of these cytokines [10]. In contrast, there is a noticeable increase in the circulating concentrations of anti-inflammatory cytokines IL-1 receptor antagonist (IL-1ra) and IL-10 [10]. Low-to-moderate intensity exercise (30 – 60% VO_{2max}) also increases the production of anti-inflammatory cytokines by T-cells (IL-4 and IL-10). Thus, regular moderate-intensity exercise might be an effective approach to enhance anti-inflammatory response, which may help to revert lymphocytopenia in COVID-19 patients. Further experimental studies will be necessary to confirm or to refute this hypothesis.

In conclusion, the pandemic of COVID-19 has become a clinical threat to the worldwide, including physicians, researchers, nurses, healthcare workers, and mostly for general population. It is a consensus that the effective treatment to avoid the high rate of contamination and the spread of SARS-CoV-2 via human-to-human transmission is social distancing. However, the practice of in-home moderate intensity exercise is recommended. Low-to-moderate exercise-induced immunomodulation might be an

important tool to improve immune responses against the progression of SARS-CoV-2 infection.

Authors declare no conflict of interest

References

1. Guan, W.J., et al., Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J*, 2020.
2. Cao, X., COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*, 2020.
3. Sarzi-Puttini, P., et al., COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol*, 2020. 38(2): p. 337-342.
4. Mehta, P., et al., COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*, 2020. 395(10229): p. 1033-1034.
5. Simpson, R.J., et al., Can exercise affect immune function to increase susceptibility to infection? *Exerc Immunol Rev*, 2020. 26: p. 8-22.
6. Leandro, C.G., et al., Physical training attenuates the stress-induced changes in rat T-lymphocyte function. *Neuroimmunomodulation*, 2006. 13(2): p. 105-113.
7. Leandro, C.G., et al., Stress-induced downregulation of macrophage phagocytic function is attenuated by exercise training in rats. *Neuroimmunomodulation*, 2007. 14(1): p. 4-7.
8. Bigley, A.B., et al., Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Part II: impact of latent cytomegalovirus infection and catecholamine sensitivity. *Brain Behav Immun*, 2015. 49: p. 59-65.
9. Senna, S.M., et al., Moderate physical training attenuates perinatal low-protein-induced spleen lymphocyte apoptosis in endotoxemic adult offspring rats. *Eur J Nutr*, 2016. 55(3): p. 1113-22.
10. Peake, J.M., et al., Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. *Exerc Immunol Rev*, 2015. 21: p. 8-25.