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Opinion Article

COVID-19 and physical activity: What is the relation between exercise immunology and the current pandemic situation?

COVID-19 and physical activity: What is the relation between exercise immunology and the current pandemic situation?

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Exercise immunology is a strong and mysterious science in sports medicine, but studies were origin more than a 100 years ago, when Schulte had already described an exercise-induced leukocytosis as early as 1893 [1]. Since then, both cross-sectional and longitudinal studies in humans have demonstrated the profound impact that exercise can have on the immune system. That is exactly why it is fundamentally important in this pandemic time to elucidate many questions and direct the athletes and non-athletes to the due care.

The current situation started with a cluster of pneumonia patients with an unidentified cause emerged in Wuhan, Hubei Province, China, in December 2019 [2]. Approximately 2 months later the World Health Organization (WHO) announced a standard format of Coronavirus Disease-2019 (COVID-19) [3] on the same day named as SARS-CoV-2 [4].

After sequence and evolutionary tree analysis, SARS-CoV-2 was considered as a member of β-CoVs [5,6] like SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) [7].

Respiratory droplets and contact transmission are the main transmission routes, but SARS-CoV-2 can be detected in the urine and stool, which gets a possible risk of fecal-oral transmission [8]. However, there is still no evidence that corroborates this route, but all possible transmission routes need vigilance during the physical exercise. COVID-19 has a probable asymptomatic incubation period (2 -14 days) which the virus can be transmitted [9]. SARS-CoV-2 has a R0 of 2.2-2.6, everyone has the potential to spread the infection to 2.2 other people [10].

Initially, the most common symptoms were reported in 41 patients

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with fever (98%), cough (76%), and myalgia or fatigue (44%) sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). More than half of patients developed dyspnea Blood test showed normal or reduced (25%) leukocytes count and lymphopenia (65%) [11].

Another study showed 140 patients diagnosed as COVID-19, where the most common symptoms were fever (91.7%), cough (75%), fatigue (75%) and chest tightness or dyspnea (36.7%). 39.6% of them complained gastrointestinal symptoms. 90 (64.3%) patients had comorbidity, the most common of which were chronic diseases, such as hypertension (30%) and diabetes (12.1%). Only two COPD patients were identified, and 2 patients reported chronic urticaria. Other allergic diseases as asthma, allergic rhinitis, food allergy, atopic dermatitis were not self-reported [12].

Persons older than 60 years old with hypertension, diabetes, COPD, cardiovascular, cerebrovascular, liver, kidney, and gastrointestinal diseases are more susceptible to the infection by SARS-CoV-2 and experience higher mortality when they develop COVID-19 [13-15].

These clinical features suggested the possibility of involvement of highly pro-inflammatory condition in the disease progression and severity. This early high rise in the serum levels of pro-inflammatory cytokines were also observed in SARS-CoV and MERS-CoV infection, suggesting a potential similar cytokine storm-mediated disease severity [16,17].

In severe cases of SARS-CoV or MERS-CoV infection, there is an increased neutrophil and monocyte-macrophages influx [18,19]. With all knowledge accumulated about previous coronavirus infections, innate immune response plays a crucial role in antiviral and against coronavirus responses.

Thereby, we need to understand immune and inflammatory conditions that involve COVID-19. A recent study of 41 hospitalized patients with high--levels of pro-inflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α were observed in the COVID-19 severe cases [11].

Another report demonstrated increased cytokine levels (IL-6, IL-10, and TNF-α), lymphopenia (in CD4+ and CD8+ T cells), and decreased IFN-γ expression in CD4+ T cells are associated with severe COVID-19 [20].

Named "cytokine storm" it may have a major role in the pathogenesis of COVID-19 may to be related a downstream cytokine cascade involving IL-1, IL-6, IL-12 and TNF-α [21], followed by the development of lung tissue damage resulting in ARDS, sepsis, and organ failure. The risk of respiratory failure in patients with circulating IL-6 > 80 pg/ml was 22-fold higher with a median time to mechanical ventilation of 1.5 days [22].

Recently, a histopathological study with 4 patients in pos-mortem presented a rigorous lungs examination showing a bilateral diffuse alveolar damage with a comparatively mild-to-moderate lymphocytic infiltrate, composed of a mixture of CD4+ and CD8+ lymphocytes. The dominant process in all cases was consistent with diffuse alveolar damage, with a mild to moderate mononuclear response consisting of notable CD4+ aggregates around thrombosed small vessels, and significant associated hemorrhage [23].

A rapid and well-coordinated innate immune response is the first line of defense against viral infections, but dysregulated immune responses may cause immunopathology [24-26]. The innate immune system utilizes pathogen associated molecular patterns (PAMPs) to recognize the invasion of the virus. After a long intracellular signaling cascade, transcription factors induce expression

of type I IFN and other pro-inflammatory cytokines and respond at the first-line defense [27]. The interferon (IFN) type I is essential to the innate immune response against viral infection in association with controlling viral replication and effective adaptive immune response. However, SARS-CoV and MERS-CoV, a SARS-CoV-2 similar virus employes multiple strategies to interfere with the signaling leading to production, function or associated to type I IFN cascade [27-29].

When talking about social isolation and pandemic, there is a need to understand behavioral aspects that can influence the health of population, being exercise a factor of interest, which can have both positive and negative effects on immune function and possible susceptibility to illnesses and upper respiratory diseases.

A single bout of exercise has a profound effect on total number and composition of circulating leukocytes. After a dynamic exercise (minutes) the total leukocyte count increases two- to threefold whereas prolonged endurance exercise (30min-3h) counts for a fivefold increment. Exercise-induced leukocytosis, mainly neutrophils and lymphocytes with a smaller contribution being made from monocytes, is a transient phenomenon, with normal counts returning to pre exercise levels (6–24 h) after exercise cessation. 30–60 min after exercise cessation, a rapid lymphocytopenia [30-32] occurs concomitantly with a sustained neutrophilia [30,33].

Acute exercise causes substantial increases in hemodynamics, which place greater mechanical forces on the endothelium, thereby the leukocytes to demarginate and enter the free-flowing circulation, in association there are more levels of shear stress within the capillary structures, driving more leukocytes into the peripheral circulation.

Physical activity results in the secretion of catecholamines and corticotropin releasing hormone and cortisol, which are importantly responsible for the mobilization of monocyte during exercise, lymphocyte within minutes of engaging in dynamic exercise and neutrophil that continue their increase, often reaching peak values within a few hours after exercise cessation [34,35].

Many studies demonstrated an important innate cells response to acute moderate-intensity exercise, for example, it enhances neutrophil chemotaxis [36], as phagocytosis is enhanced immediately after a single exercise bout [37], but neutrophil degranulation in response to bacterial stimulation appears to be impaired [38]. After moderate intensity exercise the neutrophil oxidative burst continues to be enhanced, however, this is not true after exhaustive or prolonged exercise [38,39], other findings are related to well-trained athletes that are sensitive to the increases of training load, what present loss-making alterations in the neutrophil-monocyte oxidative burst, CD4/CD8 ratios, lymphocyte proliferation, antibody synthesis, and NK-cell cytotoxic activity [41-45]. What can occur during 1-3 weeks of intensified training, generating reductions in neutrophil function, lymphocyte proliferation and mucosal IgA [42,43,46].

Immunoglobulin A (IgA) is an important part of the mucosal immune system. There is not a consensus on the impact of acute exercise on salivary IgA (sIgA), because many factors may influence the response like a training status, intensity and duration of the exercise bout, saliva collection, nutrition [30].

The inverse relationship between sIgA concentrations and risk of airway infections in exercising and non-exercising populations has demonstrated differences between these two populations [46-48]. The impact of exercise

intensity on sIgA concentrations and secretion rates has demonstrated greater decreases in sIgA associated with prolonged high intensity exercise, whereas moderate increases in sIgA occur in response to short duration moderate intensity exercise [48-51].

A study monitored the stress-induced alteration in concentrations of sIgA and cortisol, and the incidence of upper respiratory tract infections over the course of a 9-week season in college. 14 student-athletes and 14 college students, all being young and women, demonstrate decreased levels of sIgA and increase in the indices of training (load, strain, and monotony) were associated with an increase in the incidence of illness during the 9-week competitive soccer season [52].

The "open window" hypothesis is an important idea that explains when an endurance athlete repeats bouts of acute strenuous exercise without adequate recovery why opportunistic infections may enjoy this till 72h after the exercise [53]. Although exercise immunology researchers discuss the "open window" and if it is the only real association between upper respiratory infections or symptoms and the strenuous exercise, a large body of evidence supports the proposition that elite athletes undertaking prolonged heavy intensive exercise can exhibit immune changes, in association with physiological, metabolic, and psychological stressors, and pathogen/allergen exposure, that increase the risk of infection and/or airway inflammation [54].

Otherwise, regular moderate-intensity exercise has been linked a to better vaccine responses [55,56], lower numbers of exhausted T-cells [57], increased T-cell proliferation [58] lower levels of circulating inflammatory cytokines [59], increased neutrophil phagocytic activity [60], greater NK-cell cytotoxic activity [61], indicating that regular moderate-intensity exercise is capable of improving, or maintaining, immunity across the life [62]. In addition, may help prolong or reinvigorate thymic activity, which we can observe with increased plasma levels of IL-7 [63].

Concurrently, subtle elevations in stress hormones released from skeletal muscle, notably interleukin-6 (IL-6), is observed during acute bouts of moderate-intensity exercise; however, the pleiotropic nature of IL-6 appears to provide protection (versus harm) to immunity via directly suppressing potent inflammatory cytokines [e.g., tumor necrosis factor alpha (TNF-a)] in the lungs, creating an anti-inflammatory milieu for several hours post-exercise [64].

The literature presents many studies about competitions that demonstrates the profile between athlete high-level moment and illness. In the Rio Olympic Games, in a total, 11 274 athletes (5089 women, 45%; 6185 men, 55%) was reported for Rio 2016 medical staff 651 illnesses over the 17-day period (47% affected the respiratory and 21% the gastrointestinal systems) [65].

In the 2010 Fifa World Cup Ninety-nine illnesses were reported in 89 players (12.1% of all players). Most illnesses affected either the respiratory (40; 40.4%) or the digestive (26; 26.3%) system. The most frequent diagnoses were acute upper respiratory tract infection (31; 31.3%) and gastroenteritis (21; 21.2%) [66].

Another factor is the carbohydrate availability, which an essential component to the immune performance, because to perform in a state of glycogen depletion there is an increased catecholamine and glucocorticoid, creating a greater decline of the T-cell, NK-cell, and neutrophil and depressed immune function compared to exercise on a normal or high carbohydrate diet [67,68].

Therefore, the previous extensive medicine and immunological knowledge provide us with the understanding that the increased incidence of infection in athletes is multifactorial maybe physical, psychological, environmental or nutritional what suppress the immune system [69]. In addition, a variety of causes can be an association with airway symptoms and could include physical damage such as drying of the airways [70], asthma and allergic airway inflammation [71] and psychological impacts of exercise on membrane integrity [72].

Special considerations regarding exercise and immune health must be addressed for older adults who represent the growing population globally, and incidentally are the most sensitive to developing infectious disease. Immunosenescence described as the phenomenon responsible for the inextricable deterioration of immune competency that occurs with increasing age, is believed to be the primary factor explaining the lowered immune vigilance, poorer responses to vaccinations and the greater risk, and morbidity, associated with infectious diseases, including COVID-19 outbreak. Given the already described beneficial effects of habitual moderate-intensity exercise on aspects of immunity in younger populations, physical activity is suggested to be a logical therapeutic strategy to abate aging effect son the immune system. It is well supported by a growing body of evidence from epidemiological and experimental studies in older adults indicating that regular participation in moderate-intensity exercise attenuates age-related oxidative stress and reduces the frequency of various immune biomarkers that are associated with compromised immunity, thereby suggesting that exercise may delay the onset of immunosenescence and attenuate the risk of infection [73].

Suggestions

In consideration of the knowledge previously explained and possible association to doubt moment and SARS-CoV-2 risk contagion, this research group proposed some suggestions from athletes and non-athletes during the COVID-19 pandemic, looking up a health manutention and good conditions to a future return to the competitions. Thereby, avoid SARS-CoV-2 infection and/or severe complications.

1- We considered that this moment is not adequate to a high level of training/extreme physical effort. Preserve your regular physical activity and moderate intensity, avoiding greater risks of contamination and detraining. You must know that for each week of total inactivity, you can loss of up to 10% of fitness [64].

2- Measures to reduce or stop smoking has fundamental importance. Approximately six million people worldwide die due to tobacco use each year [74]. The cigarette contributes to the pathogenesis and a recognized risk factor of chronic obstructive pulmonary disease (COPD), hypertension, cardiovascular disease, cancer, chronic systemic diseases with inflammatory components such as atherosclerosis, and type 2 diabetes mellitus [75,76]. Smokers are vulnerable to respiratory viruses and the tobacco upregulates the angiotensin-converting enzyme-2 (ACE2) receptor compared to non-smokers, irrespective of tissue subset or COPD

status, increasing pulmonary ACE2 expression by 25%, which is the receptor for both the severe acute respiratory syndrome (SARS)-coronavirus SARS-CoV and SARS-CoV-2. Thereby, smokers can be more susceptible to the development of COVID-19 [77,78].

3- Avoid changes in your treatment for chronic diseases, pulmonary or not, without the advice of your physiciam.

4- Avoid medications and formulas without a scientific basis for prevention and treatment to COVID-19 infection.

5- Avoid alcohol ingest and maintain your sleep quality.

6- Aerobic or resistance activities in safe environments and respecting the adequate social distance. Preferably, in covered and closed places that can be thoroughly cleaned after the activity and following the recommendations of the competent local authorities. It is so necessary because droplets travel a distance 1.8 meters in the air and the average life of COVID-19 is 2.7 hours in the air and 13 hours on steel [77].

7- Maintain the hygiene of your sports equipment.

8- Make an adequate ingest of proteins and carbohydrates, always consulting your support professional, prioritizing a multidisciplinary work between nutritionists, doctors, physical educators, in addition to your mental health, and those around you, seek assistance from your sports psychologist and other competent professionals for your health.

9- We do not recommend training in case of fever in a COVID infection or others suggest symptoms.

10- Exercise at home using various safe, simple, and easily implementable exercises is well suited to avoid the airborne coronavirus and maintain fitness levels. Examples of home exercises include walking in the house, lifting and carrying food bags, alternating leg, stair climbing, stand-to-sit and sit-to-stand using a chair and from the floor, and sit--ups and pushups [78-80].

Conclusion

In conclusion, regular exercise training of moderate intensity is believed to exert beneficial effects on immune function and must be associated to the suggestions.

We sought to clarify the importance of the regular exercise of a moderate intensity and the likely risks evolvement to inadequate exercise associated with poor diet and habits, and physiological alteration. In this way, we advise moderation, tranquility, and patience in this pandemic period.

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