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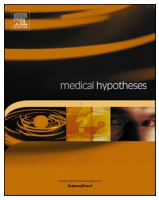

Moderate exercise may prevent the development of severe forms of COVID-19, whereas high-intensity exercise may result in the opposite

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ABSTRACT

Sedentary lifestyle increases the risk of hospitalization for COVID-19 independently of other factors. There is enough statistics to show that exercise prevents severe forms of COVID-19, but current recommendations do not set an upper limit for exercise intensity. The hypothesis presented in the paper states that intense exercise, through blood hypoxia, increases the expression of transmembrane angiotensin-converting enzyme 2 (tACE2) in the vascular endothelium, increasing the risk of developing serious forms of disease, especially in the untrained. On the other hand, moderate-intensity exercise increases the blood concentration of soluble angiotensin-converting enzyme 2 (ACE2) which has a protective role for SARS-CoV-2 infection and may prevent complications. The importance of this hypothesis consists in the revision of COVID-19 prophylaxis programs through physical exercises, with the possibility of administration of antioxidants to speed up the adaptation of vascular endothelial cells to exertion.

Introduction

A recent British study showed that physical inactivity increases the risk of hospitalization independently of other factors, such as obesity or alcohol consumption [1], suggesting that exercise could prevent severe forms of COVID-19, however the mechanism of prevention is unclear. It is theorized that physical inactivity may weaken immunity and thus promote SARS-CoV-2 damage to the immune, respiratory, cardiovascular, musculoskeletal systems and the brain [2]. Another hypothesis states that exercise may prevent severe forms of COVID-19 by stimulating the biogenesis of mitochondria throughout the body [3] and a healthy mitochondrial system is considered a prerequisite for development of immunity /resistance to SARS-CoV-2 infection [4-7]. However, the functionality of mitochondria can be negatively influenced by suppressing a counter-balancing anti-inflammatory pathway, a phenomenon produced by binding SARS-CoV-2 to its receptor, angiotensin-converting enzyme 2 (ACE2) [4], more precisely the transmembrane form of ACE2 (tACE2) [8]. SARS-CoV-2 binding to tACE2 inhibits the mitochondrial anti-inflammatory function and encodes a protein that locates to the mitochondrion, resulting in inhibition of mitochondrial anti-viral signaling proteins (MAVS) and subsequent suppression of anti-viral interferon response [4]. Thus, the binding of SARS-CoV-2 to the ACE2 receptor means not only the penetration of the virus into the cell but also a decrease of immunity and the anti-inflammatory action exerted by mitochondria.

But what happens to ACE2 during exercise? High-Intensity Interval Exercise (HIIE) increases plasma concentrations of ACE2, while Moderate-Intensity Continuous Exercise (MICE) increases the urinary concentration of the enzyme [9]. In fact, the analysis of the data presented in the above paper shows that plasma ACE2 also tends to increase during MICE. The soluble angiotensin-converting enzyme 2 (sACE2) form is present in both plasma and urine and it appears to play a role in preventing the virus from entering into the cell by competition with the transmembrane form (tACE2) - hence the synthetic forms of sACE2 being proposed for COVID-19 therapy [10]. There is a lack of data in the literature regarding tACE2 variation during physical exertion, specifically with high-intensity exercise. It has been shown that in pulmonary artery smooth muscle cells ACE2 mRNA increases in the early stages of hypoxia [11] and also it is known that intense exertion causes hypoxia in active skeletal muscle [12], which is likely to cause a statistically significant increase in plasma sACE2.

Hypothesis. High-intensity exercise would cause not only impaired immunity, but also an increase in tACE2 expression, rendering cells susceptible to SARSCOV-2 infection (acute effect) while moderate-intensity exercise should have a preventive effect by increasing plasma sACE2 concentration and thus blocking virus entry into cells.

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Our hypothesis is summarized below:

high-intensity exercise

↓

increased expression of tACE2 in cells susceptible to SARSCOV-2 infection/ after binding of the virus to the receptor

↓

- inhibition of mitochondrial anti-inflammatory function
- inhibition of MAVS proteins and suppression of the interferon antiviral response

moderate-intensity exercise

↓

increased plasma sACE2, which binds SARS-CoV-2

↓

effect of "washing" the virus and preventing infection or worsening of the disease

Validation of hypothesis

Theoretical arguments

Blood hypoxia causes increased expression of tACE2 in the vascular endothelium. The argument for this hypothesis begins with results of a study that showed that after 4 weeks of high-intensity training, compared to the basal level, ACE2 mRNA in the vastus lateralis (active muscle) is increased, while the plasma level of sACE2 is decreased [13]. It should be noted that acute increases in plasma sACE2 during and immediately after intense exercise were not measured. This can be explained by expression of ACE2 on both vascular endothelial cells [14] and striated muscle [15]. It is reasonable to assume that cellular adaptation to exertion resulted in decreased ACE2 expression in vascular endothelial cells, resulting in lower plasma concentrations of sACE2 after 4 weeks of training. This trend could not be counterbalanced by the increase of ACE2 mRNA in active muscles, most likely due to the metabolic needs imposed by the adaptation of striated muscles to exertion, - the chronic lesions of skeletal muscles being accompanied by the increase of intracellular ACE2 expression [16]. This may explain the results obtained by Magalhães et al. (2020) [9]: an increase of the plasma sACE2 concentration during MICE, a setting without vascular hypoxia (but only in the active muscles) is exclusively the result of the muscular expression of the enzyme. It should be noted that the subjects of that study were physically active, but their training did not include cycling (the effort was made by pedaling). Moreover, the training effect was avoided for both HIIE and MICE, as well as between the calibration sessions of the study.

With these arguments, Fig. 1 shows the effects of tACE2 growth in the vascular endothelium in untrained individuals that perform intense exertion. Blood sACE2 is the sum of sACE2 from striated muscle cells (active skeletal muscle) and sACE2 from vascular endothelium. By comparison, in moderate exertion, plasma sACE2 comes only from

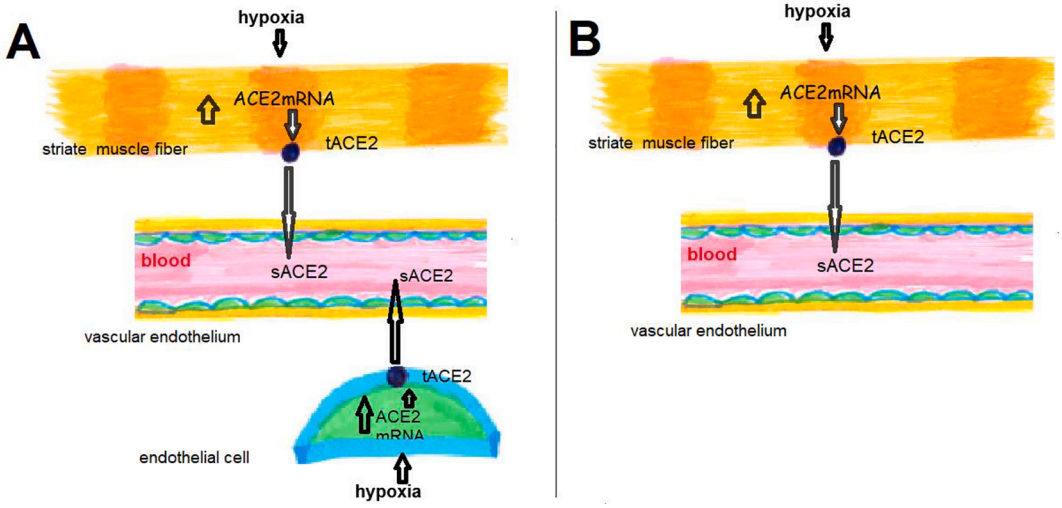

Fig. 1. Increased tACE2 in vascular endothelial cells in intense exercise (A) as opposed to moderate exercise (B) in untrained individuals.

active muscles.

Thus, the main issue for HIIE (at least in the untrained) is an increased expression of tACE2 in vascular endothelial cells is due to blood hypoxia, thus increasing the possibility of the virus penetrating into these cells. Considering that COVID-19 has been described as a vascular disease, not a respiratory one [17], one should worry about an increased risk of complications in untrained individuals who exert intense physical exertion. On the other hand, the presence of a higher amount of sACE2 (compared with the untrained) in the blood of subjects who perform moderate intensity exercise may be a factor preventing the penetration of SARS-CoV-2 into nasopharyngeal cells [18]. If one also considers the possibility that sACE2 prevents the virus from entering vascular endothelial cells, then a new hypothesis about moderate-intensity exercise preventing severe forms of COVID-19 appears sound in principle. The effect of lowering the basal level of plasma sACE2 and consequently of tACE2 in the vascular endothelium after 4 weeks of HIIE training remains debatable. It should be investigated whether episodes of acute exercise-induced hypoxia do not induce increased, albeit short-lived, synthesis of tACE2 in the vascular endothelium.

Statistical arguments

Another category of arguments that support the hypothesis presented in this paper are statistical studies. There are statistically significant differences between the results of studies regarding prevention of severe forms of COVID-19 through exercise where no difference was made between the intensity of the effort and those that quantified the effort intensity.

The first confirmation by statistical data on possible prevention of severe forms of COVID-19 through exercise came from Brazilian researchers, who found that sufficient physical activity (i.e. at least 150 min a week of moderate-intensity, or 75 min a week of vigorous-intensity) reduces the risk of hospitalization by 34.3% [19]. It is important to mention that the study was performed on people confirmed to be infected with SARS-CoV-2, with documented level of physical activity, and disease evolution was monitored. In those hospitalized, there was no correlation between the severity of the clinical forms and whether or not the patient was adequately physically active. Of course, among the study participants there may have been people who performed intense physical exertion without a sufficient level of training. A higher percentage (50%) of the decrease of the risk of hospitalization in case of SARS-CoV-2 infection was found by Sallis et al (2021) - [20], the association being valid for a moderate to strenuous effort intensity and for physical activity performed by the patient in the last 2 years before illness [20]. For the same intensity of effort (established by a questionnaire method in patients infected with the virus), Korean researchers found a 10% decrease in the risk of infection and a 53% decrease in mortality, independent of confounding factors [21]. The online completion of a questionnaire about the level of physical activity and severity of COVID-19 by participants previously infected with SARS-CoV-2 revealed that the possibility of hospitalization decreases by 64% in those able to maintain a brisk walk (thus moderate effort) [22].

The correlation between effort intensity and prevention of COVID-19 potential hospital admissions is illustrated by the Table 1:

Table 1
Relationship between effort intensity and prevention of severe COVID-19 disease.

Intensity of effort	Prevention of hospitalizable forms of COVID-19 (%)
unspecified (at least 150 min a week of moderate-intensity, or 75 min a week of vigorous-intensity) [19]	34.3%
moderate to strenuous [20]	50%
moderate to strenuous [21]	53% (mortality)/10%
moderate effort [22]	64%

Hypothesis and relationship with specialized literature data

Our hypothesis is strongly supported by a recent study (Khammassi et al., 2020 - [23]) that studied moderate-intensity continuous training effect on young male subjects. Their results show an increased number of immune cells while high-intensity interval training has the opposite effect [23]. Another study, performed on obese men, showed that a single high-intensity interval training session has anti-inflammatory effect (by decreasing the IFN-γ / IL-4 ratio) while moderate-intensity continuous training increases cellular immune function [24]. It turns out that high-intensity interval training may have a potential deleterious effect on cellular immunity in young people, and in obese subjects a decrease in IFN-γ, both resulting in impaired ability to fight SARS-CoV-2 infection.

Implications of the hypothesis

The work of Klöting et al (2020) [13] shows that sACE2 decrease in the circulating blood after 4 weeks of HIIT was more pronounced when antioxidants (vitamins C and E) were administered. It turns out that prophylactic vitamin therapy formulas developed to alleviate the potential effects of intense exercise may actually promote severe forms of COVID-19 in the untrained.

Another problem is that the new strains of SARS-CoV-2 have increased affinity for ACE2 [25], which requires increased vigilance in effort amount if exercise prophylaxis is desired. The effectiveness of current vaccines against new strains is increasingly questioned [26], however, according to data presented in this paper, the effectiveness of prophylaxis through moderate-intensity exercise will be maintained.

According to our hypothesis, the intensity of the effort should be limited to a maximum of 80% of the maximum volume of oxygen for unvaccinated individuals who want a prophylaxis by exercise of COVID-19. Despite the evidence on the effectiveness of the prophylactic role of exercise in preventing hospitalization in SARS-CoV-2 infection, a review study shows that there is no common consensus on such recommendations in the confinement caused by COVID-19 [27]. When the main goal was to improve the immune response, moderate physical activity needs to recommended in terms of intensity and duration, whereas prolonged and high-intensity effort may cause immunosuppression [28,29]. Furthermore, it is also noteworthy that traditional Chinese exercise has been proposed for the prevention and adjuvant therapy of patients with COVID-19 [30]. Yet, there is no upper limit on the intensity of effort for exercises used to prevent severe forms of COVID-19. There may be a temptation to increase the body's stress, given that a standard deviation increment in MET/week (525.3 MET-min/week) was associated with a 4% decrease in the risk of COVID-19 morbidity [21].

Most important, the development of adequate exercise programs and monitoring of oxygen saturation in peripheral blood should be performed not only in unvaccinated individuals who engage in leisure sports, but also in the case of post-COVID-19 rehabilitation programs, knowing that in these patients hypoxemia may occur more easily during exertion [31].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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