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

Bogdan-Alexandru Hagiu1*

1Faculty of Physical Education and Sports, "Alexandru Ioan Cuza" University of Iasi, Romania.

Author’s contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i4531089

Editors:
(1) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.
(2) Dr. Ana Cláudia Coelho, University of Trás-os-Montes and Alto Douro, Portugal.
(3) Dr. Begum Rokeya, Bangladesh University of Health Sciences, Bangladesh.

Reviewers:
(1) Nitin Girdharwal, KIET Group of Institutions, Dr. A. P. J. Abdul Kalam Technical University, India.
(2) Ali Mohamed Ali Ismail, Cairo University, Egypt.
(3) José López Castro, Hospital Comarcal de Monforte de Lemos, Spain.
(4) Gede Juanamasta, STIKes Wira Medika Bali, Indonesia.
(5) Jose Maria Vieitez, Hospital Ramón y Cajal, Spain.

Complete Peer review History: http://www.sciarticle4.com/review-history/64799

Received 10 December 2020
Accepted 12 January 2021
Published 30 January 2021

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.

*Corresponding author: E-mail: bogdan_hagiu@yahoo.com;
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 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]. A more 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].
Table 1. Correspondence of the effects of exercise and medication according to genetic dysfunctions related to the pathogenesis of severe forms of COVID-19

| COVID-19 complication                               | The pathogenic mechanism                                                                 | Comparative effects of exercise                                                                 | Drugs                                                                 |
|----------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| SARS-CoV-2-induced pneumonia                       | - genetic abnormalities related to the induction and amplification of type I IFNs [3]      | moderate intensity exercises, with the role of stimulating interferon secretion [5]           | administration of interferon, at least in the early stages of the disease [6] |
|                                                    | - genetic disorders of interferon receptors [3]                                          |                                                                                                  |                                                                      |
| cardiomyopathy caused by SARS-CoV-2                | p38 MAPK pathway stimulation [10]                                                        | moderate intensity aerobic training: in experimental animals, in the myocardium, p-P38 was significantly decreased [12] | intense exercises, with short duration, at intervals, have a potential negative effect [13] |
|                                                    | increasing CCR2 expression [3]                                                            | At high physically active subjects, intermediate monocyte CCR2 decreased in response to moderate intensity exercise [16] | Cenicriviroc, an antagonist of the CCR5/CCR2b receptor chemokine, inhibits SARS-CoV-2 replication in vitro [19] |
| SARS-CoV-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 degrade 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.

REFERENCES

1. Hagiu BA. The relationship between exercise and medication in preventing severe forms of covid-19 infection. Journal of Pharmaceutical Research International. 2020;32(14):164-167.

2. De Souza FR, Motta-Santos D, Santos Soares D dos, de Lima JB, Cardozo GG, Pinto Guimarães LS, et al. Physical activity decreases the prevalence of covid-19-associated hospitalization: brazil extra study. Medrxiv. 2020;2020.10.14.20212704.

3. Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in Covid-19. Nature; 2020. Available:https://doi.org/10.1038/s41586-020-03065-y

4. NIAID-USUHS Immune Response to COVID Group; COVID Clinicians; COVID-STORM Clinicians; Imagine COVID Group; French COVID Cohort Study Group; Milieu Intérieur Consortium; CoV-Contact Cohort; Amsterdam UMC Covid-19 Biobank; COVID Human Genetic Effort, Tsang JS, Goldbach-Mansky R, Kisand K, Lionakis MS, Puel A, Zhang SY, Holland SM, Gorochov G, Jouanguy E, Rice CM, Cobat A, Notarangelo LD, Abel L, Su HC, Casanova JL. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370(6515):eabd4585. DOI:10.1126/science.abd4585. Epub 2020 Sep 24. PMID: 32972996

5. Da Silveira MP, da Silva Fagundes KK, Bizuti MR, Starck É, Rossi RC, de Resende E Silva DT. Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. Clin Exp Med. 2020;29:1–14. DOI: 10.1007/s10238-020-00650-3. Epub ahead of print. PMID: 32728975; PMCID: PMC7387807

6. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370(6515):eabd4570.

7. Radom-Aizik S, Zaldivar F Jr, Leu SY, Galassetti P, Cooper DM. Effects of 30 min of aerobic exercise on gene expression in human neutrophils. J Appl Physiol (1985). 2008;104(1):236-43. DOI:10.1152/japplphysiol.00872.2007. Epub 2007 Nov 15. PMID: 18006867

8. Pan J, Fukuda K, Saito M, Matsuzaki J, Kodama H, Sano M, Takahashi T, Kato T, Ogawa S. Mechanical stretch activates the JAK/STAT pathway in rat cardiomyocytes. Circ Res. 1999;84(10):1127-36. DOI:10.1161/01.res.84.10.1127. PMID: 10347087

9. Plataniakis LC. Mechanisms of type-I and type-II-interferon-mediated signalling. Nat Rev Immunol. 2005;(5):375-86. DOI: 10.1038/nri1604. PMID: 15864272

10. Grimes JM, Grimes KV. p38 MAPK inhibition: A promising therapeutic approach for COVID-19. J Mol Cell Cardiol. 2020;144:63-65. DOI: 10.1016/j.yjmcc.2020.05.007. Epub 2020 May 16. PMID: 32422320; PMCID: PMC7228886

11. Jimenez-Guardaño JM, Nieto-Torres JL, DeDiego ML, Regla-Nava JA, Fernandez-Delgado R, Castaño-Rodriguez C, Enjuanes L. The PDZ-binding motif of severe acute respiratory syndrome coronavirus envelope protein is a determinant of viral pathogenesis. PLoSPathog. 2014;10(8):e1004320. DOI: 10.1371/journal.ppat.1004320. PMID: 25122212; PMCID: PMC4133396

12. Baghaiee B, Karimi P, Siahkouhian M, Pescatello LS. Moderate aerobic exercise training decreases middle-aged induced pathologic cardiac hypertrophy by improving Klotho expression, MAPK signaling pathway, and oxidative stress status in Wistar rats. Iran J Basic Med Sci. 2018;21(9):911-919. PMID: 30524691; PMCID: PMC6272071

13. Gibala MJ, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1alpha in human skeletal muscle. J Appl Physiol (1985). 2009;106(3):929-34. DOI: 10.1152/japplphysiol.90880.2008.
14. Combes A, Dekerle J, Webborn N, Watt P, Bougault V, Daussin FN. Exercise-induced metabolic fluctuations influence AMPK, p38-MAPK and CaMKII phosphorylation in human skeletal muscle. Physiol Rep. 2015;3(9):e12462. DOI: 10.14814/phy2.12462. PMID: 26359238; PMCID: PMC4600372

15. Galpin AJ, Fry AC, Chiu LZ, Thomason DB, Schilling BK. High-power resistance exercise induces MAPK phosphorylation in weightlifting trained men. Appl Physiol Nutr Metab. 2012;37(1):80-7. DOI: 10.1139/h11-131. Epub 2012 Jan 5. PMID: 22220922.

16. AM Blanks, TT Wagamon, L Lafratta, MG Sisk, MB Senter, LN Pedersen, et al. Impact of physical activity on monocyte subset CCR2 expression and macrophage polarization following moderate intensity exercise, Brain BehavImmun, 2 (2020), Article 100033, DOI:10.1016/j.bbih.2019.100033

17. Wells AJ, Hoffman JR, Jajtner AR, Varanoske DB, Schilling BK, Beyer KS, Mangine GT, Oliveira LP, Fukuda DH, Stout JR. Monocyte recruitment after high-intensity and high-volume resistance exercise. Med Sci Sports Exerc. 2016;48(6):1169-78 DOI:10.1249/MSS.0000000000000878 PMID: 26784277

18. Barry JC, Simtchouk S, Durre C, Jung ME, Little JP. Short-Term exercise training alters leukocyte chemokine receptors in obese adults. Med Sci Sports Exerc. 2017;49(8):1631-1640. DOI:10.1249/MSS.0000000000001261 Erratum in: Med Sci Sports Exerc. 2018;50(4):879. PMID: 28319586

19. Okamoto M, Toyama M, Baba M. The chemokine receptor antagonist cenicriviroc inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;182:104902 DOI:10.1016/j.antiviral.2020.104902. Epub 2020 Jul 30. PMID: 32739404; PMCID: PMC7392080

20. Kjaer KH, Pahus J, Hansen MF, Poulsen JB, Christensen EI, Justesen J, Martensen PM. Mitochondrial localization of the OAS1 p46 isoform associated with a common single nucleotide polymorphism. BMC Cell Biol. 2014;15:33. DOI:10.1186/1471-2121-15-33. PMID: 25205466; PMCID: PMC4165621.

21. Zhang H, Chen Y, Wadham C, McCaughan GW, Keane FM, Gorrell MD. Dipeptidyl peptidase 9 subcellular localization and a role in cell adhesion involving focal adhesion kinase and paxillin. Biochim Biophys Acta. 2015;1853(2):470-80. DOI:10.1016/j.bbapap.2014.11.029. Epub 2014 Dec 5. PMID: 25486458

22. Potla R, Koeck T, Wegrzyn J, Cherukuri S, Shimoda K, Baker DP, Wolfman J, Planchnon SM, Esposito C, Hoit D, Dulak J, Wolfman A, Stuehr D, Lamer AC. Tyk2 tyrosine kinase expression is required for the maintenance of mitochondrial respiration in primary pro-B lymphocytes. Mol Cell Biol. 2006;(22): 8562-71. DOI:10.1128/MCB.00497-06. Epub 2006 Sep 18. PMID: 16982690; PMCID: PMC1636766

23. Weisberg E, Parent A, Yang PL, Sattler M, Liu Q, Liu Q, Wang J, Meng C, Buhrlage SJ, Gray N, Griffin JD. Repurposing of Kinase Inhibitors for Treatment of COVID-19. Pharm Res. 2020;37(9):167. DOI:10.1007/s11095-020-02851-7. PMID: 32778962; PMCID: PMC7417114

24. Simon AR, Rai U, Fanburg BL, Cochran BH. Activation of the JAK-STAT pathway by reactive oxygen species. Am J Physiol. 1998;275(6):C1640-52. DOI:10.1152/ajpcell.1998.275.6.C1640 PMID: 9843726

25. Molnar AM, Servais S, Guichardant M, Lagarde M, Macedo DV, Pereira-Da-Silva L, Sibille B, Favier R. Mitochondrial H2O2 production is reduced with acute and chronic eccentric exercise in rat skeletal muscle. Antioxid Redox Signal. 2006;(3-4):548-58 DOI:10.1089/ars.2006.8.548. PMID: 16677099

26. Mrakic-Sposta S, Gussoni M, Porcelli S, Pugliese L, Pavei G, Bellisti G, Montorsi M, Tacchini P, Vezzoli A. Training effects on ROS production determined by electron paramagnetic resonance in master swimmers. Oxid Med Cell Longev. 2015;2015:804794 DOI:10.1155/2015/804794. Epub 2015 Mar 22.
27. Zhang X, Zhang Y, Qiao W, Zhang J, Qi Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol. 2020; 86:106749. DOI:10.1016/j.intimp.2020.106749. Epub 2020 Jul 1. PMID: 32645632; PMCID: PMC7328558.