Genetic Arguments for the Prevention of Severe Forms of COVID-19 through Moderate-Intensity Exercise

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Author’s contribution
The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Many severe forms of COVID-19 have genetic causes, with variants providing information and thus supporting the hypothesis that moderate-intensity exercise would have a prophylactic role. In the case of genetic abnormalities related to the induction and amplification of type I interferons, in addition to curative administration of interferon, moderate intensity exercise could be used prophylactically. The same exercises inhibit the p38 MAPK pathway, being evaluated by clinical trials the drug inhibition of that pathway. In high physically active subjects, intermediate CCR2 monocyte decreased in response to moderate intensity exercise, and Cenicriviroc, an antagonist of the chemokine CCR5/CCR2b receptor, has been proposed for therapy. Exercise prevents the increased expression of Tyk2, and for COVID-19 therapy, corresponding to the defect of this gene, kinase inhibitors or Baricitinib have been proposed. The critical analysis of the data presented in the paper shows that for the prophylaxis of severe forms of COVID-19, moderate intensity exercises could be used.

Keywords: Gene variants; COVID-19; moderate intensity exercises.
1. INTRODUCTION

In August 2020, a medical hypothesis emerged, stating that moderate intensity endurance exercise, by stimulating mitochondrial biogenesis, could prevent the emergence of severe forms of COVID-19 [1]. Subsequently, a study showed that practicing 150 hours of moderate-intensity exercise and/or 72 hours of intense exercise per week decreases the risk of developing a hospitalizable form of COVID-19 by 34.3% [2]. However, this study does not compare the effects of moderate and high-intensity exercise. That is why I propose to make this distinction in this paper, based on the latest works in the field, which shows the possibility of a genetic risk for the risk of COVID-19 worsening. The greatest risk for the development of severe forms of COVID-19 is insufficient use of interferon by cells, a disorder of genetic origin [3], or autoimmune cause [4]. At the same time, the paper aims to present drug therapies that target the genes responsible for severe forms of COVID-19. These drugs are being studied for COVID-19 therapy and can be given after exercise prophylaxis in case of illness. In principle, the search for articles was done on PubMed, using as keywords the name of the gene involved in the pathogenesis of severe forms of COVID-19 and "exercise". To highlight drug therapies, the key word "drug" was added to the gene's name.

2. GENETIC AND AUTOIMMUNE CAUSES OF SUSCEPTIBILITY

Genetic and autoimmune causes of susceptibility to severe forms of COVID-19, prevention through exercise, drug therapies.

In a review paper on the role of exercise in aiding the immune system in the fight against COVID-19, it is concluded that the initial response is given mainly by type I interferons (IFN-I), and moderate exercise stimulates secretion of interferon gamma and increases infection resolution, while high-intensity exercise increases susceptibility to infection [5]. This fact acquires a special value considering the importance of interferon in the pathophysiology of COVID-19, serious forms of infection being present in genetic or autoimmune changes characterized by disorders of interferon use. The genetic changes involved in the pathogenesis of hospitalizable forms of COVID-19 are IFNAR2 (encoding interferon receptors - low expression), TYK2 (high expression), CCR2 (monocyte/macrophage chemotactic receptor - high expression), variants for OAS1 (encoding antiviral restriction enzyme activators) and for DPP9 (encoding dipeptidyl peptidase 9) [3]. About 3.5% of patients with potentially fatal forms of SARS-CoV-2-induced pneumonia have genetic abnormalities related to the induction and amplification of type I interferons (type I IFNs), and these patients it is recommended to use interferon, at least at the beginning of the disease [6]. It can be assumed that in these subjects the exercises of moderate intensity, by stimulating the secretion of interferon, would exert a prophylactic effect. At least 10% of those hospitalized with pneumonia caused by SARS-CoV-2 infection have antibodies to interferons and its receptors (IFNAR2), which are able to block the antiviral effects of interferon even at high dilutions [4]. 30 minutes of intense aerobic exercise (80% of VO2 max) causes a 1.3-fold increase in IFNAR2 expression in neutrophils as part of JAK/STAT pathway activation [7]. But the JAK/STAT pathway can also be activated by mechanical stretching in rat cardiomyocytes [8], suggesting that an improvement in IFNAR2 function, at least for heart cells, can also be achieved through moderate-intensity exercise. This could prevent the onset of viral cardiomyopathy. But the protein kinase p38 cascade (which is required for the response to interferons) also participates in the JAK/STAT pathway [9]. And then should p38 MAPK pathway stimulation through exercise be a way to restore IFNAR2 functionality useful in preventing severe forms of COVID-19? Data from the literature show that this is not the case. In contrast, inhibition of the p38 MAPK pathway seems to be a future treatment for COVID-19, because this pathway plays a decisive role in the release of pro-inflammatory cytokines such as IL-6 and was associated with production of acute long-term injury and myocardial dysfunction [10]. SARS-CoV-2 probably produces inflammation through upregulated p38 activity, p38 inhibitors being investigated in the clinic on patients with COVID-19 [10]. An important argument, established by an experimental animal study, is that the administration of a p38 MAPK inhibitor results in increased lifespan of mice infected with SARS-CoV [11]. Experimentally, on Wistar rats, it was found that moderate-intensity aerobic training decreased cardiac hypertension characteristic of middle age by influencing MAPK signaling pathway (p-P38 was significantly decreased), and oxidative stress [12].

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Table 1. Correspondence of the effects of exercise and medication according to genetic dysfunctions related to the pathogenesis of severe forms of COVID-19

<table>
<thead>
<tr>
<th>COVID-19 complication</th>
<th>The pathogenic mechanism</th>
<th>Comparative effects of exercise</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| SARS-CoV-2-induced pneumonia | - genetic abnormalities related to the induction and amplification of type I IFNs [3]  
| cardiomyopathy caused by SARS-CoV-2 | p38 MAPK pathway stimulation [10]  
increasing CCR2 expression [3] | moderate intensity aerobic training: in experimental animals, in the myocardium, p-P38 was significantly decreased [12]  
At high physically active subjects, intermediate monocyte CCR2 decreased in response to moderate intensity exercise [16] | p38 MAPK path inhibitors [10]  
Cenicriviroc, an antagonist of the CCR5/CCR2b receptor chemokine, inhibits SARS-CoV-2 replication in vitro [19] |
| SARSCOV-2-induced pneumonia | Increasing Tyk2 activity [3] | physical exercises, which induces mitochondrial biogenesis and reduces oxidative stress, and through these actions reduces the expression of Tyk2 [24,25,26] | kinase inhibitors [23]  
Baricitinib [27] |

3. SARS-CoV-2 INFECTION AND RESISTANCE

We can therefore assume that practitioners of moderate-intensity endurance exercise are protected to some extent from viral myocarditis in the case of SARS-CoV-2 infection, and perhaps even from lung viral inflammation. Instead, intense, short-term interval exercises activate p38 MAPK signals in striated muscle [13]. Even though the study was done on laboratory animals, this raises questions about the possibility of favoring complications in the case of SARS-CoV-2 virus infection in those who perform this type of exercise. In striated muscle increased phosphorylation of p38 MAPK occurs at an intensity of 70% of VO₂ max, both at intervals (cycling) and continuously effort (in the latter case statistically insignificant) [14]. It follows that from the point of view of the prophylaxis of severe forms of COVID-19 the threshold of transition to intense exertion could not be 80% of VO₂ max, but 70%. Another particularly interesting fact is that at the same intensity, the continuous effort does not produce such pronounced effects as the one on intervals on the p38 MAPK pathway. High-power resistance exercise induces MAPK phosphorylation [15]. Thus, stimulation of the p38 MAPK pathway by high-intensity exercise may amplify the antiviral action of interferon, but clinical and experimental data suggest that p38 inhibition is required for SARS-CoV and SARS-CoV-2 infection. The partial conclusion that emerges from the above is that high-intensity exercise is not indicated for the prophylaxis of severe forms of COVID-19 in individuals with interferon use disorders. A particular situation could be represented by the small proportion of those who carry a gene variant of IFNAR2 that implies the reduced expression of the respective receptor, for which could be conceived programs whose intensity is at the limit of the aerobic-anaerobic threshold. However, the risks of
intense exercise for SARS-CoV-2 infection must be considered. Analysis of the effects of exercise on other gene variants responsible for the risk of developing severe forms of COVID-19 may provide additional information on the possibilities of prevention. In high physically active subjects, intermediate monocyte CCR2 decreased in response to moderate intensity exercise (60% of VO2 max, 30 minutes at the cycle ergometer) [16]. The same effect of decreasing CCR2 expression was found in the case of resistance exercises, both high volume and high intensity [17]. However, resistance exercises, including high-volume ones, are considered intense, so they do not stimulate interferon production, or even increase the susceptibility to viral infections [5]. Moreover, in obese adults, continuous exercises of moderate intensity, and not intense exercises at intervals result in downregulation of CCR2 [18]. There is also a potential therapeutic intervention: Cenicriviroc, the antagonist of chemokine receptor CCR5/CCR2b, that inhibits SARS-CoV-2 replication in vitro and can be used for treatment of COVID-19 because it has antiviral and anti-inflammatory actions[19]. The OAS1 p46 isoform localizes to the mitochondria [20], but some DPP9 is also associated with mitochondria (the most common association is with microtubules) [21]. The increase in mitochondrial biogenesis, characteristic of both intense and moderate exercise, may have the effect of improving the functions controlled by the respective gene variants and consequently reducing the risk of hospitalizable forms of COVID-19. The same assumption can be made for Tyk2, which participates in mitochondrial respiration [22]. Reversal of lung failure in patients with COVID-19 can potentially be done with kinase inhibitors [23], which act on Tyk2. Reactive oxygen species trigger a stimulation of the JAK/STAT pathway. Thus, H2O2 stimulates the activity of the STAT kinases JAK2 and TYK2 [24]. Experimentally, in rat skeletal muscle, mitochondrial H2O2 production has been shown to degrow by practicing acute and chronic eccentric exercise [25]. Exercise training may decrease exercise-induced oxidative stress [26], hence the expression of Tyk2. Baricitinib is a drug that has the potential to prevent the entry of SARS-CoV-2 virus into cells and to control storm cytokines induced by COVID-19, the mechanism being the intracellular inhibition of messages that promote inflammation of several cytokines by shutdown of Janus kinase (JAK) JAK1/JAK2 pathway(path that also contains Tyk2) [27]. Correlation of Tyk2 stimulation modalities with data on genetic defects in interferon use suggests that an increase in IFNAR2 expression as part of JAK/STAT pathway activation through intense exercise is not recommended. Table 1 summarizes the genetic or related pathogenetic mechanisms involved in the pathogenesis of severe forms of COVID-19, the drugs proposed according to them, as well as the comparative effects of moderate or high-intensity exercise for prophylaxis.

4. CONCLUSIONS

Two major causes for the development of hospitalizable forms of COVID-19 are genetic abnormalities related to the induction and amplification of type I interferons (type I IFNs) and genetic defects of interferon receptors. Exercises of moderate intensity, with the effect of stimulating the secretion of interferon, can be used prophylactically, and curatively it is recommended the administration of interferon, at least in the initial phases of the disease. Cardiomyopathy caused by SARS-CoV-2 may have among its pathogenetic causes the stimulation of p38 MAPK pathway, and experimental data suggest that moderate exercise, as opposed to intense exercise, inhibits that pathway. P38 MAPK inhibitors have been proposed as a pharmacological treatment. Another genetic cause is increased CCR2 expression, and in high physically active subjects, intermediate CCR2 monocytes decreased in response to moderate intensity exercise. Cenicriviroc, an antagonist of the CCR5/CCR2b receptor chemokine, which inhibits SARS-CoV-2 replication in vitro, has been proposed. It can be assumed that exercise in general, by stimulating mitochondrial biogenesis, prevents the increased expression of Tyk2, another genetic factor that increases susceptibility to severe forms of COVID-19. In case of illness, exercise prophylaxis could be continued with drug therapy: kinase inhibitors or Baricitinib, to inhibit Tyk2. The correlations between the presented data suggest that only moderate intensity exercises can exert a prophylactic effect for severe forms of COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.
COMPETING INTERESTS
Author has declared that no competing interests exist.

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