Exercise is the Most Important Medicine for COVID-19

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Abstract

COVID-19 infection and long COVID affect multiple organ systems, including the respiratory, cardiovascular, renal, digestive, neuroendocrine, musculoskeletal systems, and sensory organs. Exerkines, released during exercise, have a potent crosstalk effect between multiple body systems. This review describes the evidence of how exerkines can mitigate the effects of COVID-19 in each organ system that the virus affects. The evidence presented in the review suggests that exercise should be considered a first-line strategy in the prevention and treatment of COVID-19 infection and long COVID disease.

Introduction

The worldwide presence of COVID-19 infections continues with sporadic spikes in infection numbers (1). The virus affects multiple organ systems, including the respiratory, cardiovascular, renal, digestive, neuroendocrine, musculoskeletal systems, and sensory organs (2). In addition, long COVID (postacute sequelae of COVID-19 [PASC]) has been identified as a post COVID-19 infection condition that affects at least 65 million individuals worldwide (3). This chronic disease impacts heart, lung, pancreas, kidney, spleen, liver, blood vessels, and the neurological, gastrointestinal, immune, and reproductive systems with a wide variety of pathology (3). Furthermore, COVID-19 infection and long COVID increases the risk of medical conditions, including cardiac arrest, heart failure, stroke, pulmonary embolism, diabetes, myalgic encephalomyelitis, and dysautonomia with breakthrough afflictions of coagulation, hematological, pulmonary, and neurological conditions (3). There are currently no validated effective treatments for long COVID (3).

Consistently meeting physical activity guidelines has been associated with reduced risk of severe COVID-19 infection outcomes, *i.e.*, hospitalization (22% to 42% reduction), ICU admission (34% to 38% reduction), deterioration, and death (43% to 83% reduction) (4–7), across demographic and clinical characteristics (8). Furthermore, those engaged in regular physical activity have an 11% to 22% lower risk of infection (6,9–11). The greatest benefit is provided by achieving at least 500 metabolic equivalent of task (MET)-min per week of physical activity, which is equivalent to 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity per week (6). Studies also have found that cardiorespiratory fitness (CRF) is a predictor of COVID-19 disease progression and mortality (5,12,13).

Exerkines are signaling moieties that are released during exercise and affect multiple organ systems via endocrine, paracrine, and/or autocrine pathways (14). They are released from skeletal muscle (myokines), brown adipose tissue (baptokines), white adipose tissue (adipokines), neurons (neurokines), heart (cardiokines), and liver (hepatokines). This review explores how exerkines, via molecular signals and pathways, may ameliorate and/or attenuate the effects of COVID-19 and long COVID on organ systems. This will highlight how and why exercise is the most important medicine and an effective treatment for COVID-19, and especially for long COVID.

Organ Systems Affected by COVID-19/Long COVID and the Effect of Exercise

The Cardiovascular System, COVID-19, Long COVID, and the Effect of Exercise

Dysregulation of the renin-angiotensin-aldosterone system (RAAS) has been a characteristic feature in COVID-19 (2). This system is involved in the maintenance of electrolyte balance, vascular resistance, and thus maintenance of systemic blood pressure and cardiovascular health (15). The dysregulation may cause increased incidences of thromboembolism and hypertensive episodes. The inflammation caused in the coronary arteries during COVID-19 infection may speed up the

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1537-890X/2208/284–289
Current Sports Medicine Reports

formation of plaques and thus cause ischemic changes in the heart (16). Electrolyte imbalance induced by the RAAS dysregulation also may lead to heart ailments seen with COVID-19 (*e.g.*, hypokalemia can cause hyperpolarization of the cardiac myocytes leading to arrhythmia) (17). The hypokalemia in COVID-19 may also be caused by direct viral-mediated myocardial injury leading to decreased cardiac output (18). In long COVID, the immune-mediated inflammatory response is associated with endothelial dysfunction and thus increased risk of deep vein thrombosis, pulmonary embolism, and bleeding events (19). A reduction in vascular density also has been found in patients with long COVID (20).

It is well established that exercise reduces the risk of cardiometabolic disease and mortality (21,22). The beneficial effects of exercise on cardiovascular risk factors alone however, do not account for the effects of exercise on cardiometabolic health (14). The effect of exerkines on the cardiovascular system could further explain how exercise is a medicine for this body system. The exerkines, angiopoietin 1(myokine), fractalkine (myokine); 12,13 dihydroxy-9Z-octadecenoic acid (12,13 diHOME) (baptokine), fibroblast growth factor 21 (FGF21) (hepatokine and adipokine), IL-6 (myokine), IL-8 (myokine), musclin (myokine and neurokine), myonectin (myokine), nitric oxide, and vascular endothelial growth factor (VEGF) (myokines), enhance vascularization, angiogenesis, endothelial function, and myocardial energy utilization, thus mitigating the effects of COVID-19 on the cardiovascular system (14). Exercise has an anti-inflammatory effect (as is described in section 5), which also may oppose the systemic inflammation that occurs with COVID-19 and injures heart tissue.

In addition, the release of the muscle-derived mesenchymal stem cells during exercise has been purported to repair cardiomyocytes (23). This mechanism may be important when heart tissue has been damaged with COVID-19 infection or long COVID.

The Respiratory System, COVID-19, and the Effect of Exercise

COVID-19 can result in chronic health issues, such as impaired lung function, reduced exercise performance, and diminished quality of life. Pulmonary rehabilitation (PR) programs, including telerehabilitation programs, can be safe and effective in improving respiratory symptoms and exercise capacity in patients with COVID-19, both during the acute phase and in the postacute phase. Studies on the longer-term implications of COVID-19 have emerged, and data suggest that patients may experience prolonged symptom profiles, with recovery only 29% at 5 months posthospitalization (24,25). At 6 months, impaired reduced pulmonary diffusing capacity persists in 30% to 55% of patients, with evidence of evolving fibrosis (26). Studies have shown that PR can improve outcomes in both acute and chronic COVID-19 patients, with significant improvements in dyspnea, exercise capacity, and lung function. A review highlighted the potential benefits of PR for patients with preexisting pulmonary conditions and are recovering from COVID-19 (27). Pulmonary rehabilitation should be considered as a key component of the management of COVID-19-related respiratory symptoms. Energy conservation techniques may play a pragmatic role in PR in mild to moderately severe cases to counter post-COVID-19 fatigue (27).

While the COVID-19 virus primarily enters the body through the upper respiratory tract, it is still not completely clear which cells and tissues are initially targeted by the virus. However, there is evidence to suggest that the virus can infect and replicate in cells throughout the respiratory tract, including in the upper and lower airways.

The mucosal immune system in the upper respiratory tract plays an important role in defending against viral infections like COVID-19. Increasing aerobic capacity can enhance immunity through immune cells and immunoglobulins advancement and regulating CRP levels (28). It could act as an antibiotic and antioxidant, restoring normal lung tissue elasticity and strength (28).

Exercise has been shown to increase the levels and function of immune cells like T-lymphocytes, neutrophils, macrophages, and monocytes, as well as increase the levels of immunoglobulins like IgA, which play a vital role in fighting lung infections (29,30). Secretory IgA, in particular, is an antibody that helps to neutralize viruses and prevent them from entering cells. Further, exercise can potentially enhance the production of secretory IgA in the respiratory tract (31). Exercise duration may play a protective role in the respiratory tract through discriminatory change in mucosal immunity through the cellularity, antiviral activity, and gene expression (32).

A study that assessed whether exercise-induced myokines would mitigate the COVID-19 infectivity of the bronchial epithelium through angiotensin-converting enzyme 2 -ACE2 intonation demonstrated evidence suggesting exercise has a protective effect against COVID-19 (33).

The role of extracellular superoxide dismutase (EcSOD) (myokine) in protecting against oxidative stress-related diseases such as acute lung injury/acute respiratory distress syndrome (ALI/ARDS) has been demonstrated (34). The dysregulation and recruitment of activated neutrophils in the lung microvasculature, interstitial, and alveolar space is a key step in ALI/ARDS, leading to increased reactive oxygen species (ROS) and proinflammatory mediators. EcSOD plays a critical role in the first line of defense against superoxide generation in the lung tissue. Studies have shown that reduced levels of EcSOD are associated with disease development, while enhanced EcSOD expression is protective against ROS and oxidative damage in various pathological processes. Exercise-induced EcSOD has been suggested as an effective therapeutic intervention for prevention and treatment of numerous oxidative stress-related diseases, including ALI/ARDS (34). The evidence supports that exercise enhances immunity, antioxidative effects, function, and overall benefits for the respiratory system in COVID-19.

The Neuroendocrine, Nervous System, COVID-19, Long COVID, and the Effect of Exercise

The neurological consequences of COVID-19 infection include mild symptoms like headache, nausea, vomiting, dizziness, loss of senses (smell and taste), and severe symptoms like ataxia, convulsions, altered consciousness, ischemic or hemorrhagic stroke, meningitis, encephalitis, rarely Guillain-Barré syndrome variants, and new onset of psychotic symptoms (2). Autopsy studies in COVID-19 deceased also have shown widespread brain lesions (2). The impact of long COVID on the neurological system includes tinnitus, hearing loss, vertigo, dysautonomia, chronic fatigue syndrome, neuroinflammation, reduced cerebral blood flow, and small fiber neuropathy (3). It is suggested that neurological symptoms arise due to the direct neuropathic effect of the virus or the indirect effect of cytokine-induced neuroinflammation (2).

The exerkines apelin (adipokine and myokine), cathepsin B (myokine), FGF21 (hepatokine and adipokine), irisin (myokine), IL-6 (myokine), lactate (myokine), adiponectin (adipokine), and GPLD1 (myokine) released during an exercise session increase production of brain-derived neurotropic factor that enhances neurogenesis, improve cognition and mood and increases synaptic plasticity (14). These exerkines may thus be part of the medicine needed for COVID-19 as they oppose the effects of the virus. Furthermore, IL-6 increases both basal glucose uptake and glucose transporter (GLUT4) translocation. In addition, IL-6 increases insulin-stimulated glucose uptake (23). Thus, this exerkine may mitigate the detrimental effects of COVID-19 on glycemic control.

A recent review on neuroendocrine symptoms of COVID-19 hypothesized that exercise attenuates β-cell dysfunction and the long-term neuroendocrine effects of COVID-19 by moderating the inflammatory response, supporting brain homeostasis, and promoting insulin sensitivity (35). Long COVID also has been associated with increased stress levels, anxiety, and depression (35). Regular exercise has been shown to alleviate stress and anxiety (36) and has been associated with lower odds of incident depression or an increase in subclinical symptoms (37). The evidence indicates that exercise is an important medicine for treating these symptoms of long COVID. In summary, exercise remains a type of polypill that helps to ameliorate the harmful effects of COVID-19 on the neuroendocrine system (23).

Organ Damage, COVID-19, and the Effect of Exercise

Multiorgan damage (to heart, lungs, liver, kidneys, pancreas, and spleen) has been associated with COVID-19 (3). Mesenchymal stem cells released during exercise can repair damaged myocardium and skeletal muscle tissue (23). In addition, circulating angiogenic cells released during exercise from bone marrow mediate endothelial repair and angiogenesis. These mechanisms may help repair the tissue damage that the COVID-19 virus produces. Exercise also has been shown to generate new cardiomyocytes, which would be beneficial in the healing of damaged myocardium (38).

It also is important for damaged/nonfunctioning cells/organelles (as can occur with COVID-19 infection) to be removed so that body systems may function optimally. Exercise may help this process since autophagy occurs with every exercise session, within the heart (39), pancreas, liver, adipose tissue, brain, and skeletal muscle (23). Noteworthy for COVID-19 rehabilitation is that research has identified that mitochondria are damaged with COVID-19 infection and are involved in symptoms (such as fatigue) of long COVID (40). Exercise has been found to "clean-up" nonfunctioning, damaged mitochondria, and thus ensure that energy production is optimized and skeletal muscle health is maintained (41).

In addition, CD8+ and CD4+ T cells infiltrate injured skeletal muscle tissue. Regulatory T cells migrate toward IL-33 and aid in muscle regeneration by producing factors, such as amphiregulin, that promote muscle stem cell proliferation (42).

Immunity, COVID-19, Long COVID Response, and the Role of Exercise, Including Exercise as an Immune Adjuvant

A subthreshold and delayed protective T cell-mediated adaptive immune response in symptomatic patients is pronounced in patients with severe COVID-19 in the initial period (2).

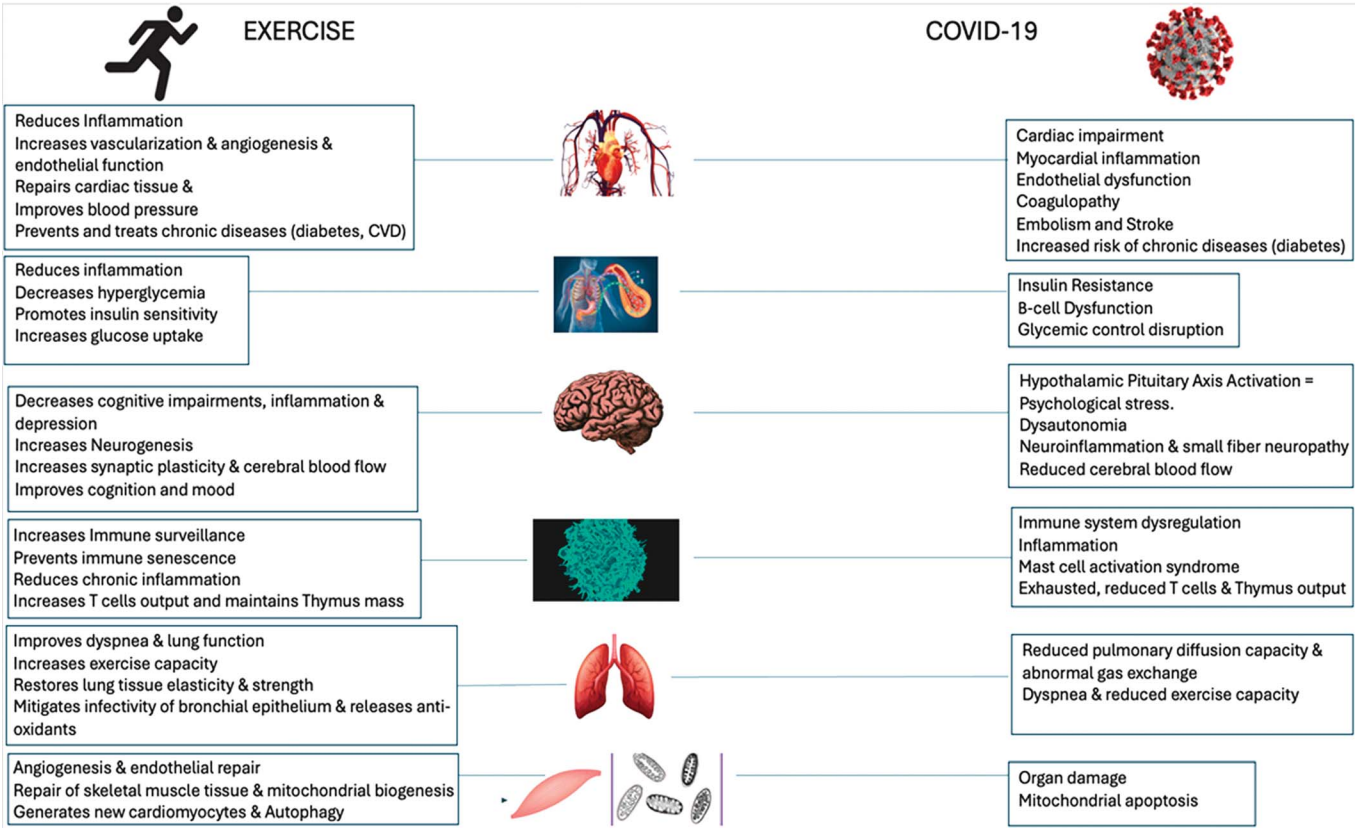

Figure: COVID-19 infection versus exercise effects.

Immune dysregulation has been reported in individuals with long COVID. This involved exhausted T cells, reduced or absent $CD4^+$ and $CD8^+$ T-cell numbers (43) and a lack of naïve T and B cells (44,45). In addition, T-cell senescence becomes an issue in the elderly, and this is a population that is at risk of severe outcomes with COVID-19 infection. With increasing age, decreased numbers of new, naïve T cells are released from the thymus, and the ability of the adaptive immune system to respond to novel pathogens (like COVID-19) declines (42).

Exercise has been shown to release the myokines IL-6, IL-7, and IL-15 that specifically increase recent thymic emigrant T-cell output from the Thymus, and promote the survival and increase the proliferation of naïve T cells (46,47). This may protect T cells from the effects of COVID-19 infection and outputs. In addition, T cells and B cells are mobilized into the blood circulation by the increase in catecholamines during exercise and at exercise cessation the myokines are proposed to affect immune cell redistribution and activation (48). The immune dysregulation and lack of response that occurs with long COVID infection, may thus be attenuated by effects of exercise on immunity.

Furthermore, the frequent redistribution of natural killer (NK) cells and viral-specific T (VST) cells with each exercise bout increases immune surveillance and reduces the accumulation of senescent/exhausted T cells, while maintaining the number and diversity of naïve T cells. In turn, this reduces infection risk, increases the manufacture of therapeutic VST cells specific to latent and nonlatent viruses and increases protection provided from vaccines (46,49).

Lastly, aerobic exercise has been shown to preferentially mobilize lymphocytes with effector functions (*i.e.*, NK cells, CD8+, CD4+ T cells, and γδ T cells) (50). As previously mentioned, these are the same T cells that have a reduced or absent response during COVID-19 infection. Could exercise be a medicine for counteracting this negative effect of COVID-19?

Initial inflammation during COVID-19 infection causes the release of pro-inflammatory cytokines (IL-6, TNF-a) (2,51) and recruitment of peripheral immune cells. This induces more tissue injury and in severe cases, leads to cytokine storm that consequently kills T cells and delayed/or suppressed B cell-mediated humoral response (2). Exercise can reduce this inflammation via the action of IL-6, which when released as a myokine during exercise, has anti-inflammatory actions via the induction of IL-10 and IL-1RA by monocyte/macrophages (46). IL-6 released during exercise also inhibits the action of pro-inflammatory cytokines such as CRP, TNF-alpha and serum amyloid A (SAA), even in the elderly (42). Exercise may help reduce chronic inflammation (that occurs with long COVID), as a result of IL-6 (myokine) enhancing lipolysis and fat oxidation (reducing visceral fat), via a mechanism that involves AMPK activation (52). Reducing adiposity may be beneficial to attenuating the effects of COVID-19, as circulating adipokine levels have been associated with COVID-19 hospitalization, but not mortality (53). Although vigorous exercise may induce short-term inflammatory effects, the overall effect of a moderate intensity exercise bout, is anti-inflammatory (42). Lastly, a review found that increasing the aerobic capacity (CRF) could produce improvements in the function of immune and respiratory systems, particularly specific to COVID-19 infections (28). Therefore, exercise is an important medicine for the immune system during COVID-19 and for long COVID as it maintains/improves immune function, prevents immune senescence, reduces inflammation, mobilizes, and redistributes virus-specific T cells, and reduces stress.

As a species, our origins as hunter-gatherers necessitated covering large distances using multiple muscle groups daily in the pursuit of food and water to survive (54). Challenging natural environments, the accompanying physical demands and resultant natural selection forged our modern-day genome (55). Being physically active was necessary for survival. In a modern-day context, the benefits of regular physical activity in promoting cardiovascular health (and with it survival) has been widespread for some time (56,57). The effects of physical activity on the immune system have more recently been well described (58) and brought to the forefront by recent research related to COVID-19 outcomes (4,7,9) and vaccine efficacy (59).

In a recent systematic review and meta-analysis, Chastin et al. (60) quantified the reduction in community-acquired infections associated with habitual physical activity as 31% with a 37% reduction in mortality. Physical activity resulted in increased $CD4^+$ counts, greater concentrations of salivary IgA and decreased neutrophil counts compared with controls. Physical activity also was associated with higher antibody responses to vaccination (60).

Interest in the potential impact of physical activity on vaccine effectiveness also was piqued by the COVID-19 epidemic as it became apparent that vaccines were a powerful tool in lowering morbidity and mortality (61). Previous cross-sectional studies and randomized controlled trials have demonstrated increased postvaccination antibody titer levels in adults who engage in regular physical activity (62,63). This effect appears to be particularly beneficial in the elderly (64). In the first study that used objectively-measured physical activity data, Collie et al., showed enhanced effectiveness of vaccination with Ad26.COV2.S (Janssen/J&J) against COVID-19 hospital admission (59). The study also suggested a possible dose-response.

Conclusion

The Figure compares the effects of COVID-19 versus the "opposing" effects of exercise to this virus. The evidence presented in this review adds to the Nieman et al. (65) viewpoint, that it is time to include "treatment for and reduced risk of COVID-19 and long COVID" to the "Exercise is Medicine list of physical activity-related health benefits." The potent, multi-organ effects of exerkines position exercise as the most important medicine for COVID-19 and long COVID. However, it should be noted that the evidence exists for non-COVID-19 patients and needs to be verified in COVID-19 and long COVID patients.

Future research needs to investigate the suggested molecular pathways and mechanisms within clinical trials of exercise interventions for long COVID. This will allow for the mapping of molecular transducers and signaling pathways that occur during exercise with individuals post COVID-19, with long COVID.

The authors declare no conflict of interest and do not have any financial disclosures.

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