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Review

The role of exercise in rehabilitation of discharged COVID-19 patients

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly caused pneumonia and pulmonary fibrosis through upper respiratory tract infection, which resulted in acute respiratory distress syndrome (ARDS) and multiorgan damage of cardiovascular, nervous, digestive, and genitourinary systems. Although the virus test turned negative after the patient recovered, the damage to multiorgan caused by SARS-CoV-2 may irreversible. Therefore, the health status of the recovered patients has gradually become the focus of people's attention. Whether coronavirus disease 2019 (COVID-19) patients can receive exercise rehabilitation training after discharge? and what's the basis? We try to analyze and answer these questions, will provide some ideas about the patients to develop a reasonable and effective exercise rehabilitation program.

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which has brought great disaster to human health, as well as economic and social development. SARS-CoV-2 infection mainly attacks the lungs, causing severe pneumonia and acute respiratory distress syndrome (ARDS). It also results in several extrapulmonary manifestations.[1] Though most COVID-19 patients are recovering from the infection, some of the aftereffects may have a significant impact on recovered patients in the future. The multiorgan damage caused by SARS-CoV-2 infection may be irreversible. The most common symptoms reported for patients recovering from COVID-19 were fatigue and more critical manifestations such as pulmonary fibrosis, stroke, myocarditis, and renal failure.[2,3] To overcome this situation, the rehabilitation of discharged COVID-19 patients is crucial.

Exercise promotes health, but relatively little research has been done on systematic rehabilitation exercises for discharged COVID-19 patients. We reviewed the mechanism and symptoms of the viral infection. This urges us to suggest that exercise may be significant in promoting the physical and mental health recovery of COVID-19 patients by direct enhancement of lung function, inhibition of the inflammatory cytokine storm and neutrophil-induced reactive oxygen species (ROS), improvement of immunity, and intestinal flora homeostasis. The purpose of this review is to provide the basis and ideas for the feasibility of appropriate rehabilitation exercises for discharged COVID-19 patients.

Mechanisms of irreversible multiorgan manifestations of SARS-CoV-2 infection

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) and enters host cells with the assistance of cellular serine protease transmembrane protease serine 2 (TMPRSS2). ACE2 is expressed in cardiomyocytes, endothelial cells, and smooth muscle cells, especially in alveolar epithelial cells. Thus, the lung is the major site for SARS-CoV-2 infection, but the heart, brain, gastrointestinal tract, kidney, and liver also be infected. It is possible that a proportion of patients who survived COVID-19 have an overall damaged health status. Recovered COVID-19 patients may have persistent multi-organ injuries (Fig. 1).

SARS-CoV-2 infection in the respiratory system

A previous study reported that 57 COVID-19 patients displayed persistent pulmonary dysfunction and fibrosis during the early recovery period.[4] A 3-month follow-up study found that most of the survivors had symptoms including fatigue, dyspnea, cough on exertion, and palpitations in the 3 months following discharge.[5] After a 6-month follow-up of 1733 patients with COVID-19, it was found that most of them still had abnormal pulmonary diffusion (22%–56%, at different severity levels).[6] Long-term lung dysfunctions may lead to reduced breathing ability, limited movement, weakness, fatigue, and powerlessness, which in the long run will impair the patient's overall recovery.

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Abbreviations

Ang II	accumulation of angiotensin II
ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
AKI	acute kidney injury
ARDS	acute respiratory distress syndrome
BDNF	brain-derived neurotrophic factor
CHI3L1	chitinase-3-like protein 1
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRS	cytokine release syndrome
EcSOD	extracellular superoxide dismutase
FGF21	fibroblast growth factor 21
FSTL1	follistatin-related protein 1
GDF-15	growth/differentiation factor-15
ICU	intensive care unit
LIF	leukemia inhibitory factor
NK	natural killer
PBMCs	peripheral blood mononuclear cells
RAAS	renin-angiotensin-aldosterone system
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TMPRSS2	transmembrane protease serine 2
TNF	tumor necrosis factor
WBV	whole-body vibration

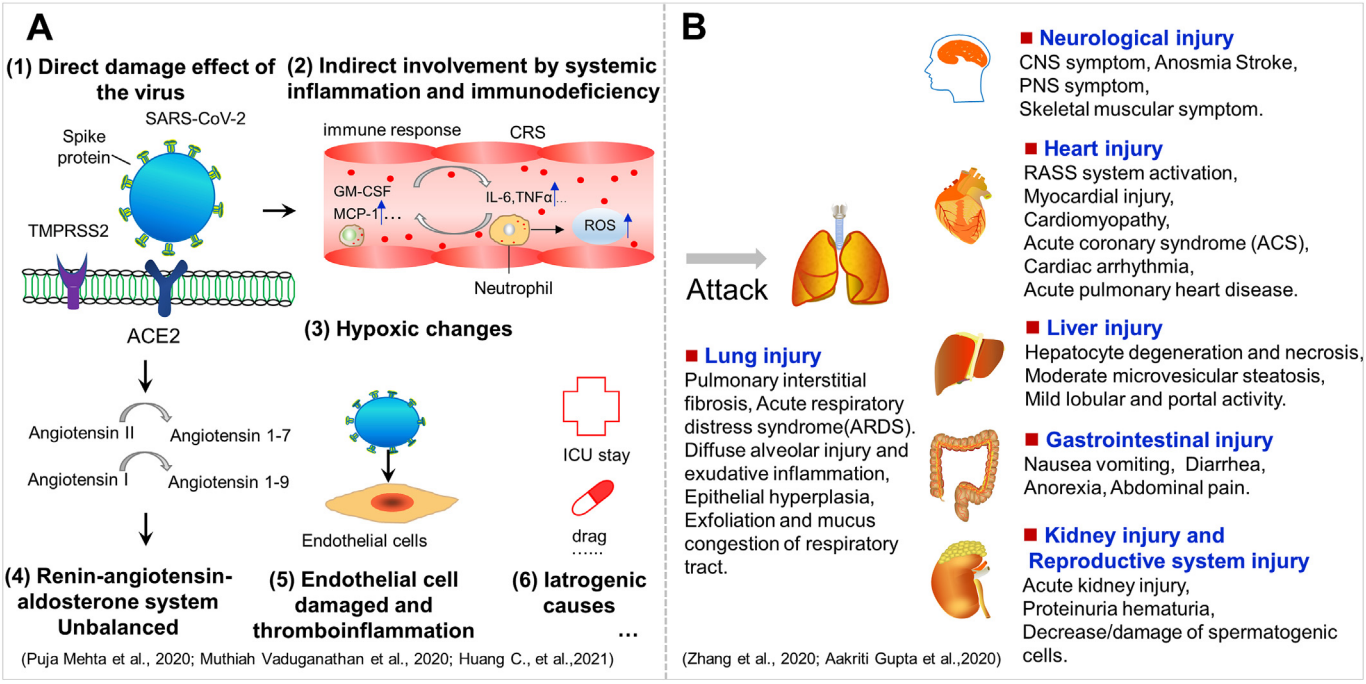

Fig. 1. Effect and mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on multiple organ injuries.
(A) Mechanism of coronavirus disease 2019 (COVID-19) induced multi-organ injury (B) SARS-CoV-2 infection-induced impairment of multiple organ functions ACE2, angiotensin-converting enzyme 2; CNS, central nervous system; CRS, inflammatory cytokine storm; GM-CSF, granulocyte-macrophage colony stimulating factor; ICU, intensive care unit; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; PNS, peripheral niveous system; RASS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome; TMPRSS2, transmembrane protease serine 2; TNF-α, tumor necrosis factor alpha.

SARS-CoV-2 infection in the cardiovascular system

SARS-CoV-2 infection may directly or indirectly cause cardiovascular sequelae through ACE2, including myocardial injury, cardiomyopathy, acute coronary syndrome (ACS), arrhythmia, and acute pulmonary heart disease.[7–9] Microvascular thrombosis was found in COVID-19 patients.[10] This condition was usually associated with cardiac insufficiency, including tachycardia, bradyarrhythmia, and acute myocardial infarction.[10,11] A report from Germany[12] showed that COVID-19 patients still exhibited symptoms such as persistent myocarditis after rehabilitation, independent of the severity of the previous illness. Hence, cardiac rehabilitation following discharge of COVID-19 patients requires attention.

SARS-CoV-2 infection in the central nervous system

SARS-CoV-2 infection involved the central nervous system (CNS) and directly or indirectly damaged neurons, resulting in long-term neurological sequelae.[13] CNS symptoms of COVID-19 patients included headache, dizziness, disturbance of consciousness, acute cerebrovascular disease, epilepsy, and peripheral nervous system symptoms such as loss of taste, smell, and appetite, as well as neuralgia.[14–16] Difficulty sleeping, anxiety, and depression were also common in discharged COVID-19 patients.[6] The underlying mechanisms may be multifactorial and include the indirect effects of the immune response, viral infection, social isolation, and intensive care unit (ICU) stay.[17] Consequently, the rehabilitation of the nervous system is indispensable for patients to resume a normal life.

SARS-CoV-2 infection in the kidney

Acute kidney injury (AKI) has been shown globally to be an important systemic complication in severe cases of COVID-19 and was associated with higher mortality rates. AKI and secondary infections were common in discharged patients with COVID-19.[18–20] Autopsy of deceased COVID-19 patients revealed proximal tubular cell and podocyte infection.[21,22] In addition, severe acute tubular necrosis with infiltration of lymphocytes and macrophages, peripheral red blood cell aggregation, acute proximal tubular injury, and glomerular fibrin thrombosis with ischemic collapse were also observed in COVID-19 patients.[21,23] The development from acute tubular necrosis to cortical necrosis may be related to thrombus affinity, hence, irreversible renal injury.[24] Furthermore, some studies have shown that most patients undergoing hemodialysis may experience mild disease process on account of decreased immune system function and decreased cytokine release syndrome (CRS).[25]

SARS-CoV-2 infection in the skeletal muscle

Patients with COVID-19 have skeletal muscle pain, significantly elevated serum creatine kinase levels,[14,15] and limited exercise ability.[4] A follow-up study found that 6 months after convalescence, the common symptoms of COVID-19 patients were fatigue or muscle weakness.[6] A 3-month follow-up survey of 538 COVID-19 patients showed that women were more prone to physical decline or fatigue, post-activity hyperhidrosis, and hair loss than men.[26] Lower exercise ability may be associated with lung dysfunction, as well as muscle pain and fatigue.

Furthermore, decreased, or damaged liver dysfunction[27] and spermatogenic cells,[28] conjunctivitis, and other digestive,[29] reproductive, and sensory organ diseases also were reported in COVID-19 patients. These symptoms may also accompany patients for a long time after they are discharged from the hospital. Therefore, methods for rehabilitation are essential to help patients recover better.

Possible mechanism of multiple organ irreversible injury induced by SARS-CoV-2 infection

Pathophysiological mechanisms of multi-organ sequelae secondary to SARS-CoV-2 infection include (Fig. 1): 1) SARS-CoV-2 directly attacked target organs lead to severe irreversible organ damage. ACE2 receptors are widely expressed in the endocardium and vascular wall, alveolar epithelial cells, skeletal muscle, and other organs. 2) Indirect involvement by systemic inflammation and immunodeficiency. SARS-CoV-2 caused dysregulated immune response and CRS.[30] Clinical studies have shown a high inflammatory response in all types of peripheral blood mononuclear cells (PBMCs) in severe COVID-19 patients, and the plasma concentrations of TNF-α and other inflammatory cytokines were increased.[15,31] 3) Hypoxic changed. Damage from neutrophil-induced oxidative stress.[32,33] 4) Maladaptive functions of the renin-angiotensin-aldosterone system (RAAS). SARS-CoV-2 down--regulated the expression of ACE2 in epithelial and endothelial cells of the lung and other organs, which lead to the accumulation of angiotensin II (Ang II) and accelerated the development of COVID-19 by increasing RAAS activity. 5) Endothelial cell damaged and thrombosis.[34,35] Endothelial injury and inflammation led to microthrombi deposition and microvascular dysfunction in the lungs, kidney, heart, small intestine, and liver of patients with COVID-19.[34,36] 6) Iatrogenic causes such as drugs, ICU stay, and ventilation to exacerbation of underlying multiple-organ diseases. There may be other mechanisms behind COVID-19 sequelae besides the aforementioned ones.

Exercise interventions help to improve the quality of life of COVID-19 patients

Mechanism of rehabilitation exercise

Several studies have considered the importance of exercise in the prevention and rehabilitation of COVID-19. There were many calls to take up regular physical exercise during the COVID-19 epidemic period in order to prevent the occurrence of the disease, promote the recovery of the body's health and avoid the risk of sequelae.[37–40] The reports demonstrated the safety and effectiveness of rehabilitation exercises for different COVID-19 patients.[41] Filgueira et al.[42] discussed the effect of physical activity on the immune defense mechanism and its contribution to alleviating severe inflammatory response mediated by SARS-CoV-2. Tang et al. found the dyspnea was alleviated in COVID-19 patients after 4 weeks of Liuzijue exercise.[43] A case reported an improvement was observed in pulmonary function and physical fitness in COVID-19 patients after a 6-week pulmonary exercise rehabilitation programme.[44] Stavrou et al. indicated that oxygen saturation, hemodynamic parameters, and dyspnea during 6 min walk test in discharged COVID-19 patients were among significantly altered as a result of an 8-week exercise rehabilitation.[45] Severe or critical COIVD-19 patients after discharged, endurance exercises and muscles training for 3 weeks helped their functional exercise capacity.[46] Although these clinical data suggested that exercise helped the process of recovery in COVID-19 patients after discharge, subsequent data regarding exercise rehabilitation after SARS-CoV-2 infection are still limited. Accordingly, it is essential to understand the mechanism behind exercise promoting patients' rehabilitation, so as to precipitate the application of exercise in patients' rehabilitation plans. We considering the possible mechanisms behind the benefit of exercise in the clinical rehabilitation of COVID-19 patients, as shown in Fig. 2.

Exercise may directly improve lung function

Respiratory muscle weakness is directly related to dyspnea and reduced exercise endurance, meanwhile, the strength of the respiratory muscles can be improved by specific exercise training.[47] After discharge from hospital, severe or critically ill COVID-19 patients have symptoms of general weakness, shortness of breath, and physical function limitation, which were manifested as pulmonary fibrosis and pulmonary function restrictive ventilation disorder.[48] Exercise stands as the effective treatment for lung diseases to improve peak pulmonary oxygen uptake, functional capacity, muscle strength, muscle size, systematic oxidative stress, and quality of life.[49,50] Wang et al., suggested pulmonary exercise rehabilitation in COVID-19 patients should be considered when possible and safe.[51] The function of the respiratory system is closely related to exercise ability. The enhancement of the respiratory muscle is one of the main factors that reduce the occurrence of exercise intolerance. Thus, proper exercise directly promotes the improvement of lung function in COVID-19 patients by increasing the strength of respiratory muscles, lung ventilation ability, as well as oxygen and alveoli combination.

Exercise may improve immunity and directly or indirectly inhibit CRS

COVID-19 is a kind of self-limiting viral disease, and the immune system is the first line of defense. Patients, with severe complications caused by COVID-19 infection, had lymphocytopenia and CRS mediated by non-T cells.[52] Hermann et al. speculated that long-term exercise may provide innate immune protection for COVID-19 patients by reducing CRS in “high-risk” groups.[53] Glucose metabolism was usually the driving

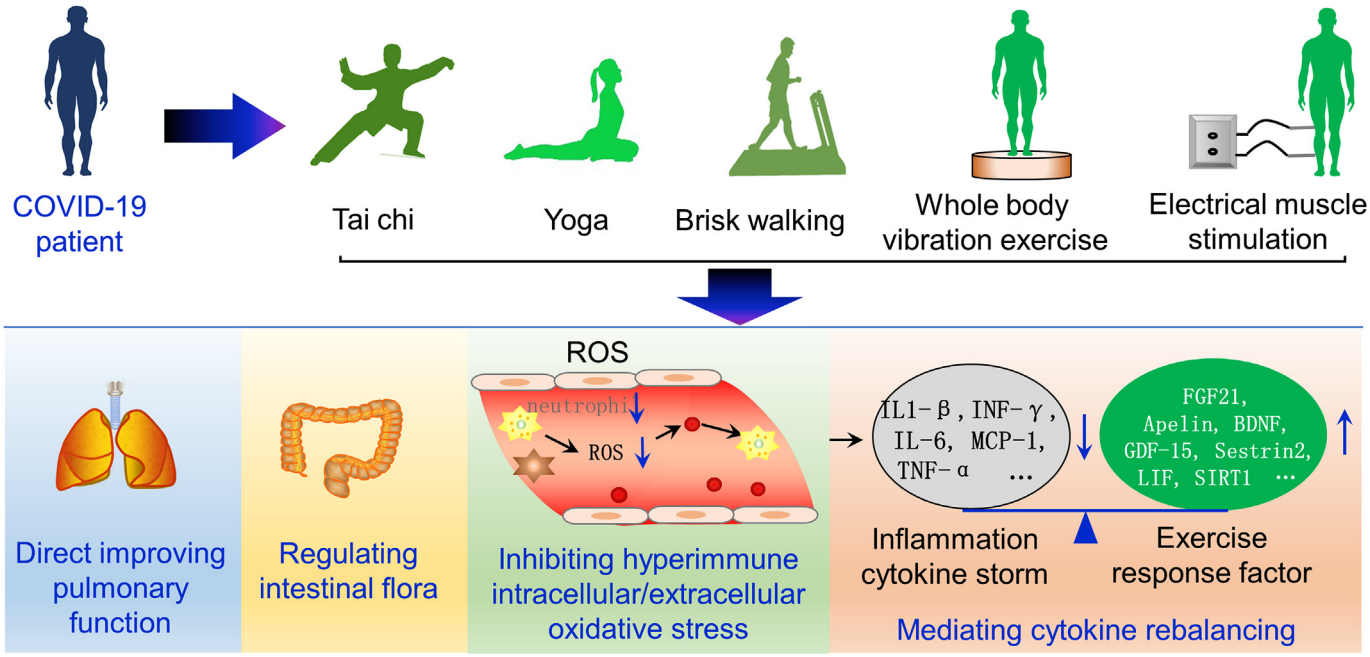

Fig. 2. Possibility and basis of exercise in rehabilitations of coronavirus disease 2019 (COVID-19) patients after discharge.
BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; GDF-15, growth differentiation factor-15; IL-1β, interleukin-1β; IL-6, interleukin-6; INF-γ, interferon-γ; LIF, leukemia inhibitory factor; MCP-1, monocyte chemotactic protein 1; ROS, reactive oxygen species; SIRT1, Sirtuin 1; TNF-α, tumor necrosis factor alpha.

force for the production of CRS leading to fatal inflammation.[54] Aerobic exercise can participate in the regulation of body glucose and correct glucose metabolism disorders caused by a variety of diseases.[55] It is well known that long-term physical exercise can inhibit the occurrence and development of viral, bacterial infections, as well as non-communicable diseases such as chronic inflammatory diseases or cancer,[56] improve immunity, and reduce the susceptibility of the elderly and high-risk groups with complications to SARS-CoV-2.[57,58] Physical exercise has also been shown to improve the response of T cells, increase the mobilization of natural killer (NK) and CD8 T cells into the blood, their migration to the tissues, and the tumor necrosis factor (TNF) activation of these cells.[59–61] In this context, we speculate that regular exercise may improve the immune response to SARS-CoV-2 by increasing the activation of NK and CD8 T cells, so as to slow the progression of severe COVID-19 disease. After moderate-intensity exercise, the levels of anti-inflammatory cytokines (IL-4 or IL-10) produced by T cells were significantly increased.[62] Moreover, moderate-intensity exercise reduced the mortality of mice in the active phase of influenza, promoted the composition of lung immune cells and cytokine transfer.[63] In this regard, we would suggest that exercise may directly inhibit the expression of inflammatory cytokines such as IL-6, IL-1 β, and TNF-α, which is caused by COVID-19.

In addition, exercise stimulated cells to release many response factors, including brain-derived neurotrophic factor (BDNF), growth/differentiation factor-15 (GDF-15), irisin, and leukemia inhibitory factor (LIF), which may be induced by inflammation and oxidative stress.[64] Fiuza-Luces et al. reviewed the cytokines fibroblast growth factor 21 (FGF21), irisin, follistatin-related protein 1 (FSTL1), and LIF that inhibited oxidative stress and inflammation, which may be activated by exercise.[65] Our previous work found that exercise inhibited myocardial inflammation alongside apoptosis by up-regulating the expression of cytokines such as FGF21, FSTL1, and IGF-1 in the myocardium. Hence, exercise may indirectly inhibit the CRS induced by SARS-CoV-2 by stimulating the release of endogenous exercise response factors.

Moreover, the effective isolation and quarantine measures adopted during the COVID-19 epidemic bring psychological pressures and negative emotions to normal people and patients. Some COVID-19 patients in hospital or after discharge had depression, irritability, memory disorders, and other anxiety symptoms.[6,66] Also, the COVID-19 recovered patients had psychological stress due to their infection. Rehabilitation exercise can relieve anxiety and tension and improve immunity,[67] which through reduced levels of TNF-α and other inflammatory factors caused by anxiety.[68] Therefore, exercise can promote the psychophysical health of COVID-19 patients after discharge by inhibiting the CRS.

In summary, although exercise does not prevent the spread of and susceptibility to SARS-CoV-2 infection, it may directly and/or indirectly inhibit the outbreak of inflammatory cytokines, enhance the function of the immune system, and reduce the multi-organ injury of COVID-19 patients to a minimum, which will accelerate the recovery process of the patients (Fig. 3).

Exercise may reduce oxidative stress injury by inhibiting intracellular and extracellular oxidative stress

CRS leads to a ROS outbreak. Exercise can reduce the level of oxidative stress intracellularly and enhance the antioxidant defense ability of the tissue.[69] Long-term exercise improved the activities of intracellular antioxidant enzymes, including superoxide dismutase (74.5%), glutathione peroxidase (41%), and catalase (around 28%).[70] Our previous work also found that exercise improved myocardial antioxidant capacity and myocardial function by activating the SIRT1/PGC-1α/PI3K/Akt pathway in ischemic cardiomyocytes.[71] Extracellular superoxide dismutase (EcSOD) is the only known extracellular antioxidant enzyme, widely expressed in organs such as the lung and kidney, which can eliminate the extracellular O_2 toxicity.[72] Oxidative stresses in lung tissues are involved in the pathogenesis of various lung diseases, including ARDS. Exercise increased the expression of EcSOD in mouse skeletal muscle and aorta as well as human aorta.[73,74] Yan et al. reported that long-term regular exercise reduced the risk of ARDS which was one of the important causes of death in COVID-19 patients. Moreover, they stated that exercise enhanced the extracellular antioxidant defense capacity of circulation and surrounding tissues via enhanced

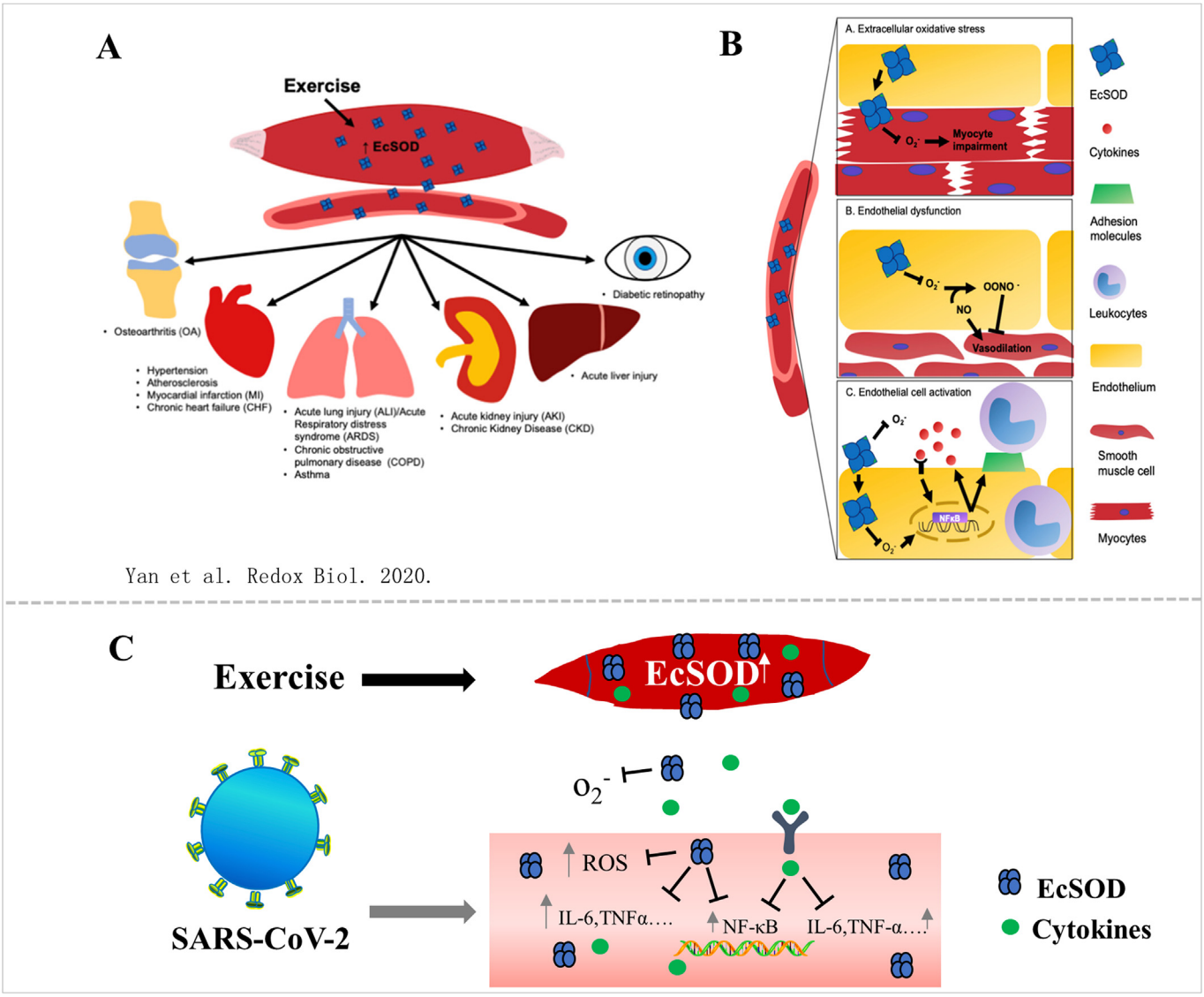

Fig. 3. Exercise activated endogenous extracellular superoxide dismutase (EcSOD) and cytokines to inhibit inflammatory cytokines and oxidative stress. (A) Enhanced skeletal muscle EcSOD expression by exercise promotes mitigation of oxidative stress and damage in a variety of peripheral tissues and disease conditions. (B) Elevated EcSOD abundance/activity prevents extracellular oxidative stress endothelial dysfunction and endothelial cell activation by scavenging superoxide anion. (C) Exercise inhibited intracellular and extracellular oxidative stress and inflammation induced by SARS-COV-2. EcSOD, extracellular superoxide dismutase; IL-6, interleukin-6; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome; TNF-α, tumor necrosis factor alpha.

expression of EcSOD.[75] It is speculated that exercise can promote the expression of endogenous EcSOD, inhibit intracellular and extracellular oxidative stress, and inhibit inflammation (Fig. 3). Therefore, a possible mechanism behind the ability of exercise to promote the recovery of COVID-19 patients is the inhibition of intracellular and extracellular oxidative stress.

Exercise improves gastrointestinal symptoms in patients with COVID-19 by regulating intestinal flora

Manifestations of SARS-CoV-2 infection include gastrointestinal symptoms, diarrhea, nausea, vomiting, and loss of appetite, a decreased microbial level, and changes in lung microbiota.[76–78] Intestinal flora can enhance antiviral immunity by increasing the number and function of immunocytes. The intestinal flora enriched the lung microbiota, which was related to the onset of ARDS and long-term prognosis.[79] Improving the proportion of intestinal microflora and their metabolites may be a potential strategy for the prevention and treatment of COVID-19.[79,80] Exercise regulated the intestinal microbiota by increasing the number of beneficial microorganisms and enriched the diversity of the flora.[81,82] After 8 weeks of aerobic and resistance combined training, the composition and activity of the human intestinal microflora changed moderately.[83] Hence, it is speculated that exercise will exert a positive effect on the recovery process of COVID-19 patients by regulating the intestinal flora.

Exercise method selection

As we all know, proper exercise can improve cardiopulmonary function. But it's worth noting that during the COVID-19 pandemic, physical exercise has a 2-sided effect. COVID-19 infection increases the risk of heart damaged and heart death during exercise, even later in recovery. This implies that we should be more cautious in formulating exercise prescription. Woods et al. raised it was feasible for mildly infected patients to exercise, some severe COVID-19 patients may require testing prior to exercise.[40] Fatigue or muscle weakness, and pulmonary

dysfunction were the main symptoms of COVID-19 discharged patients. Choosing the right exercise prescription can improve the recovery of patients with COVID-19. The choice of exercise mode and time should be specific for patients with different disease levels. For mild patients, moderate aerobic or resistance exercise can be selected; yoga and tai chi represent an appropriate complement or alternative to the exercise rehabilitation programs. Rong et al. evaluated the Baduanjin as a safe and effective exercise intervention for rehabilitation after COVID-19,[84] which should be considered by COVID-19 patients. According to previous reports, it is possible that vibration exercise and skeletal muscle electrical stimulation have the effect of simulating exercise.[85–88] The world association of vibration exercise experts assessed the potential of whole-body vibration (WBV) exercise as an effective and safe intervention to promote recovery of COVID-19 patients from their disease state.[38] Whole-body vibration improved pulmonary function and quality of life in patients with severe chronic obstructive pulmonary disease (COPD).[89] Kensuke et al. and Simone et al. reported on severe COVID-19 patients treated with muscle electrical stimulation in the ICU ward.[90,91] Therefore, for people with more severe COVID-19 illness, WBV or electro muscle stimulation may play an important role in their physical rehabilitation.

The latest research shows that the B.1.617.2 (delta) variant of the SARS-CoV-2, the virus that causes COVID-19, has been responsible for a surge in cases in many countries and has now been detected across the globe.[92–95] The Delta variant has greater transmissibility and higher viral RNA loads, fully vaccinated people can carry as much delta virus as unvaccinated people.[96] In this context, adults infected with Delta variants may become more need exercise rehabilitation to return to pre-infection status.

Conclusion

Taken together, problems of recovered COVID-19 patients following discharge, deserve attention as does the role of exercise in their rehabilitation. This study provides a theoretical basis for exercise to promote the recovery of COVID-19 patients. Exercise may be a momentous way for promoting the rehabilitation of patients who have COVID-19. Exercise directly enhances lung function and improves immunity by correcting cytokine imbalances in the body. Moreover, it also reduces intracellular and extracellular oxidative stress. Another benefit of exercise is the regulation of the intestinal flora homeostasis. We suggest that the effect of exercise on the rehabilitation of COVID-19 patients should be considered, and appropriate exercise training can reduce the complications due to injury suffered by patients and promote a swift return to normal life. Future research will focus on specific exercise prescriptions under the different exercise modes.

Submission statement

The manuscript has not been published and is not under consideration for publication elsewhere.

Authors' contributions

Z.T., W.B., and Y.X contributed to the writing and editing of the manuscripts.

Conflict of interest

The authors declare no competing interests.

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