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CONSIDERATIONS ON THE PROPHYLAXIS OF SEVERE FORMS OF COVID-19 THROUGH ENDURANCE EXERCISES

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ABSTRACT. Prophylaxis of severe forms of COVID-19 can be achieved by combating sedentary lifestyle, preferably through moderate intensity endurance exercises, dosed so as not to cause immune disorders. The mechanism is likely to be to protect the mitochondria from oxidative stress. The anti-inflammatory effects may also occur in the organs affected by the virus. The high intensity of the effort (interval training or resistance training) can promote, in addition to immune disorders, even the penetration of the virus into the target cells (according to a hypothesis to be confirmed by future studies). However, there are preliminary results according to which some high-intensity exercises can be adapted to avoid hypoxia and thus be used for COVID-19 prophylaxis. Prevention of serious complications of SARSCOV-2 infection through exercise may be of interest to obese, diabetic and the elderly, high-risk categories.

Key words: *COVID-19, exercises, mitochondria*

REZUMAT. ***Considerații privind profilaxia formelor severe de covid-19 prin exerciții de anduranță.*** Profilaxia formelor severe de COVID-19 se poate realiza prin combaterea sedentarismului, de preferință prin exerciții de anduranță de intensitate moderată, dozate astfel încât să nu provoace tulburări imunitare. Este posibil ca mecanismul să fie protejarea mitocondriilor de stresul oxidativ. Se poate ca efectele antiinflamatoare să se manifeste inclusiv în organele afectate de respectivul virus. Intensitatea mare a efortului (antrenament pe intervale sau antrenament cu rezistență) poate favoriza, pe lângă tulburările

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imunitare, chiar și pătrunderea virusului în celulele țintă (conform unei ipoteze ce urmează a fi confirmată de studii viitoare). Există însă rezultate preliminare conform cărora și unele exerciții de intensitate mare pot fi adaptate în sensul evitării hipoxiei și astfel să fie folosite pentru profilaxia COVID-19. Prevenirea complicațiilor grave ale infecției cu SARSCOV-2 prin exerciții fizice poate fi de interes pentru categoriile cu risc ridicat: obezi, diabetici și vârstnici.

Cuvinte cheie: *COVID-19, exerciții, mitocondrii*

Introduction

A statistical study conducted in the UK shows that the physically inactive population is more exposed to developing forms of COVID-19 that require hospitalization, the paper concluding that the adoption of simple lifestyle changes results in decreased risk of severe SARSCOV-2 infections (Hamer et al., 2020). According to the medical hypothesis published in the International Journal of Pharmaceutical Research (Hagiu, 2020a), moderate intensity endurance exercises are indicated for the prevention of severe forms of COVID-19. The arguments are that exercise induces an adaptation of mitochondria to oxidative stress (Lawler et al., 2016), which is particularly important given that these organelles are indirectly attacked by the SARSCOV-2 virus by increasing the concentration of plasma iron, mitochondrial damage contributing to the cytokine storm that characterizes COVID-19 complications (Saleh et al., 2020). The purpose of this review is to analyze, based on the literature, whether mitochondrial biogenesis interested organs affected by SARSCOV-2 virus, what effect the various types of exercise have on the immunity and virus ability to enter cells, and the applicability of the hypothesis in some pathological situations.

Stimulation of mitochondrial biogenesis through exercise in organs affected by complications of COVID-19

Because liver damage in COVID-19 can be attributed to inflammatory storm rather than direct viral attack (Ali, 2020), the question arises whether exercise stimulates liver mitochondrial biogenesis. Recent work shows that exercise has the effect of modulating the structure and functions of liver mitochondria (Stevanović et al., 2020). Also in the case of myocarditis that appeared as a complication of COVID-19, the etiology is inflammatory rather than the direct attack of the virus on myocardial cells (Pirzada et al., 2020). The benefit of endurance training on myocardial energy metabolism in heart failure has been shown (Ventura-Clapier et al., 2007). Exercise increases the biogenesis of mitochondria in the brain, the experiment being performed on experimental animals (mice), and the exercises can be assimilated to endurance (treadmill) (Steiner et al., 2011). This fact can be taken into account if we consider the possibility of neurological complications in the case of COVID-19 infection (Sheraton et al., 2020), complications that have become more frequent in recent times.

Why moderate intensity endurance exercises?

Citrate synthase may be a marker of mitochondrial oxidative stress, and it is proposed to protect this enzyme with antioxidants (Chepelev et al., 2009). It is also a marker of adaptation to oxidative stress induced by sports training in striated muscle, being admitted a relationship with total aerobic capacity (Vigelsø et al., 2014). After 6 weeks of endurance training (continuous training of moderate intensity) citrate synthase activity increases (Meinild Lundby et al., 2018), so probably the resistance of mitochondria to oxidative stress present in the evolution of COVID-19. Mitochondrial biogenesis can also be stimulated by high-intensity exercise (Bishop et al., 2019), but these may have some disadvantages for the prevention of severe forms of COVID-19. First, it is considered, there is a consensus, that regular bouts of short-lasting (ie up to 45 minutes) moderate intensity exercise is beneficial for host immune defense, particularly in older adults and people with chronic diseases (Simpson et al., 2020). In young subjects an interval training session (HIIT) induces a modest systemic inflammatory response, and two weeks of training did not alter the inflammatory response to an acute bout of HIIT exercise (Zwetsloot et al., 2014), a fact that I consider unfavorable in the presence of an COVID-19 infection. In contrast, in elderly people with rheumatoid arthritis, ten weeks of HIIT improved innate immune function (Bartlett et al., 2018), which raises the question of whether, under special conditions and in certain subjects, this type of training could be effective in the prophylaxis of severe forms of COVID-19. However, continuous training of moderate intensity, not HIIT, improves markers of immunity in young men (Khammassi et al., 2020). High-intensity exercise increases the plasma concentration of ACE2 ("spike" protein to the angiotensin-converting enzyme 2, which conditions the entry of SARSCOV-2 virus into the cell), which is under investigation to determine whether it is beneficial or detrimental (Wackerhage et al., 2020). The main cause is hypoxia, which can promote the entry of the virus into vascular endothelial cells (Hagiu, 2020b, 2021a). Resistance training increases the respiratory capacity and intrinsic functions of skeletal muscle mitochondria (Porter et al., 2015). However, it involves a high intensity of effort and probably an increase in the plasma concentration of ACE2. On the other hand, resistance exercises also produce transient disturbances of immunity (Freidenreich & Volek, 2012).

It turns out that moderate intensity endurance is the surest way to increase the antioxidant capacity of mitochondria and thus prevent the cytokine storm as an unwanted event during COVID-19 infection. This fact is supported even by genetic arguments (Hagiu, 2021b). I believe that future research needs to be done for other forms of training. In fact, in a previous paper, we showed that during Kangoo Jumps training of moderate intensity does not reach hypoxia, even if the heart rate can exceed 80% of the maximum value (Hagiu, Turculeț & Dumitru, 2021).

Mitochondrial dysfunctions in diseases at risk for the development of severe forms of COVID-19

Obesity, insulin resistance and type 2 diabetes are conditions accompanied by mitochondrial dysfunction (Montgomery, 2019). There is evidence that exercise reverses impairments in mitochondrial density and size (Lumini et al., 2008). On the other hand, mitochondrial dysfunctions are known in the elderly (Haas, 2019), but there is the possibility of restoring those cellular organs through exercise (Nilsson & Tarnopolsky, 2019). Obese people, diabetics and the elderly are at risk for developing severe forms of COVID-19, and this risk can be reduced by practicing exercises. According to Wang et al (2020), obese sufferers can benefit from exercise programs to prevent mortality with COVID-19, but the authors propose combining medium-intensity endurance with interval exercise.

Conclusions

Decreasing the incidence of cases requiring hospitalization for COVID-19 infection can be achieved by combating physical inactivity, probably best through moderate intensity endurance exercise. The anti-inflammatory effects of exercise-stimulated mitochondrial biogenesis may also occur in organs directly or indirectly affected by the virus. Interval resistance training, due to the high intensity of the effort, can produce immune disorders, and even, according to a hypothesis being tested, favors the penetration of the virus into the target cells. The same goes for high intensity resistance training. So, until these phenomena are elucidated by future research, these types of exercises should probably be avoided for the intended purpose. However, the possibility of avoiding hypoxia during high-intensity training is a direction for research into COVID-19 prophylaxis through exercise. The prophylaxis of severe forms of COVID-19 through exercise can benefit including the obese, diabetics and the elderly, all categories at high risk.

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