Review Paper

Effect of exercise in the recovery process after the inflammation process caused by coronavirus

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ABSTRACT

Coronavirus (SARS-CoV-2 - COVID-19) disease causes severe acute respiratory syndrome. During infection, activation of macrophages and pro-inflammatory granulocytes produces cell damage, inducing lung inflammation that leads to the characteristic symptoms of fever, cough, fibrosis, and high increase in pro-inflammatory cytokine levels. In general, during the inflammatory process and infection by coronavirus, cytokines are elevated, particularly IL-1, 6 and 12, TNF-α, and TGF-β. In addition, patients with complications and lethal prognosis present increased serum levels of IF-I and γ compared to healthy individuals or patients with moderate symptoms. On the other hand, it is known that physical activity favours an adaptation of the immune system function. In this context, we suggest that appropriate exercise programs could improve recovery of people who have suffered from COVID-19 disease, improving the quality of life and reinforcing the protection against future infections. The immunomodulatory properties of exercise and physical activity could act as prevention tools for different chronic diseases in healthy individuals and complement therapeutic tools in sick patients. Nevertheless, exercise must be adequate both in time and intensity, taking into account the patient's clinical situation as well as their previous physical activity.

Keywords: Coronavirus; COVID-19; Cytokines; Exercise; Immunomodulators; Inflammation.

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INTRODUCTION

The World Health Organization (WHO) designated SARS-CoV-2 as the cause of an international outbreak of respiratory disease known as COVID-19 (Coronavirus disease-2019) (Zhao et al. 2020; Lu et al., 2020). Around 15-30% of common colds are caused by human coronaviruses, such as HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1. Coronavirus (CoV) family causes severe acute respiratory syndrome (SARS) illnesses. In this context, SARS-CoV-2 causes SARS with high transmissibility and pathogenicity (Merad & Martin, 2020; Rothan & Byrareddy, 2020; Sarzi-Puttini et al., 2020). The virus is transmitted from human to human through breath droplets and cause respiratory tract pathology. The disease starts as a self-limiting respiratory tract illness, displaying fever, dry cough, dyspnoea and headache. Then, it progresses to a severe pneumonia that is potentially life threatening, ending with multiorgan failure and death. The most exposed population segments with poorer prognosis are older age groups with allergic diseases, asthma and chronic obstructive pulmonary disease, among other potential risk factors (Al-Shaibani, 2020). During infection, macrophages and pro-inflammatory granulocytes produce cell damage, inducing lung inflammation that results in the characteristic symptoms of fever, cough, fibrosis, and high increase of pro-inflammatory cytokine levels (Chousterman, Swirski, & Weber, 2017).

Cytokines are produced by leukocytes and regulate different functions of cells in the immune system (Chousterman et al., 2017; Zhang & An, 2007). Cell processes modulated by cytokines include activation, proliferation, differentiation, maturation and apoptosis as well as particular effector functions on lymphocytes and accessory cells. Cytokines also participate in the regulation and distribution of circulating leukocytes and exert modulatory effects on cells in various organs and body systems (Chousterman et al., 2017; Germolec, Frawley, & Evans, 2010; Zhang & An, 2007). Cytokines are pleiotropic extracellular messengers. Otherwise said, they can be produced by various cell types and at the same time, exert their action on different targets. The cytokine family includes growth factors, interferons, interleukins and colony-stimulating factors (Germolec et al., 2010). In addition, cytokines have overlapping activities to regulate proliferation or differentiation on the target cells involved. Therefore, cytokines act as messengers between immune cells and the cells that receive the signal (target cells). These cells can proliferate, secrete additional cytokines, migrate from the affected area, differentiate into another cell type or die by apoptotic mechanisms (Chousterman et al., 2017; Germolec et al., 2010; Zhang & An, 2007). Interleukins (IL) are the main group of cytokines responsible for leukocyte communication. Other cytokines act as colony-stimulating factors for macrophages and granulocytes, stimulating cell growth. Finally, some cytokines cause tumour cytotoxicity and inhibition of viral replication, such as tumour necrosis factors (TNF) and interferons (IFN), respectively (Chousterman et al., 2017; Germolec et al., 2010; Zhang & An, 2007).

During an inflammatory process, such as during an infection by coronavirus, cytokines IL-1, IL-6 and TNF-α expression are increased. This makes them candidate targets for therapeutic intervention. In this context, and just like certain drugs do, physical activity and exercise are effective helpful tools for many chronic diseases at different levels, including prevention, therapy and immunomodulation (Kawanishi, Mizokami, Niihara, Yada, & Suzuki, 2016; Ozemek, Lavie, & Rognmo, 2019). In addition, the changes caused by exercise in the immune response may be responsible for better survival after respiratory virus infection (Lowder, Padgett, & Woods, 2006). Furthermore, exercise has an accumulative effect on the immune system at both innate and adaptive levels (Walsh et al., 2011). In this context, exercise interventions have not been clearly defined as part of the strategy to recover from coronavirus infection. In the face of the current situation, the present mini review aims to address the inflammatory consequences of infection by coronavirus, as well as to discuss the potential use of exercise as an efficient therapeutic complement against the deleterious effects caused by COVID-19.

INNATE IMMUNE RESPONSE TO COVID-19

The immune response to coronavirus starts from the first line of defence mechanism which is innate immunity. The immune signalling pathways are initiated by nucleic acid sensors, a family of proteins that detect the presence of unusual nucleic acids (DNA or RNA) introduced by a virus. Nucleic acid sensors are located in different subcellular compartments and include Toll-like receptors (TLRs) in endosomes and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) in the cytosol, among others. When coronavirus RNA enters the cell, RLRs are activated triggering a transduction pathway that culminates in phosphorylation of several transcription factors known as interferon regulatory factors. These, together with nuclear factor-κB (NF-κB), result in the activating the transcription of type I interferons (IFN-I) and additional antiviral genes (Rehwinkel & Gack, 2020).

Therefore, the result from viral RNA entry is the activation of several immunoregulatory genes and secretion of a battery of cytokines, including IFN-I, TNF-α, IL-1, IL-6, IL-8 and IL-18. IFN-I can limit CoV infection by IFN-induced transmembrane family (IFITM) proteins that inhibit SARS-CoV-2 entry. The remaining cytokines may contribute to cytokine storm formation (Hadjadj et al., 2020). Therefore, IFN-I members are antiviral agents with immunomodulatory properties, including the anti-inflammatory activity of IFN-α and IFN-β (McNab, Mayer-Barber, Sher, Wack, & O'Garra, 2015). On the other hand, IFN-γ, the only member of IFN-II, is considered a proinflammatory cytokine that regulates the expression of TNF receptors, modulates the activity of TNF-α, and induces NO synthase expression (Billiau, 1996; Green et al., 1994; Ruggiero, Tavernier, Fiers, & Baglioni, 1986; Schroder, Hertzog, Ravasi, & Hume, 2004). Experimentally, it seems that IFN-γ increases resistance to viral infection and inhibits viral replication (Lee & Ashkar, 2018). However, the virus evades IFNs and cytokines by inhibiting IFN-I induction, secretion and signalling from infected bronchial cells (Hadjadj et al., 2020).

Other mechanisms of virus evasion include shielding viral double-strand RNA by membrane bound compartments that are formed during viral replication (Knoops et al., 2008). During this process, CoV genome expression depends on a set mRNAs capped at the 5'-end that promote the synthesis of viral proteins into the infected cell. Cap methylation is carried out by CoV non-structural proteins (NSPs) 10, 13, 14, and 16 (Bouvet et al., 2010). A component of the virus replication complex is endoribonuclease NSP15 that seems to evade double-strand RNA recognition by host nucleic acid sensors in macrophages, avoiding RIG-I activation (Deng & Baker, 2018; Hackbart, Deng, & Baker, 2020).

Other innate immune cells recruited during viral infections are natural killer (NK) cells. NK cells contribute to the resolution of infection through the expression of receptors that recognize virus-infected cells, inducing their lysis. Patients with COVID-19 showed reduced numbers of NK cells in the peripheral blood, as well as impaired maturation and migration of the mature NK cells into the lungs or other peripheral tissues associated with disease progression (Giamarellos-Bourboulis et al., 2020; Song, Xu, He, & Lu, 2020). NK cells also express reduced membrane levels of CD16 and killer immunoglobulin-like receptors (KIRs), as well as reduced intracellular expression of CD107a, killer-specific secretory protein 37 (Ksp37), granzyme B and granulysin, leading to impaired cytotoxicity (Wilk et al., 2020). During COVID-19 infection, there is a secretion of immunoglobulin (Ig) G1 and IgG3 that induces CD56(dim)CD16^{+} NK cell activation through antibody receptors (Fc receptors) (Amanat & Krammer, 2020). The immune checkpoint NKG2A is increased in NK cells, inhibiting cell cytotoxicity by binding to the non-classical human immune-compatibility leukocyte antigen chain E (HLA-E), enabling viral escape (Zheng & Song, 2020).

Finally, other important cells in immunity against COVID-19 are innate lymphoid cells (ILC). ILCs are effector cells that lack the expression of T cell receptor and B cell receptor. ILCs are divided into two main groups: the previously mentioned cytotoxic natural killer (NK) cells, and the non-cytotoxic helper ILCs, which include ILCs1, ILCs2, and ILCs3 that are present in healthy lungs (Vivier et al., 2018). Particularly, ILCs2 improve lung function following infection through amphiregulin-mediated restoration of the airway epithelium and oxygen saturation. They produce IL-13 that contributes to the recruitment of macrophages to the lungs as well as the polarization of alveolar macrophages (Chang et al., 2011). Nevertheless, the role of ILCs in COVID-19 infection is still under investigation.

ADAPTIVE IMMUNE RESPONSE TO COVID-19

The second line of defence (adaptive immunity) appears when the first line of immune defence mechanism failed to eradicate COVID-19. This new line includes the participation of T and B lymphocytes.

T lymphocytes responses

T cells play a basic role in viral infections. They can differentiate into effector cells (T helper lymphocytes $CD4^+$) that help B cell for antibody production. In addition, T cytotoxic ($CD8^+$) cells can kill viral infected cells to reduce virus load. Patients with moderate and severe COVID-19 infection showed reduced numbers of both CD4 T helper and CD8 T cytotoxic lymphocytes (Nie et al. 2020). This reduction in the number of T lymphocytes is due to increased levels of inflammatory cytokines such as IL-6. In addition, IFN-I and TNF-α inhibit T-cell recirculation in blood by promoting its retention in lymphoid organs and attachment to the endothelium. The extensive cell death observed in retained lymphocytes was due to the pro-apoptotic effect of IL-6 and Fas-FasL interactions. In this context, treating patients with IL-6 receptor antagonist (tocilizumab) was found to increase the number of circulating lymphocytes (Diao et al., 2020; Guo et al., 2020; Shiow et al, 2006; Velikova, Kotsev, Georgiev, & Batselova, 2020).

T cells ($CD4^+$) express on its surface COVID-19 immunogenic epitopes, including S, N, M, and ORF3, together with HLA-I and HLA-II restricted antigenic epitopes. This stimulation leads to memory T cell formation, which is an important event in vaccination. In this context, the magnitude of $CD8^+$ memory T cells is more than $CD4^+$ memory T cells, persisting for 6 to 11 years and conferring long term immunity. Infected patients presented increased serum IFN-γ, TNF-α and IL-2 concomitant with lower levels of anti-inflammatory IL-5, IL-13, IL-9, IL-10, and IL-22 (Li et al., 2008; Ng et al., 2016). Specific $CD4^+$ T cell responses included CD154 and CD137 co-expression as antiviral mechanisms together with enhanced expression of CD38, HLA-DR isotype and the proliferation marker Ki-67 (Braun et al., 2020). The induction of vigorous T cell immunity is essential for competent virus control, while dysregulated T cell responses may cause immunopathology and determine severity of COVID-19 disease. This dysregulation includes reduced frequencies of regulatory T (Treg) cells in severe COVID-19 cases, evolving to acute respiratory distress syndrome (ARDS) inflammation and facilitating the development of COVID-19 immunopathology in lungs (Qin et al., 2020).

Another point to consider is the reduction of gd-T (γδ-T) cells, a subset of T cells with protective antiviral function in severe COVID-19 disease (Braun et al., 2020). Regarding T cell subsets during COVID infection; there is an increased level of activated T cells characterized by the expression of HLA-DR, CD38, CD69, CD25, CD44, and Ki-67. CD8 T cells seem to be more activated than CD4 T cells (Thevarajan et al., 2020). However, the progression of infection leads to an increased level of PD-1 (programmed death-1), an inhibitor of T cell proliferation by activating apoptotic mechanisms. Increased PD-1 expression together with T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) expression indicates T cell exhaustion, particularly

$CD8^+$, becoming less cytotoxic, with decreased degranulation of granzymes A and B content, as well as perforin production. These changes can be observed in COVID-19 patients on ventilator treatment and severe prognosis (Zhou et al., 2020). On the other hand, patients recovered from COVID-19 displayed higher frequencies of polyfunctional T cells with T helper $CD4^+$ producing more cytokines such as IFN-γ, TNF-α, and IL-2, and $CD8^+$ T cytotoxic cells producing more IFN-γ, TNF-α, and CD107a.

In summary, in severe COVID-19 cases, T cells are highly activated ending with exhaustion due to expression of inhibitory markers such as PD-1 and TIM-3, resulting in decreased function and cytotoxicity. Conversely, recovered patients display an increase in follicular helper $CD4^+$ T cells (TFH) with decreasing levels of inhibitory markers along with enhanced levels of effector molecules such as granzymes A and B, and perforin (Zheng et al., 2020; Channappanavar, Fett, Zhao, Meyerholz & Perlman, 2014).

B lymphocytes responses

The humoral immune response is important for the clearance of the cytopathic effect of viruses and is a main component of the memory immune responses that prevents viral reinfection. COVID-19 induces a strong B cell stimulation as observed by the rapid production of virus-specific antibodies such as IgM, IgA and neutralizing IgG antibodies (Huang et al., 2020). Seven to fourteen days after the onset of symptoms, the antibody presence increases and persists weeks after recovery (Okba et al., 2020). These antibodies are directed against external glycoproteins of viral spikes (S), specifically against receptor binding domain (RBD), which is highly immunogenic, and internal N proteins (To et al., 2020). These antibodies can block the binding of the virus to ACE2 (angiotensin converting enzyme-2) receptors, neutralizing viral particles (Ju et al., 2020). High antibody levels may contribute to pulmonary disease and pneumonia due to a type III hypersensitivity reaction (Mahdi, 2020). The humoral immune response against this virus leads to formation of plasma cells from B cells during acute and convalescent phases. These cells secrete short half-life antibodies even after resolution of infection. This results in the formation of memory B cells that can protect from the initial challenge and offer extended immunity against reinfection. This immunity may disappear 1-2 years after primary infection.

The first antibody that appears is IgM which represents the primary immune response starting after 5 days of virus exposure, increasing to reach a maximum after 10-21 days post-infection and decreasing thereafter. The second antibody formed is IgG which represents the secondary immune response, increasing after 21 days of exposure and formed against RBD and viral N antigens. This antibody decreases after 1-2 years, being undetectable in 25% of individuals (Liu et al., 2006). During patient recovery, IgG levels began to decrease 8 weeks after symptom onset (Adams et al., 2020). Therefore, viral load correlates inversely with levels of IgG antibodies (Algaissi et al., 2020). However, non-neutralizing virus-specific IgG facilitate entry of virus particles through antibody Fc-receptors of macrophages and monocytes, phenomenon known as antibody-dependent enhancement (ADE) of infection (Taylor et al., 2015).

INFLAMMATORY RESPONSE TO EXERCISE

There are many levels by which exercise can affect the immune system function, such as intensity of effort, training programme, length of activity and associated competitive environmental stressors (Shephard, Verde, Thomas, & Shek, 1991). Exercise produces a stimulation of the immune system that is proportional to exercise intensity. Exercise increases the function and mobilization of leukocytes, particularly neutrophils and monocytes (Cordova, Martin, Reyes, & Alvarez-Mon, 2004; Cordova, Monserrat, Villa, Reyes, & Soto, 2006; Cordova, Sureda, Pons, & Alvarez-Mon, 2015). These effects are more significant when performing high intensity physical activities that involve eccentric muscle contractions that provoke muscle damage. This is

associated with increased inflammatory markers, such as pro-inflammatory cytokines (TNF-α, IL-1 and IL-6), C-reactive protein (CRP), oxidative markers and counteracting antioxidant enzymes (Cordova et al., 2004; Sureda et al., 2007, Córdova et al., 2015).

The acute phase response is associated with stressor elements such as tissue damage and inflammation, as a result of exercise intensity. IL-6 is a potent intermediate of the acute phase response together with IL-1, IL-11 and TNF-α (Baumann & Gauldie, 1994; Kammuller, 1995), contributing to the catabolism of muscle proteins (Pedersen & Hoffman-Goetz, 2000). IL-6 increases ACTH (adrenocorticotropic hormone) production, subsequently priming the production of glucocorticoids (Baumann & Gauldie, 1994). Initially, corticoids potentiate the effects of pro-inflammatory cytokines such as IL-6. However, prolonged use provokes an inhibitory effect, affecting IL-6 production by the macrophages (Kammuller, 1995). At the same time, the changes of these immunomodulatory and pro-inflammatory cytokines are mediated by other anti-inflammatory cytokines (IL-1ra, IL-10 and IL-13) and cytokine inhibitor factors such as cortisol and soluble receptors against TNF-α and IL-2. These immunomodulatory agents increase in response to resistance exercises (Pedersen & Hoffman-Goetz, 2000).

In addition, the production of reactive oxygen species (ROS) promotes the activation of transcription factors such as NF-κB (Wang, Zhang, & Li, 2002). On the other hand, cytokines released from the muscle (myokines) mediate inflammatory and metabolic processes. Therefore, acute exercise primes the connection between cytokines, immune cells and other intracellular components, creating an inflammatory milieu responsible for the adaption and post-exercise recovery (Allen, Sun, & Woods, 2015). On the contrary, moderate exercise improves the recovery from systemic inflammation together with adaptations in endocrine, metabolic and immune systems. This phenomenon is accompanied by a decrease in acute phase proteins (Suzuki et al., 2002).

INFLAMMATION ASSOCIATED WITH COVID-19

Altogether, the clinical symptoms in severe cases of COVID-19 reveal an activation of the immune system, with enhanced expression of pro-inflammatory cytokines such as TNFα and IL-6 and high levels of acute phase reactants such as ferritin and CRP (Wang et al., 2020). In addition, SARS-CoV infection induces low-level expression of the antiviral cytokines IFN-α/β (Sarzi-Puttini et al., 2020; Merad & Martin, 2020). In this context, serum of SARS patients with complications compared to individuals with no complications, displays high levels of IL-1, IL-6, IFN-γ, IL-12, and TGF-β and very low levels of the anti-inflammatory cytokine IL-10. Individuals with lethal SARS presented increased gene expression by IFN together with increased IFN-α and γ levels, compared to controls (healthy) and subjects with moderate disease symptoms (Mehta et al., 2020).

The uncontrolled and acute release of pro-inflammatory messengers could play an important role in severe COVID-19 infection. In this manner, significantly increased inflammatory cytokines participate in the induction and effector phases of all immune and inflammatory responses. The major participating cytokines include IL-1β, IL-6, induced protein 10 (IP10) and monocyte chemoattractant protein 1 (MCP-1) (Lee et al., 2014). However, the mechanisms involved have not been elucidated. Kinetics of virus clearance is believed to be the trigger of this process. In this context, IFN-I seems to be the cornerstone, since the SARS process avoids its recognition by receptors, antagonizing IFN-I responses (Liu, Zhou, & Yang, 2016). In the lung, the activation of the IFN-I signalling cascade induces the expression of IFN-stimulated genes, attracting macrophages, neutrophils, dendritic cells and NK-lymphocytes (Channappanavar et al., 2016; Liu, Zhou, & Yang, 2016). In addition, the severity of the disease in patients with SARS is correlated with elevated levels of IL-6 (Tanaka, Narazaki, & Kishimoto, 2016; Pathan et al., 2004; Zhang et al., 2004). The increase of IL-6

induces the expression of vascular endothelial growth factor (VEGF), decreasing myocardial contractility and increasing the permeability of blood vessels (Polidoro, Hagan, de Santis Santiago, & Schmidt, 2020).

ROLE OF EXERCISE ON RECOVERY FROM IMMUNOINFLAMMATION

The components of the innate and adaptive immunity overlap to guarantee a state of immunity against infection. Physical activity modulates transiently or permanently many elements of the immune system that play a role in defence reactions against infections such as COVID-19. These changes are mediated by the nervous and endocrine systems that play a key role in determining exercise induced immune changes (Nieman, 1997; Surkina et al., 1994).

Prolonged high intensity exercise reduces the number of peripheral blood type 1 T helper cells (Th1) and their ability to produce pro-inflammatory cytokines such as IFN-γ (Kang, Brown, & Hwang, 2018; Nieman, 1997). Training favours the production of anti-inflammatory cytokines (IL-4 and IL-10) by increasing the number of peripheral blood type 2 helper cells (Th2) and regulatory T cells. However, due to the cross-regulatory effect of IL-4 on the production of IFN-γ and the immunosuppressive effect of IL-10, the risk of upper respiratory symptoms seems to increase (Kang, Brown, & Hwang, 2018).

Altogether, physical activity can lead to modifications in cells of the immune system. High-intensity exercise may promote a decrease of parameters related to cellular immunity, increasing the risk of infectious diseases. However, moderate exercise may stimulate the same parameters and hence decrease the risk of infection (Krüger, Mooren, & Pilat, 2016).

Dysregulation of the adaptive immune response in severe patients with COVID-19 presents a marked decrease in $CD4^+$, $CD8^+$ and regulatory T cells, accelerating the production of pro-inflammatory cytokines (Hu et al., 2020; Qin et al., 2020). Regular exercise can allow senescent T cells to be replaced by new T cells capable of responding to new antigens and increasing the naive T cell repertoire. This fact improves symptoms and biomarkers associated with immune-senescence and the immunological response to infection (Shaw, Merien, Braakhuis, & Dulson, 2018).

The immunoregulatory effects of exercise are due to the activation of anti-inflammatory signalling pathways. In this context, cortisol and adrenaline elevations are instrumental, as are the release of myokines due to skeletal muscle contraction and increase of immunoregulatory leukocytes (Krüger, Mooren, & Pilat, 2016). In addition, exercise increases the antioxidant capacity and various compensatory mechanisms in tissues, such as increased compliance of the vascular system and increased anabolic signalling in the muscle. Physical activity can modulate cytokine production at the gene level of ligand and receptor proteins (Nieman & Nehlsen-Cannarella, 1992).

Light to moderate exercise leads to leucocytosis (neutrophils, eosinophils and basophils), lymphocytosis (T helper, T cytotoxic and B cells), increased number of NK and dendritic cells especially neutrophils and lymphocytes, during and immediately after exercise. This is due to the activation of the sympathetic nervous system and hypothalamic–pituitary axis that leads to increased concentration of plasma catecholamines and cortisol. This hormonal increase leads to de-margination of vascular and pulmonary pools, inducing the release of leukocytes from bone marrow to circulation. The return to resting levels occurs immediately after cessation of exercise due to a deactivation of the sympathetic nervous system and hypothalamic–pituitary axis. Meanwhile, heavy and severe exercise leads to a continuous increase in neutrophil/lymphocyte ratio as

a response to the magnitude of stress induced by exercise (Gleeson et al., 2002; Nieman, 1997; Surkina et al., 1994).

Altogether, adaptation to regular physical activity can affect immune function, especially cellular immunity. We certainly believe that applying appropriate exercise programs to people who have suffered from COVID-19 can improve their recovery and quality of life as well as the protection against infection at the long term (Figure 1).

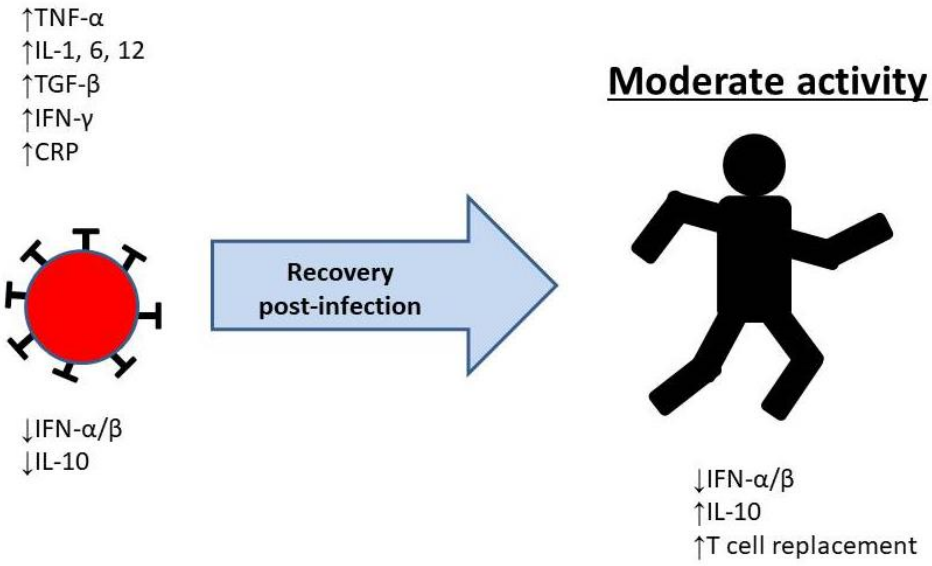

Figure 1. Cytokines alterations with the infection, effect and/or modulation through physical activity.

CONCLUSION

In conclusion, we think that physical activity and/or physical exercise or recreational sports in general can be a good alternative for the improvement of the immunological function of patients who have suffered from the coronavirus infection (Brawner et al., 2021). The anti-inflammatory potential of exercise can also improve the health status of people and promote an increase in the quality of life. Of course, the practice of exercise must be adequate in time and intensity, especially taking into account the patient's current situation and previous sports history.

AUTHOR CONTRIBUTIONS

Conceptualization, A.CM.; Methodology, A.C. and E.R.; Validation, A.CM., A.CG, D PV, JM S and E.R.; Writing-original draft preparation, A.C.; Writing-Review & Editing, A.C. and E.R.; Visualization, A.CM., A.CG, D PV, JM S and E.R.; Supervision, A.CM., A.CG, D PV, JM S and E.R.; Funding Acquisition, A.CM, and A.CG. All authors have read and agreed to the published version of the manuscript.

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