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REVIEW

Influence of Physical Exercise Practice Against SARS-CoV-2 (COVID-19) Infection: Narrative Review

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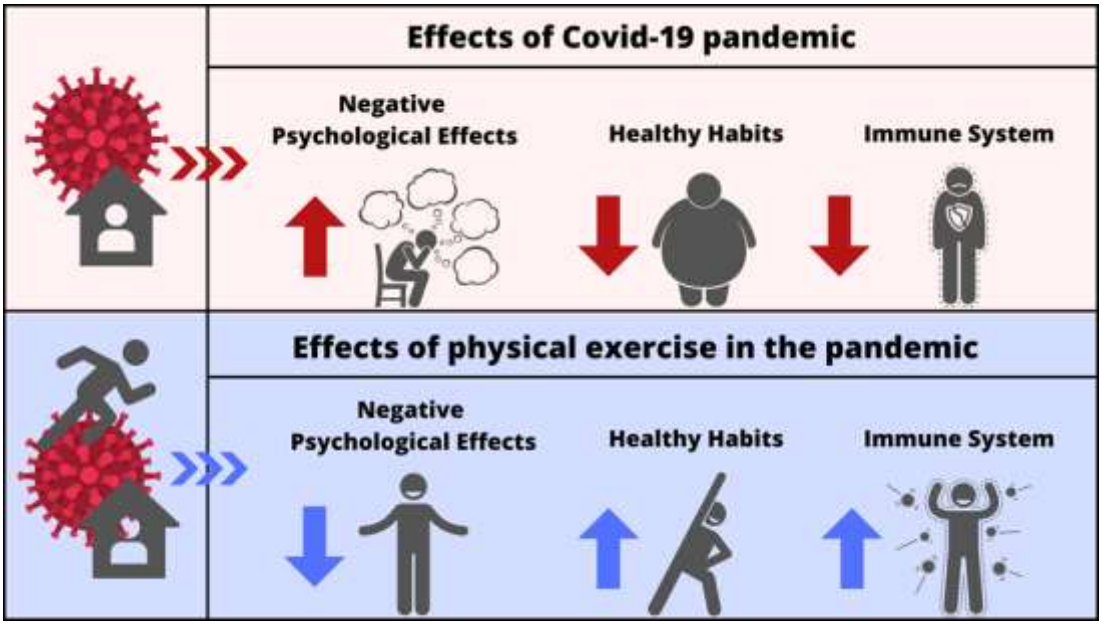
Abstract:

As a protective measure against the Covid-19 virus, the world health organization strongly recommended social isolation. Because of a decreased option of physical exercise, there was an increase in the number of physical inactivity, poor diet, and psychological disorders. In this sense, this literature review aims to address how the practice of physical exercise is important to protect the metabolic and psychological health of the population. During forced isolation, it was possible to observe an increase in sedentary lifestyle and poor diet choices. As an outcome, possible damage to the population's mental health was also identified. In contrast, it was observed that individuals who practiced physical exercise, managed to mitigate both metabolic and psychological damage. Ahead, it was also possible to observe that this practice significantly contributed to the individuals' immune system, which may collaborate with the organism in the fight against possible contamination. The main objective of this review was to identify possible implications of physical exercise on psychological and immunological aspects in coping with Covid-19. Important physiological effects of exercise were described, such as elevation of the brain-derived neurotrophic factor (BDNF), which has beneficial effects in controlling depression and cognitive performance; the control of obesity through specific training methodologies can collaborate to control pro-inflammatory cytokines and increase mitochondrial function and immune system. In addition, there are up to 205 symptoms after infection by SARS-CoV2 and physical exercise can be a great ally for recovery. Therefore, it is believed that regular exercise has positive effects over, and post-pandemic issues.

Keywords: COVID-19, Depression, Health promotion, Exercise, Immune system

Introduction



Considering the onset and evolution of the disease caused by the SARS-CoV-2 (Covid-19) virus, in practically a year and a half, the world has more than 466 million people infected and 6,06 million killed by the disease (1). Initially Patrick, Walker (2) projected that the number of infected in 2020 was 7 billion people and 40 million deaths worldwide if interventions have abstained. Thus, as measures of prevention and non-pharmacological control of the disease, social distancing standards, protection of the elderly, use of personal protective equipment, among others, were initiated (3).

Social distancing was accompanied by temporary shutdown of establishments that provided some form of agglomeration and thus dispersion and contamination by the virus, therefore, numerous places considered as non-essential were closed such as restaurants, pubs, beauty salons, among them gyms and sports centers. Social isolation changed social behaviors and caused feelings of loneliness, anxiety, fear, and psychosocial suffering that triggered psychological depression (4). In addition, new investigations suggest that SARS-CoV2 infection can cause neurological complications due to the virus entering by airways and reaching the central nervous system (CNS) (5). Furthermore, changes in eating habits were significant, there was a greater consumption of fried foods, snacks between meals, binge eating, and the use of alcoholic beverages during the week (4). Along this period, there was a decrease in the practice of physical exercise at all levels from mild to intensive, causing a greater accumulation of fat and body change during the pandemic (4, 6).

The regular practice of physical exercises is associated with the control of body weight can increase mechanisms of caloric expenditure (7), general immunity of the body through higher levels of lymphocytes, control of C-reactive protein, improvement intrinsic antioxidant and antibiotic control, besides improving the

immune response of the cell (8). Finally, physical exercise is associated with increased hippocampal neurogenesis and control of serotonin release, being a tool for the treatment of depression and cognitive improvement (9).

Thus, it is possible that regular exercise can have beneficial effects on vehicles related to the coronavirus pandemic. However, to our knowledge, there is no review to date that has correlated the various benefits of physical exercise with the problems generated by Covid-19. Therefore, the objective of this review was to seek and identify, based on the current scientific evidence, how physical exercise can act against the infection of SARS-CoV-2 and their consequences.

Obesity and covid-19

The expression of Angiotensin 2 converting enzyme (ACE2) in adipose tissue is significantly higher than in other regions of the body, which makes it a possible viral deposit (10, 11). One of the ways that the novel coronavirus infect the body is binding to ACE2 receptors. ACE2 is a homolog of the angiotensin-converting enzyme (ACE) and plays an essential role in the renin-angiotensin-aldosterone system (RAAS). ACE2 is present in several epithelial cells such as the heart, lung, kidney, gastrointestinal tract, and blood vessels, facilitating their interaction with the virus (12), the imbalance of this system can be caused by drugs, comorbidities, or dietary relationships such as increased sodium intake, foods with high-fat content, and high fructose intake (13).

The glycoprotein spike, in contact with the ACE2 receptor on the cell, awakens the type II transmembrane serine protease enzyme known as TMPR552. This interaction between the virus and the ACE2 receptor, triggers TMPR552 to cleave this complex, causing a fusion between the virus and the cell membrane, leaving the viral genome with free access to enter the cell (12).

Obesity is responsible for numerous comorbidities, such as type 2 diabetes, hypertension, excess blood cholesterol, and others (14). They are considered risk factors for Covid-19 infection, due to their interference with the angiotensin-converter enzyme 2 (ACE2), angiotensin-converter enzyme (ACE) system (13, 14). As a result of quarantine, social isolation has generated a series of changes in the daily habits of thousands of people (6). Changes in body composition were observed by changes in diet, routine and decreased physical exercise (4, 6).

An elegant study published by Cai et. al (15) investigated the influence of obesity on the worsening of Covid-19 and observed that obese people were up to 1.84 times more likely to progress to severe conditions of the disease. In another study severely obese patients with a Body Mass Index (BMI) 35 kg/m2 were three times more likely to be admitted to intensive care compared with patients in the same age category with BMI 30 kg/m2 (16). Still, obese people had a higher frequency of coughing and had higher febrile conditions than eutrophic people. However, the cardiorespiratory condition can be an important factor in defining their health. Characterized as the obesity paradox; people who have a better cardiorespiratory condition and less fat accumulation in the central region, have better survival and fewer cardiovascular problems (14).

Exercise and immunological system

The symptoms and aggravations of COVID-19 is relatively restricted to the individual's immunological health (17). SARS-CoV-2 causes an excessive immune reaction, releasing the "*cytokine storm*" that can lead to pulmonary edema due to microthrombi caused by dysregulation of RAAS due to increased virus binding to ACE2 receptors (17, 18). Obesity, aging, chronic lung disease, heart disease, and metabolic disorders are ideal conditions for the worsening of Covid-19 (19). The inadequate antiviral response caused by these factors favors the infiltration of chemokines (such as CCL2, IFNγ-induced protein 10 [IP-10], and CCL3) in the lung as, by the various pro-inflammatory cytokines such as interleukins (IL-6, IL-8, and IL-1β) and tumor necrosis factor-a (TNF-α), leading to severe cases (19, 20).

In this context, mitochondrial function is closely related to body weight control. Among the roles played by mitochondria is the synthesis of adenosine triphosphate (ATP) and the increase in its density may be responsible for muscle oxidative capacity, improvement of cellular functioning, and, consequently, interference in the daily basal caloric expenditure and physiological maintenance, that is, it can act to reduce free radicals that are harmful to the different cells of the body. (21, 22). Improvement of mitochondrial function is found essentially in the practice of exercise and with a healthy diet (23). Physical exercise can increase the size and effectiveness of mitochondria, improving immunity patterns and antioxidant responses (22). Heo et. al (24) identified that 12 weeks of physical exercise were sufficient for muscle remodeling and apoptotic control in obese mice. This response was found due to the control of apoptotic proteins (Bax and Cytochrome c) together with an improvement in mitochondrial permeability. Based on this, the practice of physical exercise has shown beneficial results in extreme cases of some diseases. Individuals with cancer, for example, undergoing chemotherapy had a wide improvement in the levels of cytokines, fatigue, and antioxidant activity through the practice of aerobic exercises of moderate intensity (25-27).

Moreno et. al (23) suggest that mitochondrial dysfunction is the trigger for all "*cytokine storm*" in Covid-19. One of the mechanisms of this mitochondrial dysregulation can alter the levels of Type I interferons (IFN-I) which are responsible for the central control of the antiviral state in non-immune cells through the inhibition of viral replication, activation of the adaptive and already acquired immune response (23, 28). Mitochondrial dysfunction is strongly related to increased fat accumulation during the aging process (21). Mitochondrial malfunction leads to dysregulation of the energetic process, inhibition of autophagic pathways, the release of pro-inflammatory cytokines, influence on respiratory capacity, insulin resistance, associated with type 2 diabetes and, mainly, on the immune system (7, 29, 30). Damage to mitochondria is caused by the aging process and metabolic diseases such as obesity (23).

The performance of moderate exercises can favor the increase of immunoglobulins and T lymphocytes (8). Divided into IgA, IgE, IgM, and IgG, immunoglobulins are considered one of the first lines of defense of the body present in the mucous membranes of the airways, they can hinder the entry of infectious viral agents (31). Unfortunately, no studies were found that sought to identify levels of IgG and other immunological parameters in athletes and sedentary individuals with Covid-19 infection. However, Saygin et. al (32) sought to identify the levels of IgA, IgG, IgM, complement C3 and C4 in sedentary individuals, distance running athletes and volleyball athletes. It was found that the levels of these immunological parameters were correlated with physical exercise. An

interesting fact that Saygin et. al (32) found was that volleyball athletes had a greater positive trend compared to long-distance runners, which can be explained by the high physiological demand. Therefore, data like this can serve as support to identify why athletes have fewer symptoms when they are infected with Covid-19.

Karacabey et. al (33) show that performing 30 minutes of moderate aerobic exercise, was able to improve the levels of IgM and IgG after 5 days. In addition, Mohamed et. al (8) in their review brings together a series of evidence of the acute effect of moderate aerobic training on immunoglobulin levels. Different training methods are used according to physical capabilities or specific goals to be developed. In recent years, the high-intensity interval training method (HIIT) and its variations, have been a great tool for weight loss and increased cardiorespiratory function. Zhang et. al (34) identified that methodologies of high-intensity training, 90% + of the maximum oxygen volume (VO2max) were superior to the traditional continuous method, with significant results in the reduction of visceral fat and increase in the peak oxygen volume (VO2peak), making it a strategy for weight control and increased respiratory condition.

The HIIT methodology can be adapted to several exercises in addition to having a short training period compared to the traditional continuous method (34). Pre-diabetic individuals performed different training methodologies for 12 weeks to verify the influence in the reduced blood glucose and insulin resistance. The HIIT training and continuous training methodologies (performed in the fatmax zone) proved to be effective for the reduction of glucose and insulin resistance and without significant difference between them. Thus, despite the longer duration, continuous exercise may prove to be a less stressful alternative for the body with effects as HIIT training, contributing to the control of risk factors for covid-19 and other diseases (35). Thus, we believed that the method HIIT would become an excellent tool for the control and increase of cardiorespiratory function, control of the immune system, and treatment of diseases, and can be performed at home and in a small space, during the lockdown period in healthy.

It's known that diabetes is a risk factor for Covid-19 infection because it affects the immune system (19). In a study carried out in monocytes, it is believed that the availability of glucose is integrally involved in the capacity for viral replication. Using monocytes from obese/diabetic humans, the increase in glucose negatively influenced the expression of ACE2 and interleukin 1 beta (IL-1β). There was also an increase in TNF-α, IL-6, and interferon (alpha, beta) (36). Medication and physical exercise are important to support its treatment (37). However, with social isolation, several gyms and sports centers were closed around the world, making it impossible to practice in the place (38). Dadgostar et. al (37) sought to analyze the effect of exercises performed under the supervision of a professional and exercises done at home following a booklet for 12 weeks in the control of type 2 diabetes. The results were positive for both groups, with reductions in waist circumference, fasting glucose and glycated glycemia, in both groups. Therefore, blood glucose control through sports can be an important ally in preventing and fighting infections caused by Covid-19.

The practice of exercises and psychological effects

In a study of 4335 people in social isolation during quarantine, it was found that 31.1% of the sample exceeded the cut-off score for a potential diagnosis of depression; 29.4% exceeded the cutoff score for health anxiety; 55.2% reported being lonely; 41.4% described a feeling of mild mental suffering (39). These conditions were accentuated in unemployed people, who live alone, among other factors (40). Strategies like a physical exercise that prevent the worsening of this situation should be analyzed, to avoid new effects of the pandemic.

As previously mentioned, physical exercise has been associated with an improvement in mild depressive disorders, neurogenesis, learning, memory, and social well-being. This connection between muscle and brain occurs through the release of myokines. During exercise, muscles release Cathepsin B, this myokine can increase the release of the brain-derived neurotrophic factor (BDNF) which, can cross the blood-brain barrier (BBB) causing hippocampal activation, improving mood, memory, and learning (41). Moon et. al (42) found that monkeys and humans had increased Cathepsin B through exercise, additionally Cathepsin B-induced cells showed increased expression of P11 protein. Svenningsson et. al (43) showed a decrease in P11 protein levels was found in animals with induced depression. Therefore, he concluded that the increase in p11 in the brain causes antidepressant effects.

Another function of physical exercise is the release of Irisin, triggering similar benefits (44). Muscle adaptation to physical exercise increases the expression of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), that is leading transcriptional regulating the energy metabolism, but can increase to the production of the membrane protein FNDC5, which when cleaved becomes Irisin and is released into the bloodstream, capable of crossing the BBB and causing the increase of BDNF (41, 45).

Exercise causes greater expression of pathways such as PGC-1α-PPARα-PPAR6 that lead to greater expression of quinurenine aminotransferase by decreasing quinurenine in blood plasma (41). Activation of the coactivator 1 alpha (PGC-1α) and peroxisome proliferator activated receptor (PPARα/δ) pathway through physical exercise plays a muscular role in the conversion of kynurenine to kynurenic acid, preventing entry into the BBB (44). Mice exposed to 8 weeks of free activity wheel, (free physical activity), resulted in an increase in gene expression of PGC-1α, additionally humans exposed to 3 weeks of planned physical exercise showed higher levels of PGC-1α , PPARα and PPARδ and potassium channels (KAT1,2,3), suggesting a therapeutic pathway through physical exercise (44).

The correct intensity and modality could be an obstacle to injury control, in some cases IL-6 can rise 100 times after acute exercise, as a form of an inflammatory response to exercise, acting as a stimulator to the immune system, inhibiting TNF-α, controlling depressive symptoms and chronic stress (46). Paolucci et. al (46) examined the influence of six weeks of different training methods on a cycle ergometer with moderate and high intensity, compared to a group of untrained ones, on factors related to mental health and pro-inflammatory cytokines as; tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), interleukin 6 (IL-6), C-reactive protein (CRP). The results demonstrate greater benefits at moderate intensity in mental health and cytokine control. This data suggests that the practice of physical exercises at a moderate intensity at home could be good relief to depressive conditions and avoid injuries caused by over-training.

Physical exercise as a means of rehabilitation after covid-19 infection

In a study conducted by Davis et. al (47) a total of 205 symptoms were found that may appear in the next 90 days of recovery after Covid-19 many of these symptoms may persist up to 7 months, including fatigue, cognitive impairment, reduced lung capacity are common symptoms after infection.

Literature has tried to explore the correlations between social habits and the possible consequences of covid-19. Mice chronically exposed to cigarette smoke had rupture of the alveolar septa, increased collagen fibers, increased reactive oxygen species. However, exposure to moderate aerobic exercise was sufficient to improve lung elasticity and antioxidant system (48). The practice of moderate aerobic exercise in water by people for 6 weeks was able to increase the inspiratory and expiratory muscle strength of the lung (49). Therefore, we believe that beyond the improvement in respiratory function after infection, moderate exercise could be a tool during the Covid-19 infection, however, it needs more targeted studies.

In this context and combined with new technologies, such as smartphones, video conferences, among others, physical exercises performed at home, can be a helper to the control of several diseases. The training performed online, proved to be an alternative for the treatment of cardiac rehabilitation, diabetes control, and body weight during the time of pandemic and lockdown (37, 38). In a study that aimed to verify the effect of virtual training, 23 subjects were submitted to 2 days of weekly low-intensity exercise for 8 weeks, investigated the effects of online exercise training on muscle adaptation, fitness, and cardiovascular parameters. The findings reveal similar effects of virtual training with the traditional control group (50).

A systematic review with 55 studies sought to assess the influence of physical exercise and increased immune response (51). The aerobic or combined physical activity (resistance training + aerobic) performed in moderate to vigorous activity had the levels of neutrophils reduced, the practice of aerobic exercises, combined or resisted for at least 4 weeks was also sufficient to improve lymphocytes and salivary IgA (51). In addition, general antibody levels were found after vaccination with influenza H1N1, H3N2, influenza type B, pneumococcal, and varicella-zoster virus, improving the immune response after vaccination. Finally, the increase in physical exercise was related to a 31% lower prospective risk of infectious diseases and 37% less mortality related to infectious diseases (51). In Table 1 we can identify the association between the number of infected people with age and we bring a set of data that support the benefits of exercise in patients who have been infected (Table 2).

Table 1: Number of infections worldwide by age

Author	Experimental design	Sample number	Place	Age
(1)	Human	464,103,184	World	Not specified
(2)	Human	Database 202 countries	World	Not specified
(15)	Human	383	Shenzhen People's Hospital	Not specified
(16)	Human	3.615	New York Hospitals	Below and above 60 years
(39)	Human	4335	Federal states of Germany	Between 18 and 95 years old
(47)	Human	3.762	World	Over 18 years of age

Table 2: Effect of physical exercise intervention

Author	*Exp. design	Sample characteristics	Interventions/treatments	Findings
(9)	Mice	Not specified	Tryptophan hydroxylase (TPH) 2 deficient (Tph2-deficient) mice	Serotonin has a direct role in chronic and acute regulation of hippocampal neurogenesis
(24)	Mice	16 animals	Treadmill exercise was performed for 12 weeks in obese mice	Exercise as a protective intervention plays an important role in regulating skeletal muscle structure and apoptosis in obese skeletal muscles.
(25)	Human	36 high dose chemotherapy patients	Infection and pneumonia risk high dose chemotherapy program patients in a supervised endurance exercise	Experiences in possibly preventing pneumonias and fever through endurance training.
(32)	Human	30 trained / 15 control group	Investigate the effect of various sports disciplines on basic elements of the acquired and natural defense systems	Moderate exercise performed regularly can positively affect the basic elements of the natural immune system.
(33)	Human	40 trained / 20 control group	Investigate the effects of acute aerobic and anaerobic exercise on humoral immune system parameters (IgA, IgG, IgM, C3, C4)	Regularly moderate exercise affects hormone release and enhances some immune system parameters as IgA, IgG or IgM.
(34)	Human	59 obese young women	12-week intervention of different methods of HIIT on the visceral fat loss	These findings suggest that visceral fat loss induced by interval training at or above 90% VO2peak
(35)	Human	32 prediabetic male patients	12-week intervention between HIIT and continuous training on preventive effects on pre-hormonal changes in pre-diabetic patients	Both protocols had similar effects on the insulin resistance index of prediabetic patients.

(37)	Human	102 diabetic women	Effect of 12 weeks of supervised and unsupervised training	Supervised group-exercise therapy was more effective than home-based exercise therapy
(42)	Cells; Mice; Monkeys; Humans	64 (mice)/ 13 (monkeys)/ 43 (Human)	Effect of exercise on processes that mediate benefits in the brain	Exercise increases cathepsin B levels in mouse, monkey, and human plasma.
(44)	Cells; Mice	Mck-PGC-1α and MKO-PGC-1α animals	To analyze the induction of physical training in kynurenine metabolism.	Reducing plasma kynurenine protects the brain from stress-induced changes associated with depression
(46)	Human	61 university students	6 weeks of HIIT/MCT in changes in depression, anxiety and perceived stress	moderate-intensity exercise may be an optimal intensity of exercise for the promotion of mental health
(48)	Mice	25–32 per group	Effect of exercise in mice of chronic cigarette smoke exposure	Moderate intensity of exercise attenuates the development of pulmonary disease induced by cigarette smoke exposure
(49)	Human	29 healthy men	Influence of continuous and non-continuous walking in the pool on lung strength	6 weeks of walking in water at 60% of heart rate increase PImax and PEmax
(50)	Human	34 individuals	Effect of online low-intensity exercise training on fitness and cardiovascular parameters	Similar training response to body mass-based training in both groups, even with virtual experiences

High-intensity interval training (HIT), moderate continuous training (MCT), maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax). *Experimental design.

Conclusion

Based on the data presented, we believe that physical exercise can be an important factor in favor of covid-19 recovery, which can help from prevention through the control of risk factors such as obesity, metabolic disorders, and immunity. As also, it can be an ally in the treatment with a better immune response to vaccination and improvement of psychological conditions. In Conclusion, the exercise could be an excellent tool in rehabilitation, after Covid-19 infection. Therefore, we recognize and recommend the importance and the practice of physical exercises, together with other precautions recommended by the World Health Organization (WHO), during the pandemic moment, becoming an essential factor in the fight against the virus.

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