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Hypothesis

Can Regular Exercise Before COVID-19 Disease Upregulate ACE2 and Downregulate TMPRSS2 in Patient's Cells?

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Abstract

The recent pandemic was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which enters cells through a known enzyme angiotensin-converting enzyme 2 (ACE2) and a protease transmembrane protease serine-2 (TMPRSS2). ACE2 and its expression at the cellular level play a vital role in dilating arteries and preventing hypertension, protecting against lung lesions, and anti-inflammatory, and antifibrotic effects. However, TMPRSS2 is an enzyme that in humans is encoded by TMPRSS2. Increased expression of this protease further activates the Coronavirus 2019 (COVID-19) virus and increases its presence in virus-infected cells. The regulation and expression of these cell surface receptors are effective in COVID-19 infection. According to the literature, various factors, such as exercise can affect the expression of these receptors. The positive effect of regular exercise on ACE2 and TMPRSS2 levels in other diseases has been investigated. At the start of this study, no data were found to indicate that exercise would protect against COVID-19; however, based on previous studies into other diseases, regular exercise before COVID-19 might increase the expression of ACE2, decrease TMPRSS2 expression, and reduce the complications of the disease.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease, which is caused by the severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2), which was first reported in December 2019 in Wuhan, China. The disease is known for symptoms, such as fever, dry cough, muscle aches, fatigue, pneumonia, and other symptoms.[1,2] Coronavirus at the extracellular level of cells in the human body uses a polysaccharide structure called heparan sulfate to bind to the angiotensin-converting enzyme (ACE2) receptor and protease transmembrane protease serine-2 (TMPRSS2).[3,4] The elderly and people with many comorbidities are most vulnerable to COVID-19.[5] Numerous factors, such as obesity, hypertension, chronic obstructive pulmonary disease, and cardiovascular disease are involved in the severity of COVID-19[6]; therefore, factors, such as severe obesity, chronic kidney disease, diabetes, hypertension, and asthma are the main causes of hospitalization.[7]

COVID-19 and immune system

After COVID-19 enters the body through respiratory droplets that are caused by coughing or sneezing, it enters the cell with the help of cell surface receptors: ACE2, TMPRSS2, and furin.[8] The virus then begins to propagate with limited innate immune responses and can be detected by nasal swabs. Then, the virus spread and reaches the respiratory tract, where it faces a more robust innate immune response. Then, the clinical manifestations of the disease start and the subsequent clinical course might be predicted by an innate response cytokine.[5] The mechanisms of the human immune system response to COVID-19 are similar to those of other viruses and foreign agents. After SARS-CoV-2 passes through the barriers, the innate immunity (rapid response) and then the adaptive immunity (slow response) act and fight the virus.[5] Once the human body is infected with the virus, a healthy immune system rapidly clears the infected cells, the virus is inactivated by neu-

Keywords: Exercise; Coronavirus disease 2019; Transmembrane protease serine-2; Angiotensin-converting enzyme 2; Receptor.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; TMPRSS2, Transmembrane protease serine-2; COVID-19, coronavirus disease 2019.

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tralizing antibodies, and inflammation and lung damage are minimized.[9]

Angiotensin-converting enzyme and COVID-19

Angiotensin-converting enzyme does not appear to be expressed by cells of the immune system[6]; however, it is widely distributed in the heart, lungs, kidneys, and testes and opposes activation of the classical renin-angiotensin system (RAS); therefore, preventing organ damage, hypertension, diabetes, and cardiovascular disease.[10] ACE2 converts angiotensin 2 (Ang II) to angiotensin 1-7 (Ang1-7) by activating the Mas receptor, which is called counter-regulatory or vasodilator of the RAS. This pathway plays an important role in protecting against lung damage, dilating blood vessels, protecting the cardiovascular system, and has anti-inflammatory and antifibrotic effects.[11] During infection with COVID-19, the virus enters the cells and reduces the expression of ACE2 proteins. Therefore, the beneficial effects of the vasodilators of the ACE2-Mas receptor pathway are reduced or compromised, and thus, contribute to the development of the respiratory syndrome.[11]

Transmembrane protease serine-2 and COVID-19

TMPRSS2 is an enzyme that in humans is encoded by the TMPRSS2 gene.[12] This gene belongs to the family of serine proteases that are involved in physiological and pathological processes. Androgen-induced upregulation of TMPRSS2 and its downregulation in the absence of androgens in prostate cancer has been shown.[13] One key role of TMPRSS2 is priming the viral spike protein (S protein) that facilitates viral entry, which is essential for viral infectivity.[14] Based on the roles of ACE2 and TMPRSS2 and its role in the entry of COVID 19 into cells, any factor (vaccine or non-vaccine) that plays a role in increasing ACE2 expression could help to further activate the Ang II to Ang 1-7 conversion pathway by ACE2 and any factor that can decrease TMPRSS expression. This could be an important step in reducing SARS-CoV-2 damage to vital organs, especially the lungs, and might play an important role in reducing hospitalization or mortality from the disease.

Hypothesis

Regular exercise can upregulate ACE2 and downregulate TMPRSS2 in patients with COVID-19 and reduce the complications of the disease, especially lung lesions.

Evaluation of the hypothesis

In this section, the effect of high physical fitness and regular exercise on the immune system, the link between exercise and COVID-19 receptors will be discussed, and the research hypothesis will be presented.

Physical exercise and immune system

The results of studies on the effect of physical exercise with different intensities and durations on the immune system are controversial. The results of previous studies indicated the positive effect of regular moderate-intensity exercise on strengthening the immune system,[15] and high-intensity exercise can increase episodes of infection.[16] In addition, recent studies rejected the open window hypothesis, and highlighted the effect of acute and long-term exercise on immune competency and reducing the symptoms of communicable diseases (*e.g.*, bacterial and viral infections.)[17] During and after physical exercise, pro- and anti-inflammatory cytokines are released, and lymphocyte circulation and cell recruitment increase.[18] Exercise causes an anti-inflammatory response in muscle and adipose tissues, which includes an increase in interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin receptor antagonist (IL-1ra), macrophages of subtype 2 (M2), Peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α), nuclear factor of activated T cells (NFAT), Adenosine monophosphate-activated protein kinase (AMPK), and a decrease in interleukin 1β (IL-1β), Tumor necrosis factor-alpha (TNF-α), Toll-like receptor 2 (TLR-2), Toll-like receptor 4 (TLR-4), and macrophages of subtype 1 (M1) in muscles. In adipose tissue, exercise increase adiponectin, IL-10, M2, and decrease leptin, TNF-α, Retinol Binding Protein 4 (Rbp4), and M1.[11] Based on Nigro *et al*.[11] regular physical activity might reduce the acute inflammatory response through at least five mechanisms: (1) reducing the inflammatory signaling pathway that is mediated by Toll-like receptors (TLRs); (2) increasing anti-inflammatory cytokines, such as IL-10 and IL-37, which could inhibit the TLR-inflammatory signaling cascade and mitigate the inflammatory action that is produced by the inflammasome; (3) reducing lung inflammation through the activation of AMPK and promoting the conversion of Ang II to Ang 1–7; (4) by the activation of the ACE2-Mas receptor vasodilator pathway, reducing lung inflammation and promoting some beneficial multi-organ effects; (5) restoring nitric oxide (NO) levels, to counteract endothelial dysfunction; therefore, contributing to pulmonary vasodilation and antithrombotic activity.[11]

Exercise and COVID-19 receptors

Exercise and ACE2

At the start of this study, no data were found to indicate that exercise would protect against COVID-19. However, this study focuses on the effect of exercise on COVID-19 cell receptors and the literature-based conclusions about these receptors.

Various studies have examined the effect of exercise on RAS, which refers to ACE/Ang II/AT1R axis downregulation, ACE2/Ang 1-7/Mas axis upregulation, and a shift in the RAS toward the ACE2/Ang (1-7)/Mas axis.[19–23] In one study, moderate aerobic swimming exercises decrease ACE levels and increased previous ACE2 levels. These changes were associated with left ventricular hypertrophy and resting bradycardia in the animals tested.[24] In a study by Prata *et al*.[20] combining moderate-intensity exercise with ACE2 activator (DIZE) in mice treated with the anticancer drug Bleomycin (which causes pulmonary fibrosis) increased Ang 1-7 through ACE2 and the reduction in pulmonary fibrosis was due to the use of anticancer drugs.[20] In that study, the ACE2 activator had a role in increasing its expression, it appeared that combining its use with exercise had a greater effect. A similar study examined the effects of exercise on improving cardiovascular function in sick mice with the help of the ACE2 activator and highlighted the effective role of combining exercise and drug use in these mice.[21] In addition, some studies were performed on human subjects. For example, Magalhaes *et al*.[19] examined the effect of two types of exercise on ACE2 levels in the urine and blood plasma of active men.[22] They showed that both types of exercise, which included

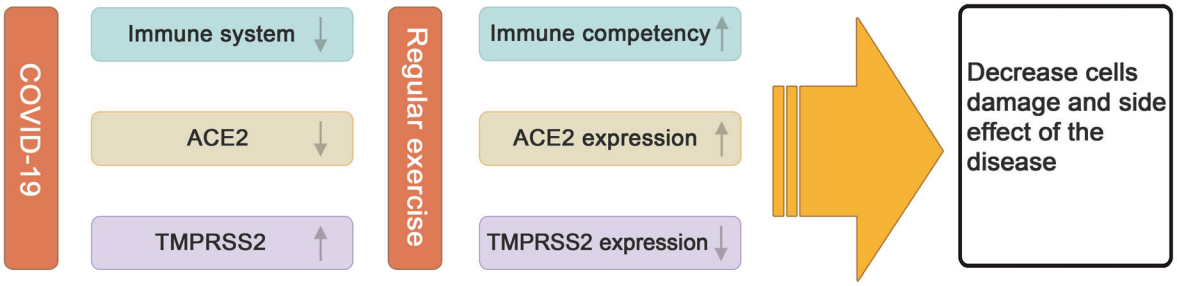

Fig. 1. Based on the literature, regular exercise leads to increased immunity, increased expression of ACE2, and decreased TMPRSS2 in other diseases. This positive effect of exercise appears to apply to COVID-19. COVID-19, Coronavirus disease 2019; TMPRSS2, Transmembrane serine protease 2; ACE2, Angiotensin-converting enzyme 2.

high-intensity intermittent exercise and moderate-intensity continuous exercise, were effective in increasing ACE2 activity, and the effect of continuous moderate-intensity exercise was greater, which indicated increased expression of this protein receptor. ACE2 prevents the effects of vascular endothelial growth factor (VEGF). However, in COVID-19 infection, VEGF levels are elevated due to ACE2 downregulation, and ACE2 cannot counteract the VEGF effects, which leads to vascular permeability and worsening endothelial damage.[11] Therefore, the role of factors that increase the expression of ACE2 appears to be important in reducing the complications from COVID-19 disease.

Exercise and TMPRSS2

The cell receptor TMPRSS2, which is a protease on the surface of the cell membrane, is one of the main contributors to ACE2 for the entry of SARS-CoV-2 into cells. TMPRSS2 and furin play vital roles in binding the S protein to ACE2. Effective binding is dependent upon S protein activation by TMPRSS2 or furin.[8] Various factors, such as androgen and COVID-19 virus[14] might change the regulation of this protease. Therefore, attention to the inhibitors of TMPRSS2 or any factor that reduces the expression of this protease is pathologically important in COVID-19. In addition, physical exercise affects the expression of TMPRSS2. The only study that investigated the effect of exercise on TMPRSS2 was cancer. In that prospective study, vigorous activity was associated with a lower risk of an increase in TMPRSS2 in prostate cancer.[25] Based on a possible mechanism they suggested that cellular stress could contribute to genomic instability and was a trigger for genomic rearrangements and physical activity might reduce oxidative stress and improve immune functions. Therefore, physical activity might protect against cellular stress, which prevents TMPRSS2–v-ets erythroblastosis virus E26 oncogene homolog (ERG) fusion. Certain cellular mechanisms, such as those that contribute to immune competency and ACE2 cell regulation play a role in the regulation of TMPRSS2.

Summary and hypothesis presentation

The regulation of COVID-19 cellular receptors appears to play an important role in the rate of viral infection and various factors might play a role in these regulations (*e.g.*, ACE2 in Ang II levels, hypoxia, and exercise, and TMPRSS2 in androgens and exercise). Therefore, by considering the previous studies and the effect of exercise on the regulation of these receptors, introducing regular exercise might be an effective factor to reduce the complications from COVID-19. Of note, until the start of this study and to the best of the author's knowledge, no study has been carried out on the effect of exercise on increasing ACE2 expression and decreasing TMPRSS2 expression in infectious and viral diseases (*i.e.*, COVID-19). Therefore, based on the effects of physical activity or exercise on COVID-19 input ports (*e.g.*, ACE2 and TMPRSS2) and the previous evidence, regular exercise might upregulate ACE2 and downregulate TMPRSS2 in patients with COVID-19 and reduce the complications from the disease, especially lung lesions (Fig. 1). This effect might be preventive or reduce the side effects from COVID-19.

Suggested steps for conducting research

This study could be performed on human and mouse subjects; however, due to the novelty of the hypothesis and the potential risks of developing COVID-19, it is suggested that it should be performed in mice. Therefore, the mice will be classified into two groups, the control and experimental groups. Before the start of the 8-week protocol, the levels of ACE2 and TMPRSS2 in both groups will be measured. Then, the experimental group performs 8 weeks of aerobic running on a treadmill, with five sessions per week, at least 1 h per session and with intensity from 50% to 60% of the maximum aerobic speed. Then, the mice in both groups will be infected with COVID-19. Since the incubation period of the disease is 2 to 14 days, the expression of virus receptors (*e.g.*, ACE2 and TMPRSS2) and the symptoms of the disease will be measured 5 days after the mice are infected with the virus. Finally, the expression of ACE2 and TMPRSS2, the severity of symptoms, and lung tissue lesion will be examined (Fig. 2). In addition, in the experimental group, after being infected with the virus, exercise could be continued to examine the effects of the infection. Of note, this training protocol has been suggested by the author of this article and due to the novelty of the subject of the article, the training protocol or research steps could be changed according to the conditions and types of exercises and their intensity.

Future directions

With this hypothesis and the steps of using and evaluating it, researchers can consider exercise as a method to strengthen the immune system and cellular structures to reduce the side effects of COVID-19. This study could increase the amount of systematic research by examining different types of exercise with different intensities and durations.

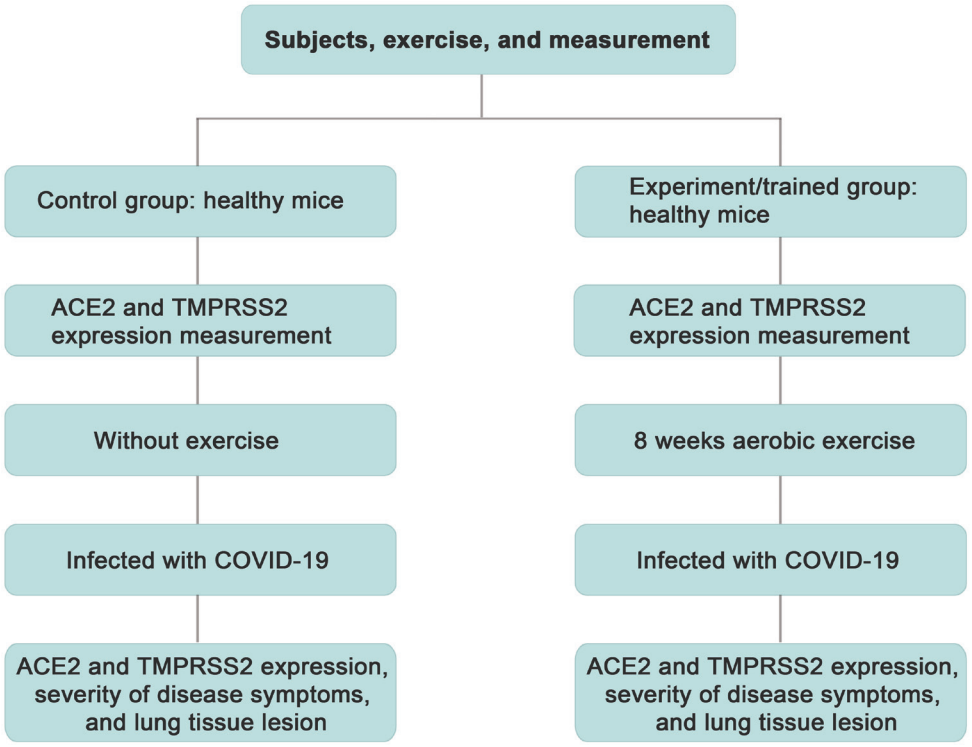

Fig. 2. Diagram of subjects, measurements, and exercise training in both groups. TMPRSS2, Transmembrane serine protease 2; ACE2, Angiotensin-converting enzyme 2.

Conclusions

The study of COVID-19 cell surface receptors is effective in identifying the incidence, tissue damage, and possible treatments. Methods to minimize the damage that is caused by COVID-19 are attractive to researchers, and by examining them, hopes could be raised to combat this pandemic. One of these methods, whose beneficial effects on other infectious diseases and the effectiveness of vaccination have been proved in previous studies, is regular exercise. However, the effect of exercise on the expression of COVID-19 cell surface receptors, such as ACE2 has been reported. Although this relies on limited literature, it reinforces the hypothesis that regular exercise might increase the expression of ACE2 and decrease TMPRSS2, which could reduce the side effects of COVID-19 (Fig. 3). Therefore, presenting this hypothesis could be the basis to start related research.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

KG was the sole author.

Ethical statement

No human or animal subjects were involved in this study.

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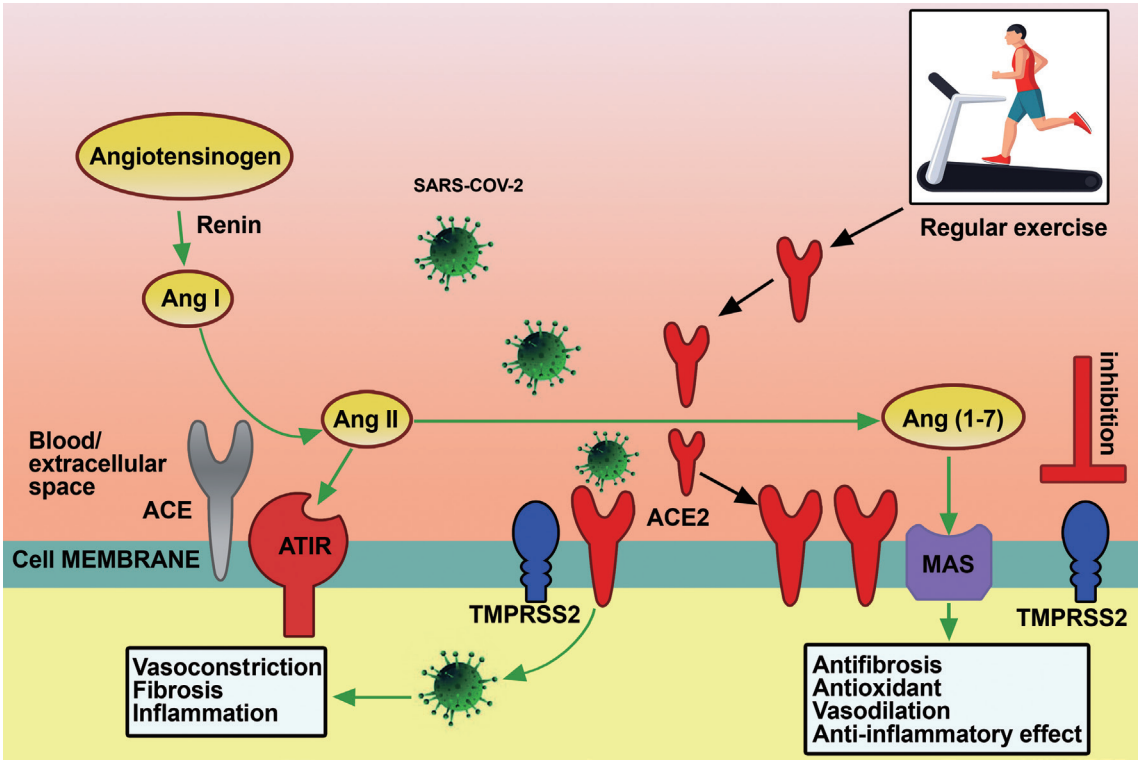

Fig. 3. Presence of COVID-19 at the cell surface and binding to ACE2 and activation by TMPRSS2 and Then, receptor dysfunction, vasoconstriction, inflammation, and fibrosis are observed. However, the potential positive effect of regular exercise on increasing the expression of ACE2 and decreasing the expression of TMPRSS2 includes anti-fibrotic effect, antioxidant, vasodilation, anti-inflammatory effect. Ang I, Angiotensin I; Ang II, Angiotensin II; ACE, Angiotensin-converting enzyme; AT1R, Angiotensin II receptor type 1; TMPRSS2, Transmembrane serine protease 2; ACE2, Angiotensin-converting enzyme 2; Ang (1-7), Angiotensin (1-7); MAS, Mitochondrial assembly receptor.

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