

# World Journal of *Clinical Cases*

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## Enhancing oxygenation of patients with coronavirus disease 2019: Effects on immunity and other health-related conditions

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### Abstract

Coronavirus disease 2019 (COVID-19) distresses the pulmonary system causing acute respiratory distress syndrome, which might lead to death. There is no cure for COVID-19 infection. COVID-19 is a self-limited infection, and the methods that can enhance immunity are strongly required. Enhancing oxygenation is one safe and effective intervention to enhance immunity and pulmonary functions. This review deliberates the probable influences of enhancing oxygenation on immunity and other health-connected conditions in patients with COVID-19. An extensive search was conducted through Web of Science, Scopus, Medline databases, and EBSCO for the influence of enhancing oxygenation on immunity, pulmonary functions, psycho-immune hormones, and COVID-19 risk factors. This search included clinical trials and literature and systematic reviews. This search revealed that enhancing oxygenation has a strong effect on improving immunity and pulmonary functions and psycho-immune hormones. Also, enhancing oxygenation has a self-protective role counter to COVID-19 risk factors. Lastly, this search revealed the recommended safe and effective exercise protocol to enhance oxygenation in patients with COVID-19. Enhancing oxygenation should be involved in managing patients with COVID-19 because of its significant effects on immunity, pulmonary functions, and COVID-19 risk factors. A mild to moderate cycling or walking with 60%-80%  $Vo_{2max}$  for 20-60 min performed 2-3 times per week could be a safe and effective aerobic exercise program in patients with COVID-19 to enhance their immunity and pulmonary functions.

**Key Words:** Oxygenation; COVID-19; Immunity; Pulmonary functions; Psycho-immune hormones; COVID-19 risk factors

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**Core Tip:** Coronavirus disease 2019 is a self-limited infection, and interventions that can increase immunity are strongly recommended. Thus, enhancing oxygenation is one of the safe and effective interventions in enhancing immunity and pulmonary functions. This review discusses the possible effects of enhancing oxygenation of patients with coronavirus disease 2019 on immunity and other health-related conditions.

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## INTRODUCTION

The coronavirus or coronavirus disease 2019 (COVID-19) is defined by the World Health Organization as a world disaster. The World Health Organization has announced that through February 11, 2021 that there were 106797721 confirmed cases, among them 2341145 deaths[1]. COVID-19 is recognized as a surrounded RNA beta-coronavirus commonly identified as the severe acute respiratory syndrome coronavirus 2[2]. Communal signs of COVID-19 include cough and fever[3]. Fever presents in 43.8% of patients with COVID-19 on early admission; though, it rises to 88.7% throughout hospitalization. The next communal symptom is cough, which happens in approximately 67.8%[2]. Other symptoms contain fatigue, dyspnea, and myalgia.

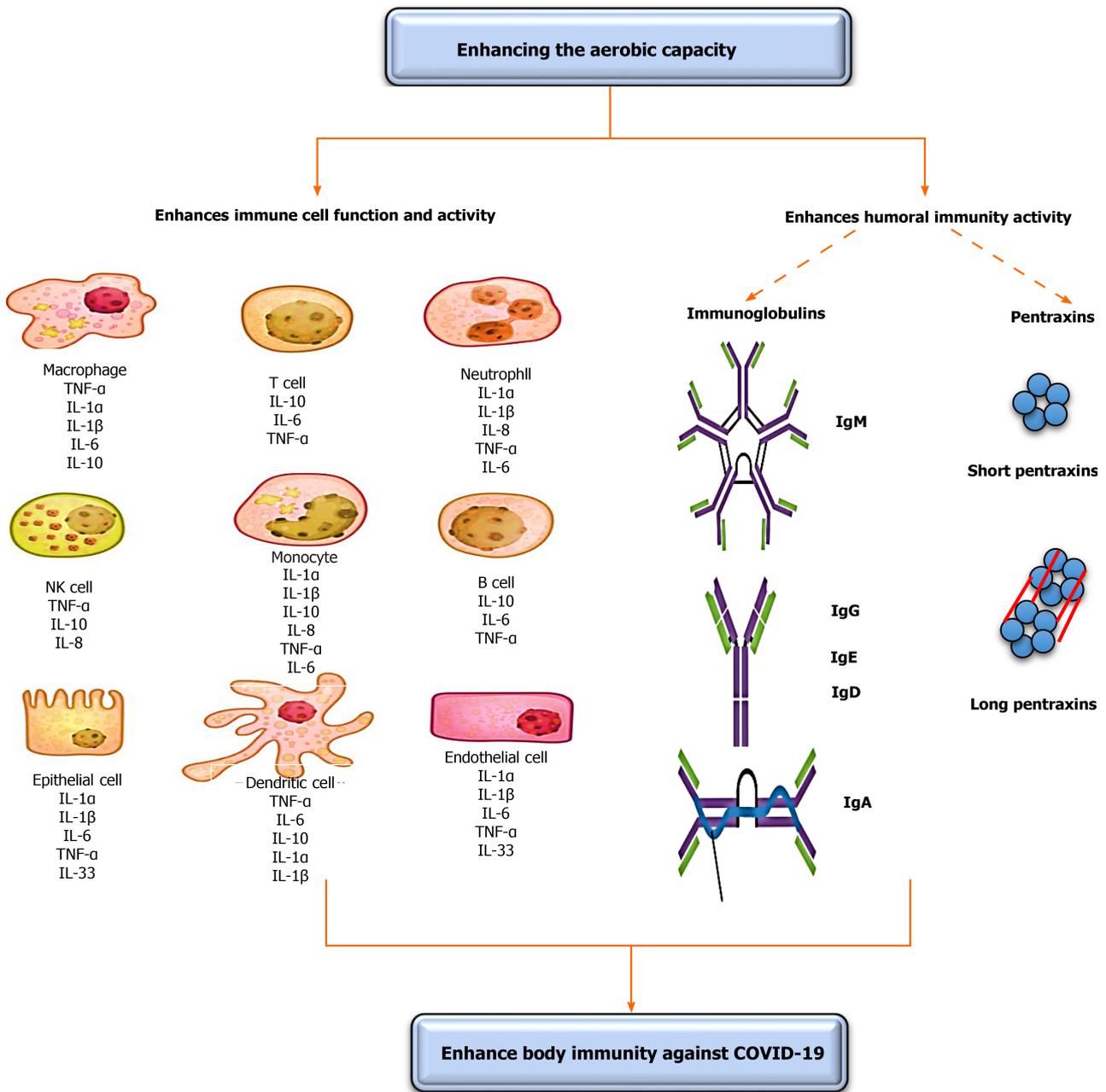
COVID-19 has been demonstrated to be self-limited where the host's immune strength plays a key role in decreasing its associated disorders and death rates[4]. Thus, interventions that increase immune functions are strongly needed to either people in lockdown or people with COVID-19. Enhancing oxygenation has been demonstrated as a safe and effective intervention to increase immune functions. The advantage of enhancing oxygenation over other interventions is that it causes an autonomic modulation; this autonomic modulation increases pulmonary functions and controls psycho-immune changes that occur due to high stressors (such as COVID-19). Thus, this review highlights the influence of enhancing oxygenation on immunity, pulmonary functions, psycho-immune hormones, and obesity. Also, this review highlights the defensive role of enhancing oxygenation on COVID-19 risk factors.

## THE INFLUENCE OF ENHANCING OXYGENATION ON IMMUNITY AMONG PATIENTS WITH COVID-19

The strength of immunity plays a fundamental role in the treatment of any infection. COVID-19 is a self-limited infection; thus, strengthening immunity might have a significant role in lessening its associated disorders and death rates[5]. However, the existence of some vaccines, the development of specific drugs to treat patients with COVID-19 could continue for about 1 year. Thus, the need for a fast and safe intervention for COVID-19 is a necessity to decreasing its associated disorders and death rates. Enhancing oxygenation can afford a safe and immediate enhancement in immunity strength[5]. This subtopic discusses the vital role of enhancing oxygenation on enhancing COVID-19 specified immunity components vital for decreasing associated disorders and death rates. Immunity mainly divides into two components, including immune cells and humoral immunity. The effects of increasing the oxygenation on immunity are illustrated in [Figure 1](#).

### *The influence of enhancing oxygenation on immune cells*

The first immunity component that fights COVID-19 infection is immune cells. COVID-19, severe acute respiratory syndrome coronavirus, and Middle East respir-



**Figure 1 Effect of increasing the aerobic capacity on immunity.** This diagram illustrates possible mechanisms of increasing oxygenation capacity in improving the immunity. These possible mechanisms include increasing the function and activity of immune cells, immunoglobulins, and pentraxins. COVID-19: Coronavirus disease 2019; Ig: Immunoglobulin; IL: Interleukin; NK: Natural killer; TNF- $\alpha$ : Tumor necrosis factor-alpha.

atory syndrome coronavirus are  $\beta$ -coronavirus subtypes, which could lead to severe lower respiratory tract and extrapulmonary symptoms[6,7]. T-lymphocytes, among all immune cells, have a principal antiviral role in fighting infection and pathogens[7]; this is attributed to the ability of T-lymphocytes to persist into infected lungs engulfing infecting viruses[8]. Thus, the T-lymphocytes have an imperative role in fighting coronaviruses. B-coronaviruses highly decrease the number of T-lymphocytes through extrinsic and intrinsic apoptosis pathways[9], which causes a significant decrease in the number of T-lymphocytes that prolongs the infection time and eases viral survival [10].

Pascal *et al*[11] stated that the response of T-lymphocytes is substantial to minimize the number of Middle East respiratory syndrome coronaviruses[11]. Chen *et al*[12] reported that the reduction of serum T-lymphocytes causes a decline in the respiratory T-lymphocyte cytokine production and neutralizing antibody, which can result in an extensive immune-intermediated interstitial pneumonia and delayed washing out of severe acute respiratory syndrome coronaviruses from infected lungs[12]. Also, T-helper cells, the most significant cells in adaptive immunity, activate the production of

proinflammatory cytokines *via* triggering the nuclear factor kappa B pathways[13]; these proinflammatory cytokines activate the secretion and relocation of neutrophils and monocytes to the region of infection to start other chemokine and cytokine cascades, such as tumor necrosis factor  $\beta$ , interleukin (IL)-1, IL-10, IL-6, IL-12, IL-8, and monocyte chemoattractant protein-1[14,15].

Enhancing oxygenation causes a short-term enhancement in the function and number of T-lymphocytes. Gonçalves *et al*[16] conducted a recent systematic review to investigate the influence of enhancing oxygenation on the function and number of immune markers. They established that enhancing oxygenation causes fast and short-term enhancements in the function and number of T-lymphocytes, B-lymphocytes, immunoglobulins, leukocytes, and interleukins. Previous studies showed that only one session of aerobic exercise causes a significant increase in almost all immune markers, including T-lymphocytes, immunoglobulins, and leukocytes in humans[17-20]. Lippi *et al*[17,18] demonstrated that mild aerobic exercise (running for 21.1 km) significantly increases the number of monocytes, leukocytes, and neutrophils among amateur runners. Lira *et al*[20] showed that a single session of moderate aerobic exercise (5 km running) significantly increases the number of cytokines, IL-10 and IL-6, for 60 min. Li *et al*[19] showed that one session of extended aerobic exercise increases the number of serum neutrophils, monocytes, and leukocytes for 9 h. Gonçalves *et al* [21] investigated the defensive role of enhancing oxygenation on artificially-produced acute lung inflammations in rats. They detected that 5 wk of low aerobic exercise significantly increased the number of neutrophils in bronchoalveolar lavage fluid, pulmonary resistance and pliability, protein leakage, tumor necrosis factor- $\alpha$ , serum IL-10, IL-6, IL-1beta, and KC (murine homolog to IL-8) levels.

### **The influence of enhancing oxygenation on humoral immunity**

The second immunity component essential against COVID-19 infection is humoral immunity. Humoral immunity consists mainly of B-cell subdivisions; these subdivisions present with phenotype features of modest and un-isotype interchanged method. They consist of antibody-secreting and memory cells, which rise during coronavirus infection[7,22]. The antigen stimulation of coronavirus is detected *via* employing a particular 9-mer peptide "CYSSLILDY" that lies in the zone from 437-445 of the S-glycoprotein region[7,22]. This construction has the supreme B-cell antigenicity outline to form high connections to major histocompatibility complex class I alleles into a computerized model[23]. Several reports mentioned the important role of humoral immunity in controlling the exitance period of coronavirus infection[24-26].

The normal humoral immunity involves numerous elements, such as serum complements (C3-C9), pentraxins [C-reactive proteins (CRPs)], immunoglobulins [IgM, IgE, IgG, and IgA and contact cascades (FXIIa)][27]. The serum complements primarily act in the antiviral defense, and they are strongly regulated by specific proteins produced into the bloodstream. Viruses regularly include encrypted proteins that aid them to evade their discover by serum complement[7,28]. Thus, increasing the function of the serum complement system might aid in recognizing these encrypted proteins.

To the best of our knowledge, infrequent human articles examined the influence of enhancing oxygenation on role of complements in respiratory infections. These infrequent studies concentrated more on athletes than normal subjects to examine the influence of overtraining syndrome in weakening immunity among athletes. In these studies, there were conflicts among their results[29-32]. These high conflicts might have occurred because of athletes' highly strenuous and repeated activities, which can cause negative effects on immunity (overtraining syndrome)[33].

The influence of enhancing oxygenation on the function and level of serum immunoglobins has been extensively documented in the literature. Immunoglobulins play a chief role in fighting COVID-19 infection and decreasing the severity of its associated disorders. Immunoglobulins chiefly are IgA, IgG, IgE, and IgM. The IgA and IgG are the predominant Ig in the mucosal fluid, and they have a vibrant role in inhibiting upper and lower respiratory tract infection[34-36]. The influence of enhancing oxygenation on increasing the function and activity of immunoglobulins has been documented in the literature. Karacabey *et al*[30] showed that the performance of continual moderate aerobic exercise significantly increased the secretion of immunoglobulins IgM, IgA, and IgG. Mohamed *et al*[37] examined the long influence of aerobic *vs* anaerobic exercise on serum immunoglobulins amid obese females. They observed that unlike anaerobic exercise, aerobic exercise significantly increased serum Ig, predominantly IgG and IgM.

The second subdivision of humoral immunity is CRPs. CRPs in the body principally act in inflammatory mechanisms and responses to viral infection by encouraging the production of serum complements, nitric oxide secretion, phagocytosis, apoptosis, and cytokines[38]. Increasing CRPs levels is a natural body defense mechanism to counter viral infection. Conversely, persistent high serum CRPs can cause considerably fast lung destruction because high serum CRPs lead to a resultant decrease in lung function[39]. The serum CRPs are considered a chief laboratory test to detect COVID-19 infection. Patients who suffer from COVID-19 have elevated serum CRPs[40,41]. Enhancing oxygenation plays an exciting role in controlling serum CRPs by creating a temporary slight rise in serum CRPs[42-44] to counter lung infection and a lasting reduction in serum CRPs[45,46] to inhibit the decline in lung functions.

## THE INFLUENCE OF ENHANCING OXYGENATION ON PULMONARY FUNCTIONS AMID PATIENTS WITH COVID-19

COVID-19 negatively disturbs respiratory functions leading to respiratory disorders, particularly pneumonia and acute respiratory distress syndrome (ARDS)[47-51]. The respiratory symptoms that commonly arise amid patients with COVID-19 are fever and cough. The subtopic discusses in-depth the important role of enhancing oxygenation in improving COVID-19-associated respiratory disorders and symptoms. The effects of enhancing oxygenation on pulmonary functions are shown in [Figure 2](#).

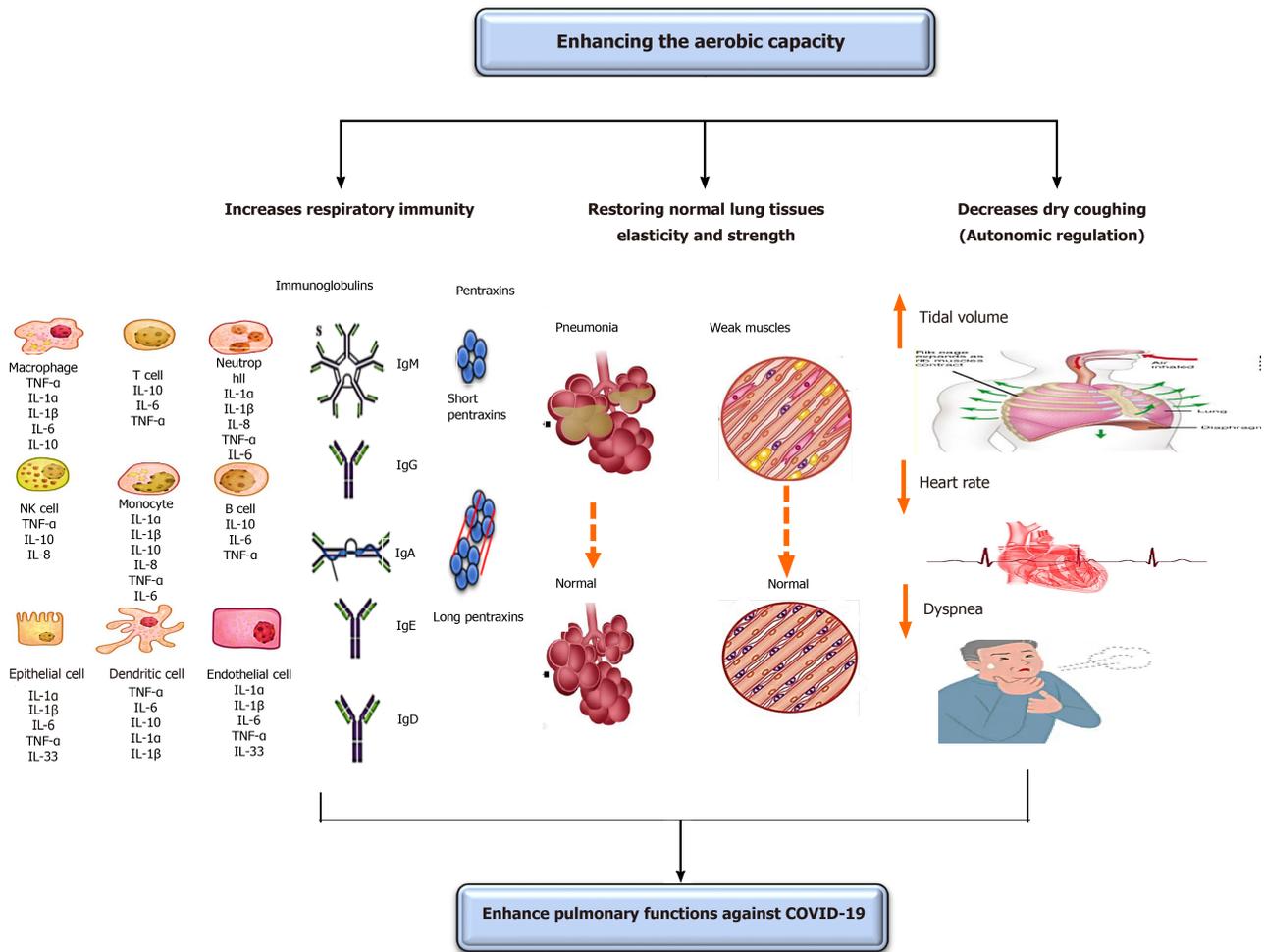
### ***The influence of enhancing oxygenation on COVID-19-associated disorders***

Enhancing oxygenation can inhibit pneumonia or reduce its development from moderate to severe. Baumann *et al*[52] stated that the performance of aerobic exercise for a short time can inhibit the incidence of fever and pneumonia in patients with malignancy. Williams[53] has shown that mild aerobic exercise, like walking and running, significantly declines the peril of pneumonia and aspiration pneumonia death. Stravinskis Durigon *et al*[54] showed that the performance of aerobic exercise for 8 wk averts *Pseudomonas aeruginosa* prompted bacterial settlement and lung inflammation among older mice. Neuman *et al*[55] demonstrated that enhancing oxygenation plays a key role in reducing the incidence of pneumonia in United States women. Olivo *et al*[56] reported that the performance of mild aerobic exercise has an important anti-inflammatory influence in patients with *Streptococcus pneumoniae*, which aids in offsetting pulmonary inflammations.

Also, enhancing oxygenation can limit the development of ARDS or reduce its advance from moderate to severe. Rigonato-Oliveira *et al*[57] showed that enhancing oxygenation prevents acute lung inflammation by diminishing oxidative stress signs and inflammatory cytokines in rats and people. Vieira *et al*[58] stated that enhancing oxygenation significantly rises serum IL-10, which has an indispensable role in immunity strength to decline recent lung injuries. A very fresh study conducted by Shi *et al*[59] has revealed that the performance of mild aerobic exercise for 5 wk prevents the occurrence of acute lung injuries in rats *via* forming neutrophil extracellular traps (NETs), which play a key role in limiting recent lung inflammation. Neutrophil extracellular traps are structures that have an extracellular web-like shape and particularly are comprised of neutrophil elastase, DNA, histones, and myeloperoxidase. These formed neutrophil extracellular traps can proficiently trap attacking pathogens by using high local amounts of antimicrobial peptides to destruct virulence elements. Interestingly, enhancing oxygenation has a superior role in COVID-19 respiratory-related symptoms than breathing exercise[5]. The influence of enhancing oxygenation on COVID-19 respiratory-related symptoms can be summarized in four mechanisms.

### ***The influence of enhancing oxygenation on respiratory immunity***

Enhancing oxygenation acts as antimycotic or antibiotic prophylaxis. It was previously mentioned in the section of “the influence of enhancing oxygenation on immunity” that enhancing oxygenation improves respiratory and bodily immunity through: (1) Enhancing the level and function of immune cells, such as T-lymphocytes, macrophages, monocytes, and neutrophils, which are necessary cells in the body’s resistance to infection; (2) Enhancing serum immunoglobulins “IgA, IgM, IgG,” predominantly IgA as a result of its chief function to counter lung infection; and (3) Adjusting serum CRP levels, by producing a transient rise in them to counter lung infection and a latent reduction to prevent falling of lung functions.



**Figure 2 Effect of increasing the aerobic capacity on pulmonary functions.** This diagram illustrates possible mechanisms of increasing oxygenation capacity in improving pulmonary functions. These possible mechanisms include increasing the function of pulmonary immunity, restoring normal lung elasticity and strength, and decreasing coughing through autoimmune regulations. COVID-19: Coronavirus disease 2019; Ig: Immunoglobulin; IL: Interleukin; NK: Natural killer; TNF-α: Tumor necrosis factor-alpha.

**The influence of enhancing oxygenation on lung tissues elasticity and strength**

Enhancing oxygenation can significantly enhance the pliability of lung tissues and increase the strength and stamina of respiratory muscles. A short-term increase in oxygenation can increase lung tissue elasticity and recoil properties. Guimarães *et al* [60] studied the influence of aerobic exercise on the incidence of an artificially created emphysema in rats. They observed that the performance of mild aerobic exercise for 4 wk significantly increased lung biomechanics and flow acceleration ratio by decreasing lung hyperinflation and increasing elasticity and strength of lung tissues. Park and Han[61] examined the effect of performing regular aerobic exercise on peak expiratory lung capacity in elderly females. They observed that the performance of mild aerobic exercise for 20 min and lasting for 12 wk significantly increased alveoli functions and lung pliability. Taskin *et al*[62] examined the influence of aerobic exercise on respiratory muscle strength in people with ankylosing spondylitis. They observed that the performance of mild aerobic exercise for 40 min/d and lasting for 12 wk significantly augmented the end maximal exercise capacity, respiratory muscle strength, and inspiratory muscle performance and lessened dyspnea perception.

**The influence of enhancing oxygenation as an antioxidant**

Enhancing oxygenation has an antioxidant role to diminish free radicals and oxidative stress in the blood. Free radicals, like reactive oxygen species, are formed during ordinary cellular functions as one of the normal physiological mechanisms in all living creatures. Free radicals play both useful and poisonous effects. Once serum-free radicals extremely raise and can no longer be handled, they lead to an oxidative stress [63]. Oxidative stress can significantly help in the development of numerous diseases, amid them lung infection and diseases[63,64]. Mild aerobic exercise can aid in the

removal of these increased serum free radicals and decrease the incidence of lung infection and disorders such as pneumonia and ARDS.

Also, enhancing oxygenation increases the body's resistance to consequential oxidative challenges by enhancing the mitochondrial function and permitting enhanced oxygenation of body and lung tissues[63,65]. Toledo *et al*[66] studied the influence of aerobic exercise on the incidence of pulmonary disorders in rats. They assessed the reactive oxygen species as a biomarker of the beginning of lung disorders. They observed that mild aerobic exercise implemented for 24 wk significantly decreased serum reactive oxygen species in the bronchoalveolar lavage fluid in rats. They concluded that increasing oxygenation is vital to inhibit or reduce the worsening of ARDS and pneumonia. Da Cunha *et al*[67] studied the consequence of performing aerobic exercise on induced oxidative stress by an artificially occurring lung injury in rats. They observed that the performance of mild aerobic exercise for 20 min significantly inhibited the accumulation of nuclear factor kappa B/p65, reactive species, and nitrite amounts. They proposed that mild aerobic exercise may have a major function as a protector to counter the development of recent lung inflammation.

### ***The influence of enhancing oxygenation on the cough mechanism***

Enhancing oxygenation can decrease coughing in patients with COVID-19; this mainly occurs through modulating the autonomic nervous system over mucociliary clearance [68,69]. Borghi-Silva *et al*[69] examined the consequence of routine aerobic exercise on the function of lungs in patients with chronic obstructive pulmonary disease. They observed that performing mild aerobic exercise for 6 wk significantly reduced respiratory rate and elevated the tidal volume during exercise; these changes mainly occurred due to autonomic modulations, which caused a decrease in the heart rate. Recently, Leite *et al*[68] explored the influence of aerobic exercise on the cough and function of autonomic nervous system in patients with chronic obstructive pulmonary disease. They observed that performing 12 wk of mild aerobic exercise significantly reduced the cough and heart rate. The influence of enhancing oxygenation on reducing heart rate might be valuable in lessening dyspnea observed in patients with COVID-19[69]. Thus, performing mild aerobic exercise might significantly reduce both cough and dyspnea, which often arise in patients with COVID-19 over breathing exercise as they significantly control the parasympathetic nervous system leading to a major drop in these two signs.

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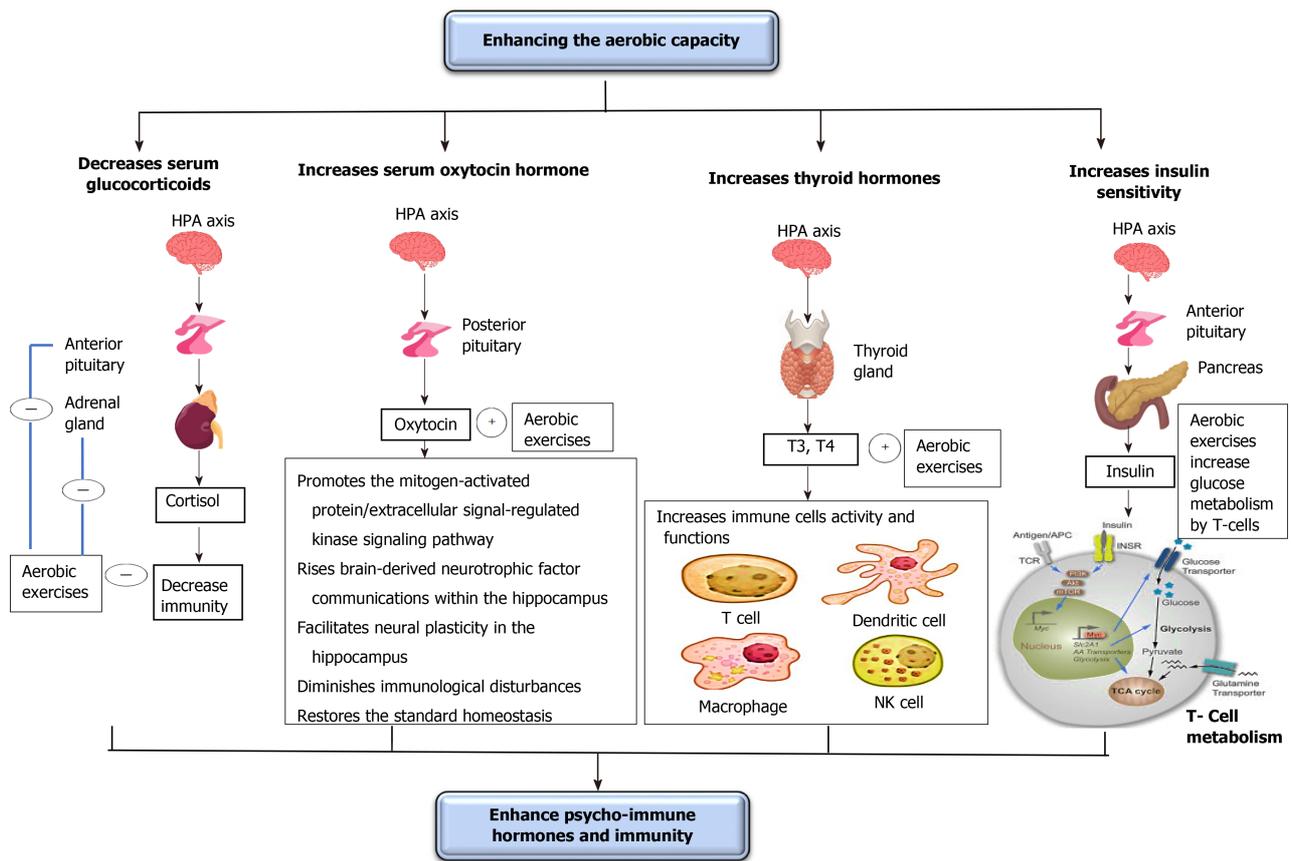
## **THE INFLUENCE OF ENHANCING OXYGENATION ON PSYCHO-IMMUNE HORMONES AMONG PATIENTS WITH COVID-19**

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Psychological problems usually occur in both healthy people throughout the lockdown (who have difficulty going to psychiatrists) and patients with COVID-19 (who are waiting for the death to come at any moment)[70]. These psychological problems can significantly decrease immunity and cause the development of several disorders including diabetes and hypertension. Thus, controlling these psychological problems is a must to either decrease COVID-19 associated disorders and death rates or prevent the development of other disorders (diabetes and hypertension). This subtopic discusses the influence of enhancing oxygenation on renormalizing the psycho-immune hormones, mostly those involved in the fight or flight reaction, including glucocorticoids (GCs), oxytocin, thyroid (THs), and insulin hormones through clarifying the impact of regulation of these hormones on enhancing immune functions essential to counter COVID-19. The effects of increasing the oxygenation on psycho-immune hormones are illustrated in [Figure 3](#).

### ***The influence of enhancing oxygenation on decreasing serum glucocorticoids***

GC release starts by stimulating the hypothalamus to secrete corticotropin-releasing hormone (CRH) and arginine vasopressin. CRH-containing neurons, present in the hypothalamus (paraventricular nucleus), attach to the noradrenergic areas in the spinal cord and brainstem. The locus coeruleus of the brainstem directly connects with the autonomic nervous system neurons in the brainstem and spinal cord[71]. Stress activates the locus coeruleus to stimulate the sympathetic activity through triggering  $\alpha 1$ -adrenoceptors and inhibit the parasympathetic activity through activation of  $\alpha 2$ -adrenoceptors[71]. The sympathetic nervous system activation increases the secretion of CRH from the paraventricular nucleus of the hypothalamus causing a stimulation of the hypothalamic-pituitary-adrenal axis to secrete adrenocorticotrophic hormone



**Figure 3 Effect of increasing the aerobic capacity on psycho-immune hormones.** This diagram illustrates the possible mechanisms of increasing oxygenation capacity in improving the psycho-immune hormones and immunity. These possible mechanisms include decreasing serum glucocorticoids and insulin sensitivity and increasing glucocorticoids and oxytocin hormones. HPA: Hypothalamic-pituitary-adrenal; NK: Natural killer.

(ACTH) from the anterior pituitary gland[71].

Adrenocorticotrophic hormone, in turn, activates the release of GCs from the adrenal cortex[72]. These GCs act as transcript factors to control cell functions, even after the stoppage of acute stresses. GCs can overwhelm immunity and avert the central secretion of inflammation mediators (leukotrienes and prostaglandins); this happens as a result of the decreasing effect of GCs on the action and function of immune cells (T-lymphocytes, B-lymphocytes, macrophages, neutrophils, basophils, eosinophils, and mast cells)[73,74].

Short periods of aerobic exercise can significantly decrease serum GCs, arginine vasopressin, and CRH. Lu *et al*[75] studied the influence of aerobic exercise on GC receptor message on blood leukocytes in healthy and asthmatic young persons[75]. They detected that regular mild aerobic exercise performed for 8 wk significantly declined the GC receptor message on blood leukocytes. Hill *et al*[76] investigated the influence of aerobic exercise on serum GCs in moderately skilled athletes[76]. They observed that the performance of low aerobic exercise for 30 min significantly reduced serum GCs. Silva *et al*[77] examined the influence of aerobic exercise on GC receptor communication in rats[77]. They observed that the performance of mild aerobic exercise for 60 min with 50% of maximal exercise capacity significantly reduced the communication of the GC receptors in rats. Fediuc *et al*[78] investigated the influence of aerobic exercise on sensitivity of the hypothalamic-pituitary-adrenal axis and serum GCs in Sprague-Dawley rats[78]. They found that the performance of mild intensity aerobic exercise for 5 wk significantly declined both serum GCs and sensitivity of the hypothalamic-pituitary-adrenal axis.

**The influence of enhancing oxygenation on increasing serum OX hormone**

OX hormone is produced from magnocellular and parvocellular neurons inside the paraventricular nucleus and the supraoptic nucleus of the hypothalamus and then is transmitted by axonal transport to the posterior pituitary where it deposits until its secretion into the blood. OX hormone receptors exist in many regions of the brain, including the cerebral cortex, hypothalamus, hippocampus, amygdala, and nucleus

accumbens[79].

The increase in serum OT levels can help in decreasing stress, anxiety, and depression; however, the actual mechanisms by which the OT system decreases these disorders are still unclear[79]. However, the importance of increasing oxygenation on enhancing OT function still needs more investigations particularly on humans.

Numerous studies have shown that OT has a significant antidepressant function in diminishing anxiety and stress[80-84]. The antidepressant function of OT may occur due to enhancing the mitogen-activated protein/extracellular signal-regulated kinase signaling path and intensifying brain-derived neurotrophic factor communications within the hippocampus; this enhancing the neural plasticity function in the hippocampus[79]. Also, OT plays an important role in diminishing immunological disturbances and returning the standard homeostasis because its relationship with several usual immune cytokines, such as IL-1 $\beta$ , in addition to prostaglandins, endocannabinoids, nitric oxide, and nitric oxide[85].

Short periods of aerobic exercise can increase blood OT, which promotes both decreasing stress, anxiety, and depression and increasing immune functions. Yüksel *et al*[86] examined the influence of aerobic exercise on serum OT in female mice[86]. They observed that the performance of mild aerobic exercise for 6 wk significantly elevated serum OT and this helped in reducing anxiety. Arabacı Tamer *et al*[87] studied the influence of aerobic exercise on oxytocinergic motion in rats[87]. They detected that the daily repetitive moderate aerobic exercise for 30 min for 5 d significantly reversed the artificially produced negative-regulated oxytocinergic motion. Martins *et al*[88] studied the influence of aerobic exercise on serum OT in mice[88]. They detected that the performance of mild-aerobic exercise for 3 mo significantly elevated serum OT.

### **The influence of enhancing oxygenation on increasing serum TH hormones**

The TH gland activity usually decreases in stressful circumstances. In stress, serum 3,5,3',5'-tetraiodothyronine thyroxine (T4) and 3,5,3'- triiodothyronine (T3) decay, and the TH-stimulating hormone (TSH) release ceases as a consequence of the rise of serum GCs[89,90]. TH hormones, principally T3 and T4, are indispensable hormones in controlling numerous functions in human bodies, such as oxygen utilization, protein, lipid, and carbohydrate absorptions, adolescence, intermittent bleeding, and stress lessening[90].

In humans, various neurons in the paraventricular nucleus of the hypothalamus, mainly parvocellular zone, stabilize the hypothalamic-pituitary-TH axis activity. The hypothalamic-pituitary-TH axis triggers the release of thyrotropin-releasing hormone into the median eminence. The thyrotropin-releasing hormone triggers the frontal pituitary gland to release TSH. TSH voyages throughout peripheral vessels to activate the release of T3 and T4 from the TH gland. T4 generally transmutes into T3 by deiodinase enzymes present in the utmost body tissues. TH hormones have adverse feedback function by exciting T hormone receptors present in the pituitary and hypothalamus to stop the release of TSH[89,91].

The decrease in serum TH hormones, mainly T3 and T4, can decrease the function of various immune cells (*e.g.*, lymphocytes, monocytes, natural killer cells, and macrophages), consequently decreasing the activity of various infection-related processes, including chemotaxis, phagocytosis, cytokines release, and reactive oxygen species production. The real mechanisms behind this relationship are still unclear[92, 93]. Preceding studies have demonstrated that patients with hyperthyroidism usually have a rise in the activity of macrophages, leukocytes, and lymphocytes[94,95]. Other studies have demonstrated opposite outcomes in patients with hypothyroidism[96,97].

Short periods of aerobic exercise can significantly increase serum T3. Altaye *et al*[98] investigated the influence of continued aerobic exercise on the alteration in serum TH hormones in teenagers with intelligence debilities[98]. They detected that routine mild aerobic exercise for 3 mo significantly raised serum T3, T4, and TSH. Fathi *et al*[99] examined the influence of aerobic exercise on TH hormones in obese postmenopausal females[99]. They observed that mild aerobic exercise implemented for 8 wk significantly increased serum T3, T4, and TSH levels. Rone *et al*[100] studied the influence of serum T3 in males[100]. They observed that athletes had greater serum T3 than sedentary controls during kinetic analysis.

### **The influence of enhancing oxygenation on decreasing insulin resistance**

Insulin is considered a peptide hormone released by the  $\beta$ -cells present in the pancreatic islets of Langerhans. Insulin maintains normal serum glucose by facilitating the digesting of cellular glucose to facilitate carbohydrate, protein, and lipid metabolism and promote cell splitting by its mitogenic characteristics[101]. Stress causes an increase in serum insulin; if the stress continues for longer periods, it causes

insulin exhaustion, serum glucose elevation, and diabetes mellitus (DM) occurrence [101,102]. Insulin resistance upsurge is a compensatory mechanism to sustain ordinary serum glucose. The dysfunction of this compensatory mechanism causes an increase in serum glucose and the development of DM. Insulin also has a direct connection with numerous hormones, such as growth hormone, GCs, glucagon, norepinephrine, and epinephrine because all these hormones participate in the control of glucose and carbohydrate digestion and undergoes the same neural control [103]. Several studies have revealed there is a direct relationship between prolonged psychological stress and the depletion of insulin and the development of DM [104-106]. Also, several studies have reported that DM leads to a decline in immunity strength, though the actual mechanisms by which low insulin level or increased insulin resistance causes a decrease in immunity strength are not clear yet [107-109]. It might be that insulin has a crucial role in glucose metabolism, which is vital in delivering vitality to immune cells against viral infection.

Enhancing oxygenation can increase insulin levels and enhance glucose metabolism. The increase in insulin production might be caused by the influence of increasing the oxygenation on lowering serum GCs. There is strong evidence in the literature to support the beneficial role of implementing aerobic exercise on increasing glucose metabolism and insulin sensitivity [110-114]. Winnick *et al* [110] studied the influence of aerobic exercise on the sensitivity of insulin in overweight persons having type II diabetes [110]. They observed that the performance of aerobic exercise for a week significantly elevated insulin sensitivity. Schwaab *et al* [111] compared the influence of anaerobic and aerobic training on glucose tolerance in persons with type II diabetes and coronary artery illnesses [111]. They observed that aerobic exercise implemented for 16 wk, unlike anaerobic exercise, significantly reduced glucose tolerance. Karstoft *et al* [112] examined the influence of mild aerobic exercise on physical fitness, glycemic control, and body structures in persons with type II diabetes [112]. They observed that alternating mild and high aerobic exercise implemented for 4 mo significantly elevated insulin sensitivity and reduced glycemic control. Nassis *et al* [113] investigated the influence of aerobic exercise on insulin sensitivity between overweight girls [113]. They observed that the performance of mild aerobic exercise for 12 wk significantly reduced insulin sensitivity.

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## THE DEFENSIVE ROLE OF ENHANCING OXYGENATION ON COVID-19 RISK FACTORS

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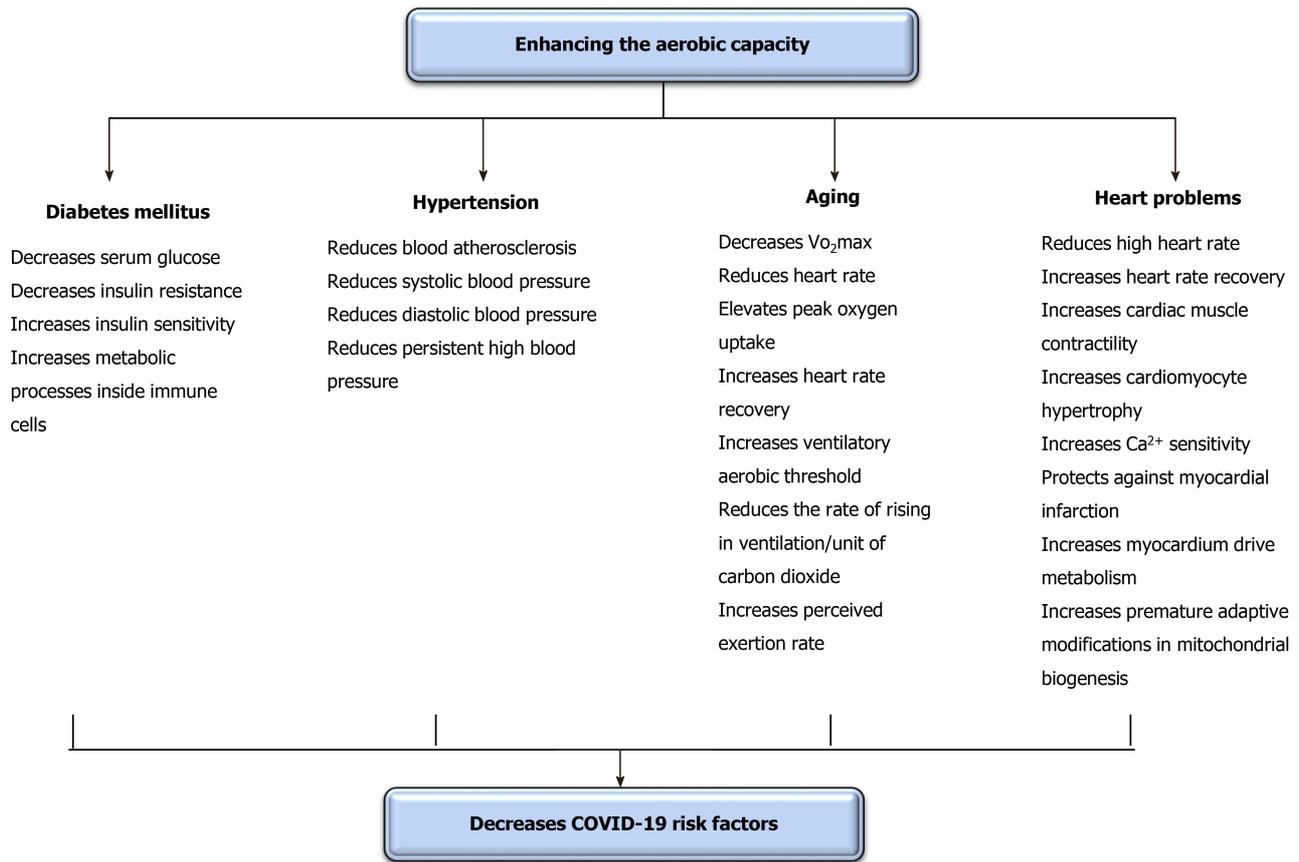
Brief periods of aerobic exercise can significantly regulate COVID-19 risk factors. Interestingly, this effect in some studies occurred after a single session only. Thus, this subtopic mainly focuses on the instantaneous and short-term influence of enhancing oxygenation on COVID-19 risk factors as these risk factors can increase spread and progress rates [47]. The communal risk factors occurring with COVID-19 are hypertension, aging, heart problems, and diabetes [115]. The defensive role of enhancing oxygenation on risk factors of COVID-19 is illustrated in [Figure 4](#).

### **DM**

DM negatively affects numerous body structures [116], including immunity [117] and pulmonary functions [118]. Enhancing oxygenation can cause an immediate decline in serum glucose in both types of DM. Yardley *et al* [119] studied the immediate influence of aerobic *vs* anaerobic exercise on serum glucose in individuals with type I DM [119]. They observed that 45 min of mild aerobic exercise significantly reduced serum glucose more than resistance exercise. However, this reduction quickly returned to the pre-exercise level following the session. Bacchi *et al* [120] studied the immediate influence of aerobic *vs* anaerobic exercise on serum glucose in individuals with type II DM [120]. They observed that, unlike anaerobic exercise, mild aerobic exercise significantly reduced serum glucose during the session and for the following entire night. Yokoyama *et al* [121] studied the temporary influence of aerobic exercise on stiffness of arteries in peoples with type II DM [121]. They observed that 45 min of mild aerobic exercise implemented for 3 wk significantly reduced the stiffness of common carotid and femoral arteries, and this decrease was accompanied with an improvement in tissue resistance to insulin.

### **Hypertension**

Short periods of aerobic exercise can yield an acute substantial decrease in high blood



**Figure 4** Effect of increasing the aerobic capacity as a defensive role in coronavirus disease 2019. This diagram illustrates possible mechanisms of increasing oxygenation capacity to decrease the severity of coronavirus disease 2019 risk factors, associated disorders, and death rates. The effects of increasing the oxygenation capacity include its effects in decreasing the incidence of diabetes mellitus, hypertension, aging, and heart problems. COVID-19: Coronavirus disease 2019.

pressure (BP)[122]. Ciolac *et al*[123] inspected the influence of aerobic exercise on BP in persons with lasting untreated hypertension[123]. They observed that just a seldom session of aerobic exercise significantly declined ambulatory BP. Lund *et al*[124] inspected the influence of aerobic exercise on ambulatory BP amid woman cleaners [124]. They observed that one session of aerobic exercise significantly reduced ambulatory BP, and this reduction continued for 25 h after the session. Guimarães *et al* [125] studied the influence of immediate aerobic exercise in warm water on general BP in people with resistant hypertension[125]. They detected that performing mild aerobic exercise for 2 wk significantly declined systolic BP and diastolic BP and cardiovascular size either subsequent the exercise or through the subsequent 24 h. Nascimento *et al*[126] studied the instant and extended influence of aerobic exercise on BP in people with resilient hypertension[126]. They detected that mild aerobic exercise implemented for 8 wk significantly decreased BP.

**Aging**

Aging significantly reduces bodily function and activity exposing these structures to dysfunction and failure. Older patients with COVID-19 commonly have greater death rates than younger patients. Thus, reducing the influence of aging on body structures could assist in reducing these death rates. Giallauria *et al*[127] studied the influence of mild aerobic exercise on recovery of normal heart rate in older adults. They observed that the performance of mild aerobic exercise for 8 wk significantly elevated peak oxygen uptake, heart rate recovery, and ventilatory aerobic threshold and reduced the rate of rising in ventilation/unit of carbon dioxide release anticipating that mild aerobic exercise can modify the autonomic nervous system activity by raising the vagal/sympathetic balance. Chapman *et al*[128] studied the acute influence of mild aerobic exercise on cardiovascular fitness in older adults. They observed that a routine of mild aerobic exercise for 6 wk significantly enhanced both perceived exertion rate and  $VO_{2max}$ .

### Heart problems

Heart and pulmonary problems usually come with together. Thus, heart problems could increase the declined rate in lung function and disorders (heart-lung interaction) [129-131]. Enhancing oxygenation can cause significant short-term enhancements in heart disorders. The immediate and chronic enhancements in heart, functions, rates, and volumes were demonstrated in the preceding paragraph [54,127,128]. Animal studies have demonstrated that the performance of mild aerobic exercise significantly improves heart functions. Wisløff *et al* [132] studied the short-term influence of aerobic exercise on cardiac muscle contractility, cardiomyocyte hypertrophy, and  $Ca^{2+}$  sensitivity in rats after an artificially-induced myocardial infarction. This study detected that a routine of mild aerobic exercise performed for 8 wk significantly enhanced cardiac contractility and  $Ca^{2+}$  sensitivity and reduced the hypertrophy of cardiomyocytes. Tao *et al* [133] studied the impact of aerobic exercise in ending the artificially-produced acute myocardial infarction in mice. They observed that the performance of mild aerobic exercise for 3 wk significantly protected rats from acute myocardial infarction by enhancing myocardium driven metabolism and inducing premature adaptive modifications in mitochondrial biogenesis.

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## AEROBIC EXERCISE PRESCRIPTIONS IN PATIENTS WITH COVID-19

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This subtopic intends to scrutinize the previous studies that examined the influences of aerobic exercise on immunity amid healthy individuals as an effort to afford aerobic exercise prescriptions for patients with COVID-19. In this section, we analyzed eleven studies [19,20,37,46,134-140] performed on healthy subjects and accomplished an increase in immunological markers [141]. The recommendations and prescriptions of aerobic exercise for patients with COVID-19 are shown in Table 1.

### The type of aerobic exercise

The type of aerobic exercise implemented in the discussed studies were chiefly running and cycling. Most of the included studies implemented pedaling [19,134-138, 140], while the other studies implemented either running [37,139] or both pedaling and running [20,46]. Based on these findings, treadmill biking or running would be the appropriate type of aerobic exercise in patients with COVID-19. Also for older patients or patients who have balance problems, the bicycle may be a decent selection for them [142].

### The intensity of aerobic exercise

The intensity of aerobic exercise performed in the previous studies was measured by maximum heart rate (MHR) or  $VO_{2max}$ . In the studies that were implemented for short times, most of them implemented aerobic exercise using  $VO_{2max}$  as the main indicator to determine its intensity, and mostly the intensity ranged from 55% to 85%  $VO_{2max}$ , including two studies used 55%  $VO_{2max}$  [19,134], two studies used 55%-85%  $VO_{2max}$  [136, 140], one study used 60%  $VO_{2max}$  [137], and one study used MHR instead of  $VO_{2max}$  at 60%-70% MHR [139]. In the studies that were implemented for prolonged times, most of them implemented aerobic exercise using MHR the main indicator to determine its intensity, and mostly the intensity ranged from 60%-80% MHR including one study used 60%-75% MHR [37], one study used 70%-80% MHR [135], one study used 70%  $VO_{2max}$  [20], and one study used 75%  $VO_{2max}$  [138]. Based on the aforementioned intensities, implementing aerobic exercise at an intensity range from 55% to 85%  $VO_{2max}$  would be the recommended intensity in patients with COVID-19. The starting intensity should be determined personally to avoid the development of exhaustion [143] because exhaustion can adversely affect immunity [144]. Thus, aerobic exercise should be graded starting from light activity through performing extended warming-up and cooling-down, then a rise in the intensity should followed.

### The duration of aerobic exercise

The duration of aerobic exercise performed in the earlier studies fluctuated from 18-80 min. In the studies that studied the immediate effects of aerobic exercise, the time of the session fluctuated from 18 to 60 min [136,140], two studies implemented exercise for 45 min [134,139], and two studies implemented exercise for 60 min [19,137]. In the studies that tested the long-term effect of aerobic exercise, the duration of the session ranged from 30 to 80 min, including one study implemented exercise for 30 min [138], one study implemented exercise for 45 min [135], one study implemented exercise for 50 min [37], one study implemented exercise for 60 min [46], and one study used a

**Table 1** This table shows the recommended aerobic exercise settings in patients with coronavirus disease 2019, including type, intensity, duration, and frequency of aerobic exercise

	Type of exercise	Intensity of exercise	Duration of exercise	Frequency of exercise
Aerobic exercise recommendation and prescriptions	Cycling	55%-85% VO <sub>2max</sub>	18-60 min	2-3 sessions/wk
	Light running	60%-80% MHR		

MHR: Maximum heart rate.

specific distance (5 km) instead of a duration[20]. Therefore, 20-60 min of aerobic exercise can be a fitting time of the aerobic exercise session for patients with COVID-19. If the patient is sedentary and cannot perform the session time without exhaustion, day-to-day several short bursts of aerobic exercise could be used.

### The frequency of aerobic exercise

The frequency of aerobic exercise performed in the earlier studies fluctuated from 1 session/wk to 3 sessions/wk. In the studies that studied the short-term effects of aerobic exercise, exercise frequencies included: 4 studies implemented aerobic exercise for only 1 session[136], 1 study implemented aerobic exercise for 2 sessions (one session/wk)[19], and 1 study implemented aerobic exercise for 3 sessions for only a week[134]. In the studies that studied the long-term effect of aerobic exercise, exercise frequencies included: 1 study implemented aerobic exercise for 2 sessions/wk for 8 wk [46], one study implemented aerobic exercise for 3 sessions/wk for 5 wk[20], one study implemented aerobic exercise for 3 sessions/wk for 9 wk[138], one study implemented aerobic exercise for 3 sessions/wk for 10 wk[135], and one study implemented aerobic exercise for 3 sessions/wk for 12 wk[37]. Based on the aforementioned findings, the frequency of 3 sessions/wk can be helpful and safe in patients with COVID-19.

Limitations of this review include that most comprised studies were conducted on animals as a result of the deficiency of human studies addressing these intended effects, predominantly infection-related ones. Also, the searched databases were the most cited ones to ensure the quality of the included studies.

## CONCLUSION

Improving oxygenation in patients with COVID-19 is crucial because it has a significant role in improving immune and pulmonary functions. In addition, it helps in decreasing COVID-19 risk factors that increase the severity of symptoms. Finally, it helps in controlling hormones that are involved in bodily infection-fighting mechanisms. To increase immunity, particularly immunological markers, patients with COVID-19 should implement a continuous aerobic exercise session at an intensity of 55%-80% of VO<sub>2max</sub> or 60%-80% of MHR for 2-3 sessions/wk with a duration of 18-60 min/session and using cycling ergometer or light running because these specifications could enhance immunity without developing fatigue or exhaustion.

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