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REVIEW ARTICLE

Metabolic and Hormonal Effects of COVID-19 and the Role of Exercise in Coping with It during Infection and Recovery

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ABSTRACT: Infection with the COVID-19 virus has a wide range of adverse effects on the metabolic and endocrine systems, and in fact, one of the main ways of influencing this new virus has been through these systems. This is why people with chronic underlying diseases such as obesity, diabetes, metabolic syndrome, and hypertension show more severe symptoms and higher mortality rates. On the other hand, exercise can reduce the symptoms resulting from disease and reduce its lasting effects by improving metabolic health and modulating hormonal mechanisms. Due to the new and unknown nature of COVID-19, clinical trials and experimental studies have not been performed to investigate the effect of exercise on mortality or severity and persistence of symptoms in patients with COVID-19, but exercise with modifications can improve insulin resistance, reduce the amount of mass, improve fat and anti-inflammatory properties, and increase the expression of ACE2 receptors, intracellular metabolism and other pathways that all can play a positive role in combating the virus. Due to the unknown aspects of the mechanism of COVID-19 and exercise, more studies need to be done on the dose-response relationship of exercise before and after the infection in different age groups and specific groups.

INTRODUCTION

In December 2019, an epidemic with a high mortality rate spread around the world, creating a public health crisis. The disease was caused by a virus called the new coronavirus (SARS-CoV-2) [1, 2]. At present, this disease has become a pandemic with clinical symptoms of low-grade fever, cough, dyspnea, muscle aches, acute headaches, loss of smell and taste, and issues, which have affected all countries of the world [3]. In some patients, lung involvement and multiple organ failure have also been reported [4].

SARS-CoV-2 is spread from person to person contact via airborne particles due to coughing and sneezing) and be transmitted in some instances with contaminated objects/surface s[1]. Global precautionary measures are needed to a large extent because of its rapid spread[5]. The virus affects the host organism through various

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mechanisms; in the following, the most important pathways related to metabolic and endocrine systems will be discussed. On the other hand, the physiology of the effect of exercise training on the severity of symptoms, mortality rate, and recovery of patients with this virus from the beginning of this pandemic has attracted the attention of researchers, which we will discuss below. Therefore, the purpose of this paper is to review the metabolic and hormonal effects of COVID-19 and the role of exercise in coping with it during infection and recovery.

Metabolism management as a defensive way to deal with SARS-CoV-2

The pathogenicity of COVID-19 virus is directly related to the effects of the virus on the host organism and the type of response depends on various factors[6]. It is useful to study the relationship between the courses of the disease and also to examine how the virus works, as well as the host response in achieving the response and determining the type of treatment strategies to combat COVID-19.

Clinical Trial studies performed on the viral effect in individuals with SARS-CoV-2 have shown that the peak viral load during the first 7 determines the time of onset of clinical manifestations and the severity of symptoms and continues with a decrease in uniformity in the second week [7-10]. As soon as the viral load decreases, the pro-inflammatory phase begins, in which the virus undergoes various changes of infection. Infection. To treat SARS-CoV-2, resistance strategies, including host immune response and antiviral therapies that kill the virus, have been most effective in treating people, even among asymptomatic patients. It has been shown that targeting fat metabolism in the epithelium of infected individuals may have therapeutic and antiviral properties. Adolescents diagnosed with viral upper respiratory infections experience high blood sugar uptake into their lungs[11]. In this regard, the bronchi of people with the flu show high levels of glycolysis and glutaminolysis, which are needed for the virus to multiply. Improving physiological defense barriers helps increase survival and recovery. However, antiviral agents in the asymptomatic stage with mild clinical symptoms improve the patient's ability to cope with the disease[12].

The rapid global and epidemic growth of Coronavirus 2019 worldwide has caused acute respiratory syndrome caused by this virus[13], which has appeared with different symptoms and intensities and varying degrees of mortality, and even it has been asymptomatic in some people. Current evidence suggests individuals affected by obesity are at increased risk of death from coronavirus disease 2019 (COVID-19)]14]. There have been reports from countries such as the United Kingdom[15], China[16]and the United States[17] that people with obesity have experienced far more severe symptoms, at least during hospitalization. One symptom includes acute respiratory distress syndrome (ARDS)[18]. Obesity causes atelectasis (depression of parts of the lungs), especially in the posterior wall[19], which causes the collapse of capillaries associated with air bubbles[20], reducing the recoil action of lung tissue. Also, parenchymal heterogeneity leads to high shear forces, and even when vinyl pressure is used, the pressure does not reach normal levels [21]. This is consistent with findings related to demographic observations and causes impaired pulmonary function [22]. However, it has become increasingly clear that obesity exacerbates the conditions of COVID-19, which is caused by metabolic and inflammatory damage, and not merely mechanisms and effects of increased adipose tissue [23]. For instance, according to the classification of overweight and obesity has been observed that even this classification has been able to determine the severity of symptoms among people with English COVID-19 (people over 60 years old) [15] and this distribution has been similar to the obesity epidemic among British men [24]. In 112 Chinese adults, the prevalence of the disease and the mortality rate among people with cardiovascular disease have been much higher, and in fact it can be said that the body mass index can be used as an indicator to predict the severity of symptoms and mortality [16]. Therefore, there may be fundamental individual and proportional differences between people with normal weight compared to individuals who are overweight or have obesity, with the literature indicating a strong correlation between body mass index and mortality

rate among people with COVID-19. A larger study in France found that patients with COVID-19 with obesity required seven times more ventilators than normal patients[25].

These observations are similar to the results of large studies conducted in 2009 on patients with the H1N1 flu, which have demonstrated that obesity is associated with a higher risk of death from the virus [26]. It can also be said that an underlying disease such as Syndrome X is associated with a high incidence of COVID-19[2, 15, 27, 28], as seen in 2003 and the SARS epidemic due to diabetes and the disorder. In the regulation of lipid profile, they are more prone to developing COVID-19 and its complications[16, 19]. One of the reasons for this is the high prevalence of fatty liver in these individuals[28]. Hypertension is also associated with adverse effects of the disease[29, 17 and 20]. These findings suggest that the disease tends to cause severe liver dysfunction in older men and individuals with high blood pressure and high blood sugar.

Mechanism of association between insulin resistance and severity of COVID-19 Virus

Insulin resistance results from insulin dysfunction in various target tissues such as the adipose tissue, liver, and skeletal muscle as a result of beta-cell dysfunction or due to defects in cascading and post-receptor insulin signaling pathways [30]. While various factors such as physical activity, free radical stress, and inflammation can regulate insulin action, high levels of insulin resistance are associated with metabolic diseases and affect different tissues. Under normal plasma insulin concentrations levels, these tissues are unable to modulate coordinated physiological responses to glucose depletion by suppressing dextrose production in the liver and glucose uptake and glycogen synthesis in skeletal muscle. As a result, insulin dysfunction has been shown to be associated with increased circulating insulin concentrations[31]. The angiotensin-converting enzyme 2 (ACE2) may provide a molecular link between insulin resistance and the severity of COVID-19. This is the pathway through which the SARS virus affects the cells of the host body[32]. ACE2 is found in various tissues, including the lungs and epithelial cells, small intestine, and pancreatic beta cells[33]. The overall physiological function of ACE2 is the conversion of angiotensin 2, which causes vasoconstriction and pro-fibrotic and pro-inflammatory molecules, to angiotensin 7-1, which is a vasodilator[34]. PhysiologicallyACE2 plays an important role in the renin-angiotensin-aldosterone (RAAS) system that controls insulin resistance and vascular dysfunction[35, 36]. ACE2 protects insulin resistance by reducing angiotensin 2 through inhibiting the oxidative effects of RAAS by reactive oxygen species, enhancing insulin signaling and insulin sensitivity[36]. Given ACE2's protective role, several studies have aimed at investigating the underlying mechanisms[37]and have confirmed that ACE2 expression in animal models fed with a high sucrose diet [38] or with increased insulin sensitivity [39].A randomized controlled trial by Rao et al. has demonstrated increased lung ACE2 expression through identifying several traits of diabetes-related phenotypes[42]. The effect of insulin on ACE2 expression is tissue-dependent and is associated with decreased expression in glomerular podocytes of NOD[40](non-diabetic) mice, but increased ACE2 expression in the lungs of NOD mice increased after insulin injections[41]. In a study by Muniyappa et al., researchers indicated an association between diabetes and the severity of COVID-19, but it is hypothesized that increased glucose rather than increased insulin is a major metabolic factor in increasing ACE2 expression [43]. However, a study by Rao et al. showed regular insulin administration was independently associated with ACE2 expression [42]. This differentiation may be clinically relevant because it can determine whether normal prioritization of blood sugar over insulin is preferred to reduce ACE2 expression reducing the severity of COVID-19. It is also clear that independent of ACE2 expression; there are other mechanisms involved in the more severe diabetes-related phenotype in COVID-19[44]. "Cytokine Storm" has shown to be involved in multiple organ failure which may be associated with COVID-19, and there is strong evidence from Middle Eastern respiratory syndrome models that demonstrate that have type II diabetes alters individuals cytokine profiles and may exacerbate causing an altered immune response, worsening

lung function [45]. Research has also shown that the increase in plasma glucose and having type II diabetes independently with risk factors and mortality in patients with SARS [46] and COVID-19 [28] is somewhat questionable, but the state of insulin resistance and high levels of insulin increases ACE2 expression in the lungs and epithelial cells and also exacerbates the severity of the disease.

Role of insulin resistance and Application in the severity of COVID-19 symptoms

Clinicians with experience in endocrinology and other sub-specialties tend to know whether patients have insulin resistance[23]. This can make it difficult to determine the real impacts of insulin resistance on patient outcomes in early COVID-19 studies published to date. This is because it was not a main clinical outcome variable, and that data was not ready. Due to it not being a variable of interest, it makes it difficult to determine its effectiveness in predicting the severity of COVID-19, responding to interventions or therapies, or assessing its relative importance compared to other risk factors such as obesity and high blood pressure, or type II diabetes. It is suggested that measuring insulin resistance be part of the routine clinical evaluation of these patients. However, it seems reasonable to explore the potential of insulin-resistant phenotype as a prognostic indicator and to determine changes in insulin sensitivity during COVID-19 infection and its association with symptom severity[23]. Measuring the ratio between leptin to adiponectin has shown to be a good physiological indication of the body's insulin sensitivity, as demonstrated in epidemiological studies[47, 48]. Adipocytes releases both leptin and adiponectin, which both have shown to play strong role in metabolic homeostasis. Leptin signals to the hypothalamus and plays a vital role in regulating food absorption and energy expenditure[49] in people with obesity with high levels of leptin[50]. In contrast, adiponectin Tissue fat oxidation decreases free fatty acids[51].

People with diabetes, severe obesity and hypertension are more prone to infection and the risk of infection and associated with high mortality rates[52]. The China Centers for Disease Control and Prevention reports an increase in mortality in people with diabetes from among 72314 people with COVID-19 [53]. Obesity and hypertension have been reported in 15% and 64% of people with diabetes, respectively. Virus-infected cells appear to require high metabolic changes to meet high anabolic requirements during the virus replication period.

The role of lipid membrane metabolism and formation

The biogenetic pathways of host cell lipids are involved in regulating virus replication. Lipids can function as direct receptors for cofactors for various viruses to enter at the cellular level or endosomes[54, 55] and explain the complexity of viral replication with the energies required for virus replication[56, 57]. Lipids can also regulate viral cellular dysfunction and protein function, as well as monitor the assembly, tracking, and release of microbial micro particles [58, 59]. In order for a viral genome to have multiple viruses first disarms the host's cells and forces them to create new intracellular membranes.

For different viruses to protect reproductive organs, a unique phospholipid is required[60, 61]. Survivors of the SARS virus have been shown to be more susceptible to heart disease, infectious lung issues, tumors, and abnormal blood sugar metabolism than normal individuals and controls. It has also been shown that survivors of the SARS virus have high levels of phosphatidylinositol and lyso-phosphatidyl inositol compared to non-sick groups.

Virus internalization: lipid-mediated endocytosis

Endocytosis is defined as internalizing various substances into a cell, in which different fluids and substances enter the cell. This process occurs through the intrusion of the plasma membrane and the internalization of the various components of a cell via membrane vesicles. Virus entry occurs through o the binding and bonding of viral membranes with plasma membranes[62, 63]. At present, the role of fat shuttles in the entry of the virus into host cells is of great importance for this study and the epidemic

of COVID-19. Lipid shuttles are made of sphingolipids, cholesterol, and cell membrane proteins. Lipid shuttles are vital for several viruses, such as SARS, especially in the early stages of duplication, although research has demonstrated that the angiotensin 2-converting enzyme 2 (ACE2) from a localization standpoint does not increase[64]. This can be remedied with covalent and clathrin, which play important roles in the process of pinocytosis and virus entry. This process facilitates binding and accelerates the release of the viral genetic material into the host cell, which envelops the virus, which includes coronaviruses leading to lower the intracellular PH of the endosomes and facilitating the binding and release of the viral genetic material[64].

Individuals with Type II diabetes have shown to be at a higher risk of developing COVID-19. Of course, type II diabetes and high blood pressure are the most popular common and non-communicable diseases, and people with these diseases are more prone to SARS and MERS [64]. According to reports from the US Centers for Disease Control and Prevention, patients with metabolic syndrome and/or type II diabetes are ten times more likely to develop COVID-19; however, type II diabetes and metabolic syndrome increase the risk of severe COVID-19 symptoms, risk of death, and infectious diseases, highlighting the need for some metabolic aspects in Coronavirus infections that should be considered separately [65].Hyperglycemia and the diagnosis of type 2 diabetes are independent factors that have been a strong predictor in patients with SARS [46]. These findings suggest that these patients have a history of metabolic inflammation and experience increased production and secretion of cytokines. For COVID-19, cytokine storms (mainly inflammatory cytokines) cause failure in several different organs and exacerbate symptoms[66].

Direct endocrine communication

SARS Coronavirus acts through human cells and glycoprotein receptors, which are responsible for transmitting the virus from host to host. Glycoproteins are present on the surface of cells where the angiotensin-converting enzyme attaches to the ectoenzyme. In the respiratory system, ACE2 converts angiotensin 2 to angiotensin 7-1, a key regulator of the angiotensin system. When ACE1 activity increases, ACE2 activity stops, and angiotensin 2 acts through the angiotensin one receptor or AT2R for inflammatory responses; therefore, it rouses aldosterone secretion. The effects of this process elevate systolic and diastolic blood pressure resulting in hypokalemia, can increase local vascular permeability, heightening the risk of respiratory distress syndrome[65]. In contrast, angiotensin 7-1 acts through the copper receptor pathway and leads to anti-inflammatory and anti-fibrotic responses, which are essential for the recovery status of patients with COVID-19. It can be stated that people with severe symptoms of COVID-19 have a blunted response activation of these pathways, which rises with the activation of AT1R and AT2R, which can lead to type II diabetes, hypertension, and reduced insulin sensitivity [65].

Immediate metabolic connection

In addition, there is a strong connection between coronavirus infection and high blood pressure, which also appears to be associated with type 2 diabetes. The binding of the SARS virus to the ACE2 receptor in the pancreas has shown to damage the receptor reducing the pancreas insulin production function. A study that examined patients with SARS having no history of type 2 diabetes and no history of steroid therapy was compared with their healthy siblings. This study demonstrated that 50% of patients later developed type 2 diabetes. Following three years of recovery from viral infection has a 5% survival rate. Due to the body's pancreas upregulating ACE2 expression, it is possible that the coronavirus may cause acute damage and dysfunction of stem cells, leading to acute hyperglycemia and transmission to type II diabetes. Most importantly, evidence has shown that diabetic mice increase ACE2 activity in the pancreas. These findings suggest that patients with type II diabetes may be at a higher risk of coronavirus infection. In addition, type II diabetes leads to the expression of angiotensin-converting enzymes in other organs, including the lungs, liver, and cardiac muscle,

which may be a possible mechanism of multi-organ failure in related infections or coronavirus.

Long-term effects of metabolic complications on survivors of COVID-19

Patients exhibiting serious COVID-19 symptoms have a long road of recovery to get rid to the long-term effects of the infection resulting in a long time of healing[67]. One of these long-term effects is likely metabolic dysfunction.

Following a 12-year gap of studying individuals with SARS from China, people exhibited metabolic disorders, which included hyperlipidemia, insulin resistance, hyperglycemia, type I diabetes, and type II diabetes [12]. Serum metabolism studies have demonstrated that these individuals have impaired levels of lipids, phosphatidylinositol, lysophosphatidylcholine (LPC) and lyso-phosphatidyl inositol.

Another study of critically ill patients found demonstrated that individuals with acute kidney injury were more likely to experience the onset of diabetes compared with the people in the control group during the recovery period[68]. The underlying mechanisms involved in the long-term adverse effects of severe COVID-19 symptoms can be complex and include factors such as psychological, emotional, and biological factors that can have lasting effects.

Psychologically, survivors of acute respiratory distress syndrome (ARDS) develop long-term cognitive defects leading to hypoxic and inflammatory conditions that cause impaired ventilation[69, 36]. People with inadequate memory function tend to eat uncontrollably due to being less sensitive to hunger and internal satiety, which leads to body mass gain and higher body mass indexes [69]. Emotionally, individuals who have survived ARDS have been shown to have increased levels of depression and post-traumatic stress disorder, which can have negative effects on metabolism, leading to forced eating, reduced motivation, and physical activity [70]. Cognitive training and promotion of emotional health are necessary to rehabilitate these people and those with COVID-19 to maximize metabolic health and bring people to a state of health before infection. Physiologically, damage to the endocrine system or organ systems such as the liver, pancreas, and muscle tissue fatty tissue may promote the creation of metabolic syndrome in patients with COVID-19. Among people with COVID-19, the spread of pancreatic damage has been reported during infection, indicating increased levels of circulating pancreatic enzymes. The pancreas triggers the expression of ACE2, through which the SARS virus enters cells, causing damage to the pancreas and a decrease in insulin release[71], which may lead to stable diabetes in survivors of the SARS virus. People with ARDS and other clinical problems experience a high rate of severe muscle mass loss due to metabolic disorders and immune responses due to infection, which leads to decreased mobility and necessitates medical intervention with mandatory nutrition. During the first few weeks, these individuals lose 20% of their body mass after undergoing difficult initial periods[39]. The results of patient survivors in the United States United States, have shown to reach their normal weight about a year after the onset of the disease. However, body composition analysis has shown that mass body gain occurred due to an increase in abdominal fatty tissue without gaining net body mass [1]. Survivors of ARDS also experience myopathy because of acute muscle weakness due to dysfunction of muscle fibers[72]. In survivors of infection, longstanding skeletal muscle weakness and loss of body mass have been reported, which can lead to mitochondrial dysfunction and metabolism altering satellite cell function, which is critical for the reproduction of skeletal muscle cells [73]. It is possible that chronic changes noted above may explain the overall decline in physical conditioning associated with skeletal muscle weakness and changes in the functional capacity of survivors of this dangerous disease [74]. Decreased functional capacity and lean body mass can reduce insulin function in survivors. However, to our knowledge, cases have been reported in individuals diagnosed with COVID-19 that may be reported in very severe cases. Rhabdomyolysis, defined as the breakdown and damage of lean muscle mass, has been reported in people with COVID-19[75]and may affect long-term functional impairment and muscle health. Stroke is one of

the most important complications of COVID-19. During the recovery period, these people are more at risk for stroke due to possible vascular complications[76]. Long-term in which altered metabolism may be an important factor for possible future events occurring in tissues. Weight loss and lack of nutritional consumption have been observed regularly in these individuals during recovery[76]. Effects associated with long-term changes in plasma lipid levels include free fatty acids and triglycerides[76]. High and stable levels of lipids can lead to cardiovascular dysfunction in individuals recovering from SARS and COVID-19 disease. Like people with SARS, people with COVID-19 are more likely to experience metabolic syndrome in the future. Due to the longstanding side effects, it is possible that the long-term outcomes depend largely on the types of medical treatment delivered as well as the social variables that affect metabolic health. It is suggested that metabolic health should be the main focus in which patients or individuals undergo extensive psychological counseling and physical therapy and occupational therapy rehab programs, which will enhance their metabolic health, allowing patients to return to their normal pre-disease state.

Possible effects of exercise on metabolic and hormonal systems with COVID-19

The COVID-19 pandemic is currently exacerbating the low physical activity pandemic[77]. According to the World Health Organization, it is estimated that 3.2 million deaths occur each year due to a sedentary lifestyle [1]. For many, social isolation and quarantine with the closure of clubs, fitness centers, and public parks have created an irreplaceable preventing structure to maintaining an active lifestyle. From a public health perspective, the importance of not having a safe place on-site should be reinforced by staying in place. Here, we will discuss exercise as an effective therapeutic strategy for boosting COVID-19 resistance through its effects on the angiotensin-converting enzyme[78]. Because the ACE2 receptor is known to be an important site for SARS virus entry, there is much debate about the importance of using angiotensin-converting enzyme inhibitors and angiotensin-2 blockers in the management of Corona-virus patients with hypertension [78]. Animal studies have shown that ACEi /ARBs may be effective in rearranging the expression of ACE2 receptors. This has raised concerns about the use of ACEi /ARBs in people with hypertension, which may heighten the risk of COVID-19 symptoms, its severity, and mortality. Other researchers support the blocking of ACE2 (or the management of angiotensin II) as a potential strategy to reduce the viral entry of SARS into cells that express ACE2[79]. The association of ACEi /ARB use in the health facility setting has been investigated in 1128 patients with coronavirus and hypertension. The results showed that the use of ACEi /ARB in the hospital was linked with a lower risk of death among patients with COVID-19 compared with those who did not use it[78]. Nevertheless, brilliant results have been obtained on the complex issue of the relationship between ACE2 and the pathophysiology of COVID-19. ACE2 exerts its anti-inflammatory and anti-fibrotic properties through the production of angiotensin 7-1 by Mas receptors. Thus, the ACE2-Ang1-7 Mas receptor and the ACE-Ang II-AT1 receptor are potential complementary pathways necessary for good health. The binding of COVID-19 to ACE2 reorganizes it, and it can be said that the ACE2-Ang1-7 mass receptor over activated the ACE2-Ang1-7 mass receptor pathway[78]. By reducing the availability of ACE2 for the conversion of angiotensin to angiotensin 7-1 and its anti-inflammatory and anti-fibrotic effects, more angiotensin is produced by ACE2, which leads to an inflammatory environment, lung damage and increased expression of prophylactic alpha-osmosis muscle actin and TGF-B1 genes [80]. Therefore, discontinuation of ACE /ARBs is not recommended in patients with hypertension and may in fact lead to increased mortality in patients with COVID-19[81]. Nowadays, the concept of "exercise is a drug" should be more noticeable for sedentary individuals. Exercise may be an ACE in solution to reduce the risk of COVID-19 infection and minimize its cardiopulmonary consequences during recovery[82, 83].

DISCUSSION

The main question is whether it is appropriate to do sports during COVID-19? To answer this question, we must first discuss the effects of high-intensity exercise on immune responses. So far, studies have demonstrated that moderate exercise strengthens the immune system's response to respiratory infections [83]. After moderate-intensity exercise and in neutrophils and the number of natural killer cells is evident, and mouth immunoglobulin A concentrations increase [83, 84]. Moderate-intensity exercise increases cortisol levels, which in turn increases inflammation[84]. This strengthens the immune system against viral infections by changing the response ratio of Th1/Th2 cells. A 20-30% reduction in upper respiratory tract infections has been reported who participate in moderate exercise daily[84]. However, vigorous exercise chronically leads to suppression of the immune system [83-85]. Moderate-intensity exercise strengthens the immune system and reduces the risk of respiratory tract infections. However, high-intensity exercise weakens the immune system for a longer period of time, increasing the relative risk of respiratory tract infections over a period of time[85]. It can be said that moderate-intensity (rather than intense) exercise may be beneficial for the health of the immune system of people without clinical symptoms. However, as mentioned above, due to the heightened risk of transmission and the spread of the disease (person to person or from contaminated surfaces), such as exercising at home appears to be a feasible option to decrease risk.

Exercising in the comfort of your home using a combination of simple and varied modalities can be a useful tool to fight possible coronavirus infections while also maintaining a high level of physiological function at home programs can include strength-based exercises using bodyweight, free weight, or resistance bands, flexibility exercises, and balance exercises, or a combination of them [86]. Also, the utilization of brisk walking at moderate exercise intensity outdoors while social distancing may also be a viable option. However, high-intensity interval training in public gyms/clubs and highly populated environments can be dangerous and should be avoided.

Likewise, there are serious challenges to holding sports competitions[87]. First, athletes at these levels need to train hard to be prepared for sports competitions, which can suppress the immune system over a period of time. Second, the majority of athletes who need close contact with teammates, rivals, or the environment (for example, water polo, diving, powerlifting, javelin throwing, and discus throwing) are at high risk of contracting the COVID-19 virus. This can help spread the virus across nations. Therefore, a 2-week rigid quarantine outside of competition camps is highly recommended for those who may be afflicted with the virus[87]. Therefore, it makes sense to cancel or delay sport competitions. However, competitions can be held without spectators and in accordance with health protocols. Given these factors, there is great concern about major sporting events such as the Olympics. Another important question is about maintaining and recovering physical fitness during and after an upper lung infection. Symptoms of upper lung infections are limited to the throat and neck, such as coughing, convulsive expulsion, and throat pain, in which case the person is only asked to exercise for only 10 minutes. If an individual is experiencing symptoms, the person should cease physical activity until proper recovery occurs. If the person's posture remains stable after 10 minutes of jogging, the person is allowed to engage in the moderate-intensity exercise below 80% of maximal oxygen consumption. However, if the signs and symptoms of the disease reach the lower limbs, such as muscle pain, fever, and gastrointestinal symptoms, the person should rest completely until complete recovery [84, 88]. In patients diagnosed with pneumonia, individuals experience a slower return to the participation of physical activity, which should be performed within four weeks[85]. However, this appears to be observed in healthy active individuals with unstimulated immune system function which may not be translational to the whole general population. Otherwise, given the new symptoms of COVID-19 and its unfortunate effects on the immune function and heart complications, including myocarditis, it makes sense to be cautious enough to continue exercising

in symptomatic patients. Therefore, by understanding the pathophysiology of COVID-19 and how it adversely affects people with poor metabolic health and enhances the severity of symptoms, we can understand that it is possible to reduce the severity of the disease and achieve desirable results [12]. What is certain is that the mechanism for dealing with COVID-19 should not be limited to strengthening the immune system and related issues. What is certain about metabolic health, COVID-19 virus, and sport is that, at present, sport has moved away from its traditional definition and the concept of "sport is a drug" has materialized. In fact, it can be said that regardless of the effect of exercise on strengthening the immune system, the aspect of improving the health of the fuel and its metabolism has a greater effect on neutralizing the side effects of this virus in infected individuals.

CONCLUSIONS

As mentioned in this review article, people afflicted with the virus experience a wide range of metabolic and hormonal changes, and in fact, it even appears to be a metabolic and infectious complication. But the fact is that there is a two-way relationship between the responses of this virus to different bodily organs. This means that if a person has poor metabolic health, contracting the virus will act as a chronic disease associated with metabolic disorders. This problem multiplies the complication in people who have underlying diseases and metabolic problems. It is also important to note that in the long term, survivors of the virus show symptoms of the disease with metabolic manifestations and maybe much more likely to develop chronic non-communicable diseases than the general population.

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Conflict of interest

Authors declare that there are no financial or other relationships that might lead to a conflict of interest.

REFERENCES

1. Liu S., Selvaraj P., Lien C. Z., Nunez I. A., Wu W., Chou C.K., Wang T. T., 2021. The PRRA insert at the S1/S2 site modulates cellular tropism of SARS-CoV-2 and ACE2 usage by the closely related Bat raTG13. Journal of virology. 95(11), e01751-20.

2. Guan W.j., Ni Z.y., Hu Y., Liang W.h., Ou C.q., He J.x., Liu L., Shan H., Lei C.l., Hui D.S., 2020. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 382(18):1708-20.

3. Wang D., Hu B., Hu C., Zhu F., Liu X., Zhang J., Wang B., Xiang H., Cheng Z., Xiong Y., Zhao Y., 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan China. Jama. 323(11), 1061-9.

4. Zahra Syeda M., Diabakte K., Geng X., Ji F., Ouyang L., Pan S., Fu Z., Li Y., Jia F., Chen, Z., Li W., 2020. The Ongoing Epidemic of 2019 Novel Coronavirus (SARS-CoV-2): Infection and Fatality Trends in Wuhan, Hubei and Across China. Bmj. 69(13), 382.

5. Tang B., Bragazzi N.L., Li Q., Tang S., Xiao Y.,Wu J., 2020. An updated estimation of the risk of transmission of the novel coronavirus (2019-nCov). Infectious Dsease Modelling. 35(11), 248-55.

6. Schneider D.S,. Ayres J.S., 2008. Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. Nat Rev Immunol. 8(11), 889-95.

7. To K.K.W., Tsang O.T.Y., Leung W.S., Tam A.R., Wu T.C., Lung D.C., Yip C.C.Y., Cai J.P., Chan J.M.C., Chik T.S.H., Lau D.P.L., 2020. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infec Dis. 20(5), 565-74.

8. He X., Lau E.H., Wu P., Deng X., Wang J., Hao X., Lau Y.C., Wong J.Y., Guan Y., Tan X., Mo, X., 2020. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat med. 26(5), 672-5.

9. Zou L., Ruan F., Huang M., Liang L., Huang H., Hong Z., Yu J., Kang M., Song Y., Xia, J., Guo Q., 2020. SARS-

CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 382(12), 1177-9.

10. Wölfel R., Corman V.M., Guggemos W., Seilmaier M., Zange S., Müller M.A., Niemeyer D., Jones T.C., Vollmar P., Rothe C., Hoelscher M., 2020. Virological assessment of hospitalized patients with COVID-2019. Nature. 581(7809), 465-9.

11. Smallwood H.S., Duan S., Morfouace M., Rezinciuc S., Shulkin B.L., Shelat A., 2017. Targeting metabolic reprogramming by influenza infection for therapeutic intervention. Cell Rep. 19(8), 1640-53.

12.Ayres J.S., 2020. A metabolic handbook for the COVID-19 pandemic. Nat Metab. 2(7), 572-85.

13. Chow N., Fleming-Dutra K., Gierke R., 2020. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep. 69(13), 382.

14.Reese H., Iuliano A.D., Patel N.N., Garg S., Kim L., Silk B.J., 2021. Estimated incidence of coronavirus disease 2019 (COVID-19) illness and hospitalization—United States, February–September 2020. Clinical Infectious Diseases.72(12), e1010-e7.

15. Yanai H., 2020. Metabolic syndrome and COVID-19. Cardiology Research.11(6):360.

16. Yudong P., Kai M., Hongquan G., 2020. Clinical characteristics and outcomes of 112 patients with cardiovascular disease infected with novel coronavirus pneumonia. Zhonghua Xin Xue Guan Bing Za Zhi. 48(6), 450-455.

17. Formica S., González-García C., Senoussi M., Brass M., 2021. Neural oscillations track the maintenance and proceduralization of novel instructions. NeuroImage. 232(11), 7870.

18. Lewandowski K., Lewandowski M., 2011. Intensive care in the obese. Best practice & research Clinical anaesthesiology. 25(1), 95-108.

19. Suratt P., Wilhoit S.C., Hsiao H.S., Atkinson R.L., and Rochester D.F., 1984. Compliance of chest wall in obese subjects. J Appl Physiol Respir Environ Exerc Physiol. 11(6), 360.

20. Rimensberger P.C., Pristine G., Mullen J.B.M., Cox P.N., Slutsky A.S., 1999. Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. Crit Care Med. 27(9),1940-5.

21. Mead J., Takishima T., Leith D., 1970. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol. 18(3), 230.

22. Steele R.M., Finucane F.M., Griffin S.J., Wareham N.J., Ekelund U., 2009. Obesity is associated with altered lung function independently of physical activity and fitness. Obesity. 17(3), 578-84.

23. Finucane F.M, Davenport C., 2020. Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of COVID-19 Infection. Front Public Health. 12(8), 184

24. Cooper R., Huang L., Hardy R., Crainiceanu A., Harris T., Schrack J.A., 2017. Obesity history and daily patterns of physical activity at age 60–64 years: findings from the MRC National Survey of Health and Development. J Gerontol A Biol Sci Med Sci. 72(10), 1424-30.

25. Simonnet A., Chetboun M., Poissy J., Raverdy V., Noulette J., Duhamel A., 2020. High prevalence of obesity in severe acute respiratory syndrome coronavirus- 2 (SARS- CoV- 2) requiring invasive mechanical ventilation. Obesity. 28(10), 1994

26. Yang R.Z., Lee M.J., Hu H., Pollin T.I., Ryan A.S., Nicklas B.J., 2006. Acute-phase serum amyloid A: an inflammatory adipokine and potential link between obesity and its metabolic complications. PLoS Med. 8(11), 889-95.

27. Wu C., Chen X., Cai Y., Xia J., Zhou X., Xu S., 2020. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med [Internet]; 2020 [cited 2020 Mar 21]. Online ahead of print. 1;180(7), 1031

28. Yang X., Yu Y., Xu J., Shu H., Liu H., Wu Y., Zhang L., Yu Z., Fang M., Yu T., Wang Y., 2020. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 8(5), 475-481

29. She J., Liu L., Liu W., 2020. COVID- 19 epidemic: disease characteristics in children. Journal of Medical Virology. 92(7), 747-54.

30. Petersen M.C., Shulman G.I., 2018. Mechanisms of insulin action and insulin resistance. Physiol Rev. 98(4), 2133-223.

31. Kahn S., 2003. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 46(1), 3-19.

32. Kuba K., Imai Y., Rao S., Gao H., Guo F., Guan B., Huan, Y., Yang P., Zhang Y., Deng W., Bao, L., 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Mmed. 11(8), 875-9.

33. Hamming I., Timens W., Bulthuis M., Lely A.T., Navis G.J., van. Goor H., 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 203(2), 631-7.

34. Dominici F.P., Burghi V., Munoz M.C., Giani J.F., 2014. Modulation of the action of insulin by angiotensin-(1–7). Clin Sci(lond). 126(9), 613-30.

35. Underwood P.C., Adler G.K., 2013. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Rep. 15(1), 59-70.

36. Henriksen E.J., Prasannarong M., 2013. The role of the renin-angiotensin system in the development of insulin resistance in skeletal muscle. Mol Cell Endocrinol. 378(1-2),15-22.

37. Chhabra K.H., Chodavarapu H, Lazartigues E., 2013 Angiotensin converting enzyme 2: a new important player in the regulation of glycemia. IUBMB life. 65(9), 731-8.

38. Coelho M.S., Lopes K.L., de Aquino Freitas R., de Oliveira-Sales E.B., Bergasmaschi C.T., Campos R.R., 2010. High sucrose intake in rats is associated with increased ACE2 and angiotensin-(1–7) levels in the adipose tissue. Regul pept. 162(1-3), 61-7.

39. Zhang W., Xu Y.Z., Liu B., Wu R., Yang Y.Y., Xiao X.Q., 2014. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. Scientific World Journal. 90(11), 1226.

40. Riera M., Márquez E., Clotet S., Gimeno J., Roca-Ho H., Lloreta J., Juanpere N., Batlle D., Pascual J., Soler, M.J., 2014. Effect of insulin on ACE2 activity and kidney function in the non-obese diabetic mouse. PLOS ONE. 11(8),875-9.

41. Roca Ho.H., Riera M., Palau V., Pascual J., Soler M.J., 2017. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. Int J Mol Sci. 18(3), 563.

42. Rao S., Lau A., So H.C., 2020. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of SARS-CoV-2: A Mendelian Randomization analysis highlights tentative relevance of diabetes-related traits. Diabetes Care. 43(7), 1416-1426.

43. Muniyappa R., Gubbi S., 2020. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 23(6), 623-8.

44. Sumner A.E., Bagheri M.H., 2020. Identifying the waist circumference of risk in people of African descent. Nat Rev Endocrinol. 16(1), 1-3.

45. Kulcsar K.A., Coleman C.M., Beck S.E., Frieman M.B., 2019. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight. 33(5), 429-55.

46. Yang J., Feng Y., Yuan M., Yuan S., Fu H., Wu B., 2006. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 23(6), 623-8.

47. López-Jaramillo P., Gómez A.D., López-López J., López-López C., Martínez-Ortega J., Gómez-Rodríguez A., Triana-Cubillos S., 2014. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Investig. 18(1), 37-45.

48. Finucane F.M., Luan J., Wareham N.J., Sharp S.J., O'rahilly S., Balkau B., Flyvbjerg A., Walker M., Højlund K., Nolan J., Savage J., 2009. Correlation of the leptin: adiponectin ratio with measures of insulin resistance in non-diabetic individuals. Diabetologia. 52(11), 2345-9.

49. Friedman J., Halaas J.L., 1998. Leptin and the regulation of body weight in mammals. Nature. 28(10), 1994

50. Considine R.V., Sinha M.K., Heiman M.L., Kriauciunas A., Stephens T.W., Nyce M.R., 1996. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 334(5), 292-5.

51. Turer A., Scherer P., 2012. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 55(9), 2319-26.

52. Korytkowski M., Antinori-Lent K., Drincic A., Hirsch I.B., McDonnell M.E., Rushakoff R., 2020. A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic. J Clin Endocrinol Metab. 105(9), 3076-87.

53. Wu Z., McGoogan J.M., 2020. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 323(13), 1239-42.

54. Bagam P., Singh D.P., Inda M.E., Batra S., 2017. Unraveling the role of membrane microdomains during microbial infections. Cell Biol Toxicol. 33(5), 429-55.

55. Taube S., Jiang M., Wobus C.E., 2010. Glycosphingolipids as receptors for non-enveloped viruses. Viruses. 2(4), 1011-49.

56. Nagy P.D., Strating J.R., van Kuppeveld F.J., 2016. Building viral replication organelles: close encounters of the membrane types. PLoS pathog. 12(10), e1005912.

57. Diamond D.L, Syder A.J, Jacobs J.M, Sorensen C.M, Walters K.A., Proll S.C., 2010. Temporal proteome and lipidome profiles reveal hepatitis C virus-associated reprogramming of hepatocellular metabolism and bioenergetics. PLoS Pathog. 6(1), e1000719.

58. Ono A., Ablan S.D., Lockett S.J., Nagashima K., Freed E.O., 2004. Phosphatidylinositol (4, 5) bisphosphate regulates HIV-1 Gag targeting to the plasma membrane. Proc Natl Acad Sci U.S.A. 101(41), 14889-94.

59. Zhang J., Pekosz A., Lamb R.A., 2000. Influenza virus assembly and lipid raft microdomains: a role for the cytoplasmic tails of the spike glycoproteins. J Virol. 74(10), 4634-44.

60. Xu K., Nagy P.D., 2015. RNA virus replication depends on enrichment of phosphatidylethanolamine at replication sites in subcellular membranes. Proc Natl Acad Sci U.S.A. 112(14), E1782-E91.

61. Knoops K., Kikkert M., Van Den Worm S.H, Zevenhoven-Dobbe J.C, Van Der Meer Y., Koster A.J, 2008. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. PLoS Biol. 6(9), e226.

62. Marsh M., Helenius A., 2006. Virus entry: open sesame. Cell. 124(4), 729-40.

63. Mercer J., Helenius A., 2009. Virus entry by macropinocytosis. Nat Cell Biol. 11(5), 510-20.

64. Mazzon M., Marsh M., 2019. Targeting viral entry as a strategy for broad-spectrum antivirals Viruses. 11(2), 176.

65. Bornstein S.R, Dalan R., Hopkins D., Mingrone G., Boehm BO., 2020. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 16(6), 297-8.

66. Mehta P., Mcauley D., Brown M., Sanchez E., Tattersall R., Manson J., 2020. Correspondence COVID-19: consider cytokine storm syndromes and. Lancet. 6736(20),19-20.

67. Chan J., 2005. Recovery pathway of post-SARS patients. Thorax. 60(5), 361-2.

68. Lin Y.F., Lin S.L., Huang T.M., Yang S.Y., Lai T.S., Chen L., 2018. New-onset diabetes after acute kidney injury requiring dialysis. Diabetes Care. 41(10), 2105-10.

69. Sasannejad C., Ely E.W., Lahiri S., 2019. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. Crit Care. 23(1), 352.

70. Huang M., Parker A.M., Bienvenu O.J., Dinglas V.D., Colantuoni E., Hopkins R.O., 2016. Psychiatric symptoms in acute respiratory distress syndrome survivors: a one-year national multi-center study. Crit Care Med. 44(5), 954.

71. Yang J.K., Lin S.S., Ji X.J., Guo L.M., 2010. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 47(3),193-9.

72. Chan K.S., Mourtzakis M., Friedman L.A., Dinglas V.D., Hough C.L., Ely E.W., 2018. Evaluating muscle mass in survivors of ARDS: a 1-year multi-center longitudinal study. Crit Care Med. 46(8), 1238.

73. Rocheteau P., Chatre L., Briand D., Mebarki M., Jouvion G., Bardon J., 2015. Sepsis induces long-term

metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun. 15(6),10145.

74. Pfoh E.R., Wozniak A.W., Colantuoni E., Dinglas V.D., Mendez-Tellez P.A., Shanholtz C., 2016. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. Intensive Care Med. 42(10),1557-66.

75. Jin M., Tong Q., 2020. Rhabdomyolysis as potential late complication associated with COVID-19. Emerg Infect Dis. 26(7), 10.3201.

76. Haley M.J., White C.S., Roberts D., O'Toole K., Cunningham C.J., Rivers-Auty J., 2019. Stroke Induces Prolonged Changes in Lipid Metabolism, the Liver and Body Composition in Mice. Transl Stroke Res. 11(4), 837-850.

77. Hall G., Laddu D.R., Phillips S.A., Lavie C.J., Arena R., 2020. A tale of two pandemics: How will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another? Prog Cardiovasc Dis. 33(5), 429-55.

78. Heffernan K.S., Jae S.Y., 2020. Exercise as medicine for COVID-19: an ACE in the hole? Med Hypotheses. 33(5), 429-55.

79. Abassi Z.A., Skorecki K., Heyman S.N., Kinaneh S., Armaly Z., 2020. COVID-19 infection and mortality: a physiologist's perspective enlightening clinical features and plausible interventional strategies. Am J Physiol Lung Cell Mol Physiol. 318(5), L1020-L2.

80. Rey-Parra G.J., Vadivel A., Coltan L., Hall A., Eaton F., Schuster M., Loibner H., Penninger J.M., Kassiri Z., Oudit G.Y., Thébaud B., 2012. Angiotensin converting enzyme 2 abrogates bleomycin-induced lung injury. J Mol Med. 90(6), 637-47.

81.Zhang P., Zhu L., Cai J., Lei F., Qin J.J., Xie J., 2020. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circulation research. Cric Res. 5;126(12),1671-1681.

82. Gurwitz D., 2020. Angiotensin receptor blockers as tentative SARS CoV 2 therapeutics. Drug Deve Res. 81(5), 537-540.

83. Martin S.A., Pence B.D., Woods J.A., 2009. Exercise and respiratory tract viral infections. Exerc Sport Sci Rev. 37(4),157-64.

84. Harris M.D., 2011. Infectious disease in athletes. Curr Sports Med Rep. 10(2), 84-9.

85. Ahmadinejad Z., Alijani N., Mansori S., Ziaee V., 2014. Common sports-related infections: a review on clinical pictures, management and time to return to sports. Asian J Sports Med. 5(1),1-9.

86. Chen P., Mao L., Nassis G.P., Harmer P., Ainsworth B.E., Li F., 2020. Wuhan coronavirus (2019-nCoV): The need to maintain regular physical activity while taking precautions. J Sport Health Sci. 9(2), 103-104.

87. Munoz J., 2020. COVID-19 Epidemic Exercise or Not to Exercise; That is the Question. Asian J Sports Med. 11(1), e102630.

88. Eichner E.R., 1993. Infection, immunity, and exercise: What to tell patients?. Phys Sportsmed. 21(1),125-35.