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Exercise and Immune System: A Comprehensive Review in the Era of COVID-19 Outbreak

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ABSTRACT

The COVID-19 pandemic has highlighted the essential role of a strong immune system in fighting infectious diseases. Understanding the relationship between exercise, physical activity, and immune function is crucial for recognizing how lifestyle factors can improve immune resilience. This review article aims to provide a comprehensive overview of the effects of exercise on the immune system during the COVID-19 pandemic. Additionally, it presents recommendations, guidelines, and considerations for engaging in physical activity during this period. Based on the literature review, there is some controversy regarding the effects of high-intensity exercise on individuals' immune systems, whereas moderate exercise is generally beneficial in almost all cases. Also, individuals experiencing severe COVID-19 symptoms or other acute illnesses should abstain from physical activity until recovery.

Keywords: Corona virus; COVID-19; Exercise; Immune system; Physical activity

INTRODUCTION

Our body is constantly attacked by pathogens such as viruses and bacteria; consequently, evolution has caused the emergence of a powerful and multilayered immune system to defend against pathogens.[1] The immune system is divided into two arms, innate immunity (non-specific) and adaptive immunity (specific), which interact to protect the body against pathogens.[2] However, viral infections, particularly respiratory tract infections (RTIs), remain among the most significant threats to human health.[3,4] According to the World Health Organization, more than four million deaths occur annually due to acute and chronic respiratory infectious diseases.[5] Viral infections, such as rhinovirus, influenza A and B, adenovirus and coronavirus cause respiratory diseases in humans. [6] Of these, SARS-CoV-2, also known as severe acute respiratory syndrome coronavirus 2, is responsible for the COVID-19 pandemic. It is a strain of coronavirus that causes respiratory illness in humans. The virus was first identified in Wuhan, China, in late 2019. As of the latest updates (April 13, 2024), about 705 million cases and approximately 7 million deaths have been recorded worldwide since the pandemic's start.[7] The data

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highlights the virus's widespread impact and the need for sustained efforts to control its spread.

Naturally, viral infections are associated with upper respiratory tract infections, with symptoms such as fever, headache and cough are commonly reported.[8,9] Coronavirus strongly affects the body's immune system and by creating a cytokine storm, impacts many tissues, especially the lung.[10]

SARS-CoV2 infection causes a decrease in the expression of angiotensin-converting enzyme (ACE2) in lung cells. [11] The decrease in ACE2 function following a viral infection disrupts the renin-angiotensin system, impacting blood pressure, electrolyte balance, and causing inflammation as well as increased vascular permeability in the airways.[12] Additionally, COVID-19 causes the release of inflammatory cytokines into the blood. The secretion of cytokines and chemokines attracts immune cells, especially monocytes and T lymphocytes, to the infection site, i.e., the respiratory tract. This leads to reduced gas exchange efficiency in the lungs due to cell swelling.[13] The recruitment of immune cells in the respiratory tracts during SARS-CoV-2 infection can lead to lymphopenia and an increased neutrophil-to-lymphocyte ratio, which has been observed in a significant proportion of COVID-19 patients.[14] Viruses can remain hidden in the cytoplasm of a cell, making them difficult to distinguish from foreign invaders. Cytoplasmic receptors can bind to viral molecules, such as various types of nucleic acids, indicating presence of infection.[15] Cells produce cytokines like interferons, tumor necrosis factor, and IL-2 to signal leukocytes about the viral presence. Following infection, innate immunity is activated first, followed by acquired immunity.[16]

The beneficial effects of exercise on different systems of the human body, such as the heart and blood vessels, the nervous system, the metabolic system, etc., have been observed in various studies. Moreover, it has been demonstrated that exercise performed with the appropriate intensity and duration can significantly improve immune system function in both patients and healthy people. Given these benefits, it can be argued that engaging in long-term physical activities may effectively help manage respiratory diseases, such as COVID-19, by boosting the body’s immune response and overall health.[17,18]

The COVID-19 pandemic has dramatically altered lifestyles, contributing to increased obesity and potentially weakened immune systems due to widespread lockdowns and reduced physical activity. This has prompted the hypothesis that regular exercise could mitigate these negative effects. However, robust evidence on the impact of exercise on the individual immune system during coronavirus outbreaks remains limited. This review article seeks to offer an extensive examination of how exercise impacts the immune system during the COVID-19 pandemic. Furthermore, it includes suggestions, guidelines, and factors that need to be considered while participating in physical activity during this time.

Literature Search

In this literature review, articles with the keywords of “coronavirus”, “COVID-19”, “exercise and coronavirus”, “physical activity” and the “body's immune system” were searched in English and Persian databases from Scopus, PubMed, Google, Google Scholar, and Embase. We also searched the keywords in the authoritative scientific conferences of Maghiran and Noor. The search was conducted without time restrictions. Articles published between 2012 and 2024 were prioritized for further analysis.

To avoid bias, extraction and evaluation of the quality of articles were done by two independent researchers. If the articles were not accepted, the reasons for their rejection were mentioned. In cases where there was a controversy between the two researchers, the review was done by a third person. The quality of the articles was assessed using the Cochrane Collaboration’s risk of bias tool, evaluating aspects such as selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data).

Pathogenesis and Mechanisms of SARS-CoV-2 Infection

The pathogenesis of SARS-CoV-2 infection is a complex multi-stage process involving viral entry, replication, immune response evasion, and host cell damage, ultimately leading to a spectrum of clinical manifestations that range from asymptomatic infection to severe respiratory distress and death. The mechanisms involved are still being actively researched, but current understanding points to several key players.

Viral Entry and Replication

SARS-CoV-2, like other coronaviruses, utilizes its spike (S) protein to gain entry into host cells. The S protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor, primarily expressed on type II alveolar epithelial cells in the lungs, but it is also found in other tissues, including the heart, kidneys, and intestines. Following binding, the S protein is cleaved by host proteases, such as TMPRSS2, facilitating fusion of the viral and host cell membranes and subsequent viral entry.[19,20] Once inside, the virus releases its RNA genome, which is translated into viral proteins. The viral RNA replicates in the cytoplasm using the host cell's machinery, producing new viral particles that are released to infect other cells.

Immune Response Evasion

SARS-CoV-2 has evolved several mechanisms to evade the host's immune response. These mechanisms include: i) Interference with interferon signaling:(i)=It has been demonstrated that SARS-CoV-2 proteins, such as the non-structural protein 6 (NSP6), can inhibit the production and function of type I interferons (IFNs), which are crucial early antiviral cytokines.[21] This impairment of the interferon response delays the activation of the innate immunity. (ii) Immune cell dysregulation: the virus can directly infect immune cells, such as T lymphocytes and macrophages, leading to their dysfunction or depletion.[22] This contributes to the impaired adaptive immune response observed in severe COVID-19 cases. (iii) Antibody-dependent enhancement (ADE): while not definitively proven for SARS-CoV-2, ADE is a concern. Pre-existing antibodies to other coronaviruses could potentially enhance viral entry into cells, exacerbating infection.[23]

Host Cell Damage and Pathological Consequences

The primary pathological consequence of SARS-CoV-2 infection is damage to the respiratory system. Viral replication in the lungs causes cell death (cytopathic effect) and inflammation, which in turn leads to the following consequences: (i) Pneumonia: The accumulation of fluid and inflammatory cells in the alveoli impairs gas exchange, resulting in hypoxia.[24] (ii) Acute respiratory distress syndrome (ARDS): Severe cases can progress to ARDS, characterized by widespread lung inflammation, fluid buildup, and severe respiratory failure.[25] (iii) Cytokine storm: An uncontrolled release of inflammatory cytokines, often occurring in severe cases, can contribute to organ damage and multi-organ failure.[26] This can be caused by both direct viral effects and an excessive immune response.

Beyond respiratory complications, SARS-CoV-2 can affect other organs, including the heart (myocarditis), kidneys (acute kidney injury), and nervous system (encephalitis, stroke). These multi-organ complications likely result from a combination of direct viral infection and systemic inflammation. Considering that one of the most obvious complications of COVID-19 is the increase in inflammation and inflammatory indicators such as C-reactive protein and the number of white blood cells. It has been shown that, in general, different types of exercise training significantly reduce inflammation and inflammatory indicators.[27,28]

The Effect of Exercise on the Immune System

Investigating the impact of physical activity on the immune system is a relatively new area of research within sports science, referred to as “exercise immunology”.[29] Research has shown that physical activity significantly impacts the functioning of the immune system.[30] Engaging in regular moderate to intense physical activity, in line with scientific guidelines, is associated with lower levels of chronic inflammation and enhanced immune responses, especially in relation to vaccinations.[31] Moreover, improved physical and cardiorespiratory fitness contributes to better immune indicators in individuals with chronic health conditions such as cancer, AIDS, cardiovascular diseases, obesity, and mental health disorders.[32]

The COVID-19 pandemic and the connection of the disease with the immune and respiratory systems have raised many questions about whether and how physical activity can support us against viral contamination, infections and death. This concern is particularly relevant when the access of many of us to sports facilities limited and physical activity is minimized, due to lockdowns. It has been indicated that social distancing, staying at home and being hospitalized have a negative effect on our immune system. It is known that inactivity increases the risk of type 2 diabetes,[33] cardiovascular diseases,[34] cancer[35] and depression.[36]

Glucocorticoids such as cortisol increase during periods of hospitalization, stay at home, and inactivity prevent many functions of our immune system and

weakens the immune system. When we experience pressure and stress, the ability of T cells to multiply in response to infectious agents is significantly reduced, as is the capacity of specific immune cells, such as lymphocytes and natural killer cells, to recognize and destroy cells that are infected with viruses.[37] Therefore, immune cells need to maintain their ability to be re-emitted to prevent viruses and other pathogens from invading vulnerable areas of the body, such as the upper respiratory tract and lungs.[38,39] This process also reduces the effects of the virus and acceleration of treatment in case of infection becomes important.

Every exercise session, especially dynamic cardiorespiratory activity, mobilizes billions of immune cells, particularly the types of cells capable of performing important functions such as identifying and destroying virus-infected cells, prompting them to move quickly.[40] The vascular margins of the spleen and bone marrow enter the blood, and then these cells are transferred to the tissues and secondary lymphatic organs of the lungs and intestine. In these organs, an enhancement of the immune defense system may be required. Immune cells stimulated by exercise are ready to deal with external factors. The repeated and continuous movement of these cells between the blood and tissues increases the immune support for the host tissue and theoretically makes us resistant to infection, preparing our body to deal with any infectious agent invading the body.[41]

Investigations have also shown that exercise causes the release of various immune factors, especially muscle cytokines such as IL-15, IL-65 and IL-7, which help maintain immunity and increasing the body's resistance to infection.[42] In addition, regular and moderate-intensity exercise increases the immune response to vaccines and decreases the number of worn-out or senescent T cells.[43] It also increases proliferation of T cells, decreases levels of circulating inflammatory cytokines, increases neutrophil phagocytic activity, and increases L-2 production.[44]

Epidemiological evidence suggests a negative relationship between exercise and the severity and prevalence of upper respiratory tract infections (URTIs). The magnitude of the reduction in days with URTI symptoms following moderate-intensity activity is about 40-50%, which exceeds the levels reported with most drugs and supplements. A study involving 1,002 athletes over a 12-week period found that participants who exercised five or more days a week experienced 43 percent fewer days with URTI symptoms compared to those who exercised only one day a week. Additionally, athletes with higher cardiovascular fitness reported 46 percent fewer days with URTI symptoms compared to those with poorer fitness levels.[45]

Evidence regarding soccer players with mild symptoms of COVID-19 showed they were able to perform moderate-intensity activity while infected and receiving treatment. Stress hormones, such as cortisol, suppress immune function and are indicate of intense activity. However, during moderate-intensity exercise, these hormones do not reach high levels, which helps reduce inflammation.[46] This effect of exercise has great clinical value, especially for obese people and patients who are susceptible to coronavirus infection.[36]

Noteworthy, the acute response of the immune system to exercise depends on the intensity and duration of the activity. In this regard, the intensity threshold of 60% of oxygen consumption or reserve heart rate, and the 60-minute duration threshold distinguish between moderate and intense exercise. Research has shown that the response of the immune system to moderate and severe activity is different. In general, the release of immune cells into the circulation, which is known as leukocytosis, is the first obvious response of the immune system to acute activity. There isa resting state between circulating white blood cells and peripheral cells attached to the vascular wall. During exercise, the increase in shear pressure due to the increase in blood flow and decrease in the expression of adhesive molecules causes leukocytes to be released into the blood circulation; however, the magnitude of leukocytosis depends on the intensity and duration of the activity.[47]

The Effect of Exercise on Antioxidant and Anti-inflammatory Defense System

According to the reviewed studies, physical activity can enhance the human body's resistance to COVID-19 not only by modulating the immune responses but also by improving both antioxidant defense and anti-inflammatory responses.[48]

Antioxidant System

Reactive oxygen radicals (ROS) and reactive nitrogen species (RNS) are double-edged molecules. On the one hand, they act as important inflammatory factors in supporting the immune system in clearing pathogens and repairing damaged muscle tissue, on the other hand,

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they can aggravate chronic inflammation. Oxy-inflammation is the term used for the interaction between oxidative stress and inflammation. In this regard, it has been indicated that moderate-intensity exercise can directly strengthen antioxidant defense and anti-inflammatory responses, and indirectly improve problems related to anxiety and insulin sensitivity.[48]Based on the studies, exercise training strengthens the antioxidant defense through increase in catalase, superoxide dismutase, and glutathione peroxidase enzymes.[49]

Anti-inflammatory System

Studies have shown that the concentration of inflammatory markers, such as IL-6, increases dramatically in response to exercise training.[50] Interleukin 6 is one of the important interleukins of the body, which is secreted by muscle cells and is involved in inflammatory responses.[51] It has been determined that as a result of endurance training, interleukin 6 increases anti-inflammatory factors such as IL-10 and IL-1ra.[52] Additionally, IL-6 supports the tissue repair process.[53] However, depending on the intensity of the exercise, every exercise session is associated with a transient increase in white blood cells, proteins, and inflammatory cytokines, but the resting levels of these inflammatory markers are lower in fit and active people than in inactive and overweight people. Amani et al. reported that the levels of IL-CRP and IL-18 in obese people are higher than those of individuals with normal weight. Moreover, the levels of these markers are higher in sedentary lean and obese people than in active people.[48] On the other hand, an investigation showed that six weeks of continuous and intermittent aerobic exercise decreased IL-18 and CRP inflammatory markers in obese soldiers.[54] It was also reported that cardiovascular fitness has an inverse relationship with inflammatory markers CRP and IL-18.[55]

Moreover, exercise training down-regulates the expression of toll-like receptor-4, which is an important membrane receptor that is activated by many ligands, including oxidized low-density lipoproteins. This receptor is involved in the development of insulin resistance, type 2 diabetes and heart diseases.[49]

Exercise Programs to Promote Health during COVID-19 in Quarantine

Numerous studies have explored the implications of COVID-19 on various facets of human life. Following the onset of the second wave of the coronavirus pandemic, prolonged lockdown measures and the necessity of remaining at home adversely impacted individuals' physical activity levels and diminished their overall well-being, consequently exacerbating their health conditions.[56] Maintaining physical activity at home is strongly recommended for staying healthy and boosting immune system function, especially in difficult circumstances. Exercising at home with any available equipment has been shown to be safe, simple, and effective for preventing the transmission of the coronavirus while also promoting fitness and mental well-being.[45,49,57-59]

To maintain health and physical fitness, the best course of action is to find creative ways to exercise while considering social destinacing and health issues. During the COVID-19 outbreak, to reduce the spread of the virus, everyone attempting to maintain social distancing and stay at home. This issue, along with the closure of gyms, caused a decrease in people's physical mobility, which resulted in obesity, decreased muscle mass, increased stress, and decreased physical performance.

Regular physical activity and an active lifestyle can improve the function of different tissues, protect the body from various diseases and ultimately reduce visits to hospitals. Furthermore, it has been shown that regular exercise improves the function of the body's immune system, which in the case of infection with COVID-19 is effective in withstanding the complications of the disease, the body's resistance to the virus, and prompting faster recovery for the individual.[60]

To remain active and healthy while staying at home, the following instructions are recommended. Staying at home and the lack of space and facilities should not deter people from engaging in physical activities. Even if they have a small space, they should try to design and implement a special exercise program within that space. Considering the available space and individual sporting interests, individuals may utilize simple and cost-effective sports equipment, such as ropes, small yoga mats, and lightweight dumbbells, to initiate their exercise routines. Moreover, people over 65 years of age and those with chronic diseases or weekness immune systems should avoid exercising outdoors and in public places, instead gaining all the benefits of exercising by doing various rhythmic exercises at home. Additionally, intermittent aerobic activities and resistance exercises, including body weight and weighted exercises, should

be designed and implemented according to the individual's physical condition.[61]

Exercise at Home; Instructions and Considerations

The type of physical activity performed during pandemics is important. It has been found that high-intensity resistance training can cause disturbances in the body's immune system. However, moderate and low-intensity exercise is generally more effective in strengthening the immune system.[62] In this regard, Molanouri_Shamsi et al stated that by performing low-intensity exercise, can lead to a decrease in some inflammatory cytokines, such as IL-6 and IL-18, following resistance training.[1] It seems that regular periods of short-term training (up to 45 minutes) with moderate intensity enhance the immune system, while frequent periods of long-term exercise with high intensity (2 hours) can suppress it [34,36]. Performing high-load activities can increase the risk of respiratory system infections and reduce the immune system function.[63]Of course, it should be noted that trained individuals are less susceptible to these consequences due to the adaptation resulting from regular physical activity.[64] In contrast, those who do not engage in regular training may have stronger inflammatory responses, which can suppress the immune system in the case of high-intensity exercise.[65]

Aerobic exercise includes activities that are moderate in intensity and do not put much pressure on the body. This type of activity can be performed on treadmills, stationary bikes, and through rowing movements. A complete analysis of the available evidence suggests moderate-intensity exercise may improve pathological outcomes. It can also enhance the function of the immune system by inducing the release of stress hormones in viral respiratory infections such as those caused by the coronavirus.[66]

Stretching exercises and yoga at home, along with imitating authentic training videos, can be a very suitable solution for those who are used to exercising and for professional athletes. Exercises at home can be limiting, but performing plyometric or TRX exercises can effectively help maintain the fitness level of athletes. Additionally, plyometric exercises are recommended for the elderly.[67] They can also use burpee squats, jumping squats, jumping rope and jogging for home exercises. These exercises are a type of exercise with body weight that can be done with moderate intensity.

It should be considered that elderly people are more susceptible to infections or autoimmune disorders than younger individuals. It has been found that the death rate from influenza is higher in elderly people compared to adults or young people.[68] Therefore, performing high-intensity exercise can be a very dangerous factor for them. For this reason, physical activities such as walking or cycling with moderate and low intensity are more beneficial for these individuals. Also, compared to adults and middle-aged people, children experience disorders in their immune system faster as a result of physical activity, but their immune system recovers faster than that of adults.[69,70] That is why recreational exercise with moderate to low intensity is recommended for them.[71,72]

On the other hand, physical activity is prohibited for those who are suspected of having contracted coronavirus. Also, individuals with respiratory diseases or colds should refrain from exercising until their health condition improves. In this regard, it has been reported that people who have respiratory infections usually need three weeks to recover, and finally, after this period, if all the symptoms have resolved, they are allowed to engage in low to moderate exercise.[73] Engaging in physical activities during quarantine should be approached with the same level of consideration as medical prescriptions, tailored to the needs of different individuals. If a person undertakes intense exercise without proper guidance from a sports specialist, there is a heightened risk of impairing immune function and increasing susceptibility to the coronavirus.[74]

Although there is some controversy regarding the effects of high-intensity exercise on individuals, it is clear that intense resistance training can temporarily disrupt the immune system, which may increase the risk of illness. In contrast, moderate exercise is generally beneficial in almost all cases.

Table 1 presents a comparison of various studies on the effects of different types of exercise on individual immune system function.

Table 1. Studies conducted on the general impacts of exercise on the immune system function.

Type of exercise	Activity intensity	Effect on the immune system	Reference
Resistance	45, 75 and 95% of 1RM	Increase of IL-6 in intensity of 75 and 95%; No change in 1RM at 45% intensity	75
Resistance and aerobic exercises	High intensity and Moderate intensity	Enhancing the immune system	76
Aerobic exercises	High intensity	Disrupted the immune system	77
Aerobic exercises	Moderate intensity	Enhancing the immune system	78
Aerobic exercises	High intensity and Moderate intensity	High intensity temporarily decreased markers of immune function; moderate intensity improved the markers' levels	79
Aerobic exercises	Moderate intensity	Enhancing the immune system	80
Resistance, aerobic, anaerobic and endurance	Moderate intensity and high intensity	Moderate intensity enhanced the level of the immune system; High intensity disrupted the body's immune system	81
Anaerobic	High intensity	Dysfunctioned the immune system	82
Aerobic	low intensity and Moderate intensity	No effect on the body's immune system in low intensity; increased level of the body's immune system in moderate intensity	83
Anaerobic	High intensity	Enhancing the immune system	84
Physical activities	High intensity, low intensity, and moderate intensity	High intensity enhances the immune system in some cases; Moderate intensity remarkably enhances the system; Low intensity did not change or slightly increase the level of the body's immune system	85
Anaerobic	High intensity	Enhancing the immune system	86

Table 1. Continued...

Type of exercise	Activity intensity	Effect on the immune system	Reference
Different types of exercises	High intensity, low intensity, and moderate intensity	In the case of severe immune system disorders, intense exercise is more dangerous in the elderly. Low and moderate intensity can be beneficial.	87
Anaerobic	High intensity	Decreasing the function of the body's immune system and increasing tumor necrosis factor Alpha (TNF-a)	88
Anaerobic	High intensity	Long-term regular exercise improves the immune system	89
Aerobic	Moderate intensity	Enhancing the immune system	90
Anaerobic and aerobic	High intensity	Reducing the level of the body's immune system in high-intensity	91
Aerobic	High intensity	Enhancing the immune system	92
Anaerobic	High intensity	Disrupting the body's immune system	93
Aerobic	Moderate intensity	Enhancing the immune system	94
Anaerobic	High intensity	Suppressing the body's immune system	95
Aerobic	Moderate intensity	Enhancing the immune system	96

Exercise Limitations for Infected People

Notably, the responses of individuals infected with the coronavirus to physical activity have not been thoroughly examined. Additionally, the implications of various physical activities during the latent period of infection and subsequent recovery have not received adequate investigation. Having said that, there is an argument that at the time of contracting the disease of COVID-19, due to the immunological disorders and neuromuscular, metabolic, and cardiovascular effects, etc., exercise can lead to weakness in the immune system and slow down the recovery process. Similarly, in the case of other viral diseases such as influenza, it is emphasized that physical activities should be stopped during the illness. Furthermore, it is recommended that athletes who have recovered from the coronavirus disease do not engage in intense exercise activities for seven days after the disappearance of symptoms.[97]

CONCLUSION

The relatively nascent field of exercise immunology has gained critical importance in light of the COVID-19 pandemic. The emergence of COVID-19 underscores the need for continued and expanded research into the complex interplay between exercise, immunity, and viral infections. Given the likelihood of future viral outbreaks, promoting regular moderate-intensity physical activity throughout the lifespan represents a crucial public health strategy. A comprehensive literature review indicates that while moderate-intensity exercise (30-45 minutes) has demonstrated benefits for immune function, high-intensity exercise may be immunosuppressive. Therefore, a balanced approach emphasizing appropriate exercise intensity and duration is warranted. Furthermore, individuals experiencing severe COVID-19 symptoms or other acute illnesses should abstain from physical activity until recovery. Further research is crucial to optimize exercise recommendations for bolstering immunity and mitigating the impact of future pandemics.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

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