Arquivos de Asma, Alergia e Imunologia

Review Article

Vaccination and exercise: immunology in action in pandemic times

Vacinação e exercício: imunologia em ação em tempos de pandemia

Sérgio Duarte Dortas-Junior[1], Guilherme Gomes Azizi[1], Solange Oliveira Rodrigues Valle[1]

ABSTRACT

COVID-19 is a disease caused by SARS-CoV-2, which was first described in Wuhan in 2019. Since then, it has caused the death of millions of people. COVID-19 is characterized by flu-like and gastrointestinal symptoms and may become severe. The importance of understanding how to improve vaccination effectiveness has led to the investigation of factors that may influence immune response. Exercise has been associated with improved immune function and, therefore, may be a potential adjuvant to vaccine-induced immune responses. Chronic training (high levels of physical activity over a prolonged period [months/years]) or acute exercise alone (engaging in a single exercise session [minutes/hours)] are two segments related to the immune response to physical exercise. Acute exercise is known to have short-term effects on the immune system, but there seems to be contrasting effects between moderate exercise sessions and prolonged exercise. In the absence of prophylactic medication or effective treatment, vaccination plus exercise, particularly in populations at risk for immune dysfunction such as older adults, should be encouraged. Thus, in this review, we aimed to discuss and hypothesize the effects of exercise on vaccination responses. Exercise is presented as an adjuvant to improve the immunological effects of vaccination; however, as the COVID-19 vaccination advances worldwide, studies with regular monitoring will be necessary to evaluate the correlation between physical activity and the immune response to these vaccines.

Keywords: Immunology, exercise, vaccination.

RESUMO

A COVID-19 é a enfermidade causada pelo SARS-CoV-2, descrita em 2019, em Wuhan. Desde então, causou a morte de milhões de pessoas. A doença caracteriza-se entre sintomas gripais e gastrointestinais, podendo evoluir com gravidade. A importância de compreender como melhorar a eficácia da vacinação levou à investigação de fatores que podem influenciar a resposta imune. A prática de exercícios foi identificada como um fator que pode melhorar a função imunológica e, portanto, ser um potencial adjuvante para respostas imunes. O treinamento crônico, ou altos níveis de atividade física durante um período prolongado (mês/anos) e, separadamente, o exercício agudo – a realização de uma única sessão de exercício (minutos/horas), são dois segmentos relacionados à resposta imunológica ao exercício físico. O exercício agudo é conhecido por gerar efeitos de curto prazo sobre o sistema imune, mas parecem existir efeitos contrastantes entre sessões de exercícios moderados e exercícios prolongados. Na ausência de uma medicação profilática ou tratamento efetivo, a existência de vacinas e associação com a prática de exercícios, particularmente em populações em risco de disfunção imunológica, como idosos, deve ser estimulada. Assim, nesta revisão os autores buscam dissertar e hipotetizar sobre os efeitos do exercício nas respostas à vacinação. Enfim, a prática de exercícios se apresenta como adjuvante dos efeitos imunológicos sobre a vacinação, todavia, com o andamento da vacinação global para SARS-CoV-2, serão necessários estudos com acompanhamento regular para que possamos avaliar a correlação entre a atividade física e a resposta imunológica a estes imunizantes.

Descritores: Imunologia, exercício físico, vacinação.

COVID-19, a disease caused by the SARS-CoV-2 coronavirus, was initially described in late 2019 in Wuhan (China). Since then, the virus has spread throughout the world, causing the infection and death of millions of people.[1-3] The disease presents with flu-like symptoms (fever, chills, cough; 83% of patients),

1. Hospital Clementino Fraga Filho - Universidade Federal do Rio de Janeiro, Immunology Service - Rio de Janeiro, RJ, Brazil.

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pneumonia (31% of patients), severe acute respiratory syndrome (17% of patients), nausea/vomiting (1% of patients), and diarrhea (approximately 2% of patients).[4-6]

A number of drugs are being explored to treat the disease, however the best scientific evidence concludes that no medication is effective in preventing or "early treatment" for COVID-19 to date.[7] In this way, the scientific community and the biotechnology industry have been working tirelessly to develop vaccines to prevent SARS-CoV-2 infections. An ideal vaccine for SARS-CoV-2, to fight the pandemic, should have the following features: (1) promote long-lasting protective immune responses; (2) possibility of administration to all, regardless of comorbidity or age, immunological status, pregnancy/breastfeeding status; (3) unable to potentiate antibody-dependent facilitation (ADE) or immunopathology/lung inflammation; (4) be thermostable, to allow transport and storage in developing countries with unsatisfactory refrigeration facilities; (5) be highly immunogenic in the general population, including the population with antibodies resulting from previous infection.[8]

In recent times, the importance of understanding how to improve vaccination effectiveness has led to the investigation of factors that can influence the immune response. There are several well-established demographic and behavioral characteristics that are known to be associated with reduced responses to vaccination. The first one is the age group, which leads to immunosenescence; followed by other clinical conditions such as malnutrition, type 2 diabetes mellitus, cardiovascular diseases, rheumatological diseases, certain oncologic diseases and osteoporosis.[9-12] In addition, other behavioral factors, such as chronic stress, depression, excessive alcohol consumption, dietary restriction or excessive weight loss, and smoking are known to decrease the effectiveness of the immune response to vaccinations and/or change susceptibility to infections.[13]

Exercise practice has been identified as a factor that can improve immune function in some situations and, therefore, serve as a potential adjuvant for immune responses.[14] In fact, interest in exercise-induced changes in immune function can be seen in two segments: exercise or chronic training, or high levels of physical activity over a prolonged period (months/years), and separately acute exercise: the performance of a single exercise session (minutes/hours).[14]

Acute exercise is known to have many short-term effects on the immune system, but there seem to be contrasting effects between moderate exercise sessions and prolonged/intense exercise sessions.[14,15] A single bout of exercise is referred to here as "acute exercise," but the intensity and duration can have different effects on the immune system. Prolonged intense exercise, such as completing a marathon, appears to result in temporary suppression of the immune system, described as the "open window hypothesis", related to a higher rate of self-reported symptoms of upper airway infection when compared to those who perform physical activity of lower intensity and duration[14-16] After intense and prolonged exercise, the phagocytic function of neutrophils, the number of natural killer (NK) cells and the total lymphocyte count are reduced during the following 2-24 hours.[17] On the other hand, moderate exercise stimulates the immune system, exemplified by the sudden influx of both NK cells and $CD8^+$ lymphocytes (increasing to 10-fold and 2.5-fold, respectively), which favors an effector memory immune response. This effect is driven by the stimulation of beta-2-adrenergic receptors on the surface of lymphocytes (due to adrenaline released during exercise), leading to endothelial detachment and lymphocyte recirculation, which also induces the expression of $CD4^+$ B cells and regulatory T cells. In addition, exercise helps maintain immune homeostasis by homing in the bone marrow and increasing apoptosis of worn-out/senescent T cells, thereby stimulating the production and release of new progenitor cells (IFN-producing $CD8^+$ T cells).[16]

The ability of exercise to induce a pro-inflammatory environment in the muscles may result in an increase in lymphocytes directed to the vaccine administration site, and/or an increase in antigen uptake and processing, making the initial phase of the immune response more efficient. In fact, exercise seems to mobilize leukocytes with tissue-directed return potential, which could contribute to the development of a proinflammatory environment.[18] Another mechanism is the well-known leukocytosis in response to exercise, which is driven by neuroendocrine mechanisms, and is associated with an increase in the number of circulating monocytes and dendritic cells from antigen-presenting cells (CAA), increasing the possibility of migration of these cells to the site of antigen exposure. Finally, lymphatic drainage is also known to be elevated during muscle contractions, and therefore exercise may enhance the immune response by transporting cells from the site of antigen administration (vaccination site) to the draining lymph nodes.[19]

Given the importance of vaccination in preventing morbidity and mortality due to infectious diseases, including viral infections, and the variability of the vaccine response, particularly in vulnerable populations, the role of exercise as an important moderator in the effectiveness of vaccines is determined. In addition, it is possible that the elderly obtain great benefits for their immune health induced by exercise.[14]

In this narrative review, the authors seek to discuss and hypothesize about the effects of exercise on responses to vaccination, through some clinical studies on the effects of exercise on responses to vaccination.

Edward et al. carried out two studies where they identified that a moderate cycling session or an activity of the same duration (45 min) are able to significantly increase antibody responses to vaccinations for influenza and meningococcal meningitis. However, the improvements were not uniform, with only women showing a significant increase for the influenza vaccine, and only men showing a significant increase for the meningococcal vaccine.[20,21]

We selected 133 participants without comorbidities, randomized to one of four groups that received the anti-pneumococcal (anti-Pn) vaccine. Specific or control physical exercise, receiving a full or half dose of anti-Pn vaccine. Before vaccination, the groups selected for exercise performed arm and shoulder exercises for 15 minutes, the control groups rested in silence. Antibody levels to the 11 pneumococcal strains of this vaccine were assessed at baseline and at one month. The exercise groups showed a significantly greater increase in antibody levels than the control groups. When doses were compared, it was found that those who exercised had significantly greater responses than those who rested in the half-dose group, but in the full-dose groups the responses were similar.[22]

Three cross-sectional studies with adult subjects who exercise regularly found statistically significant positive effects of higher levels on the response to vaccination. Using the anti-influenza vaccine, Kohut et al. reported higher concentrations of IgG and IgM in individuals who exercised vigorously, suggesting that the practice of regular exercise for at least one year may contribute to a greater increase in the immune response to immunization against influenza in the elderly.[23-25]

Four randomized clinical trials evaluated the elderly. Three studies employed similar interventions for 10 months with groups of moderate-intensity aerobic exercise, three times a week, for 25-60 min per session, and control groups participating in flexibility training for similar periods. All three studies found beneficial effects on vaccine responses in exercise groups.[26-28] The latest randomized clinical trial evaluated influenza vaccine response in older adults randomized to participate in three 60 min classes of Taiji and Qigong (a fusion of martial arts and meditation) per week for 20 weeks or to maintain usual activities. In this study, vaccination was administered in the first week of intervention, and at weeks 3 and 20 the exercise group had significantly higher antibody titers than at baseline, while the control group had no increase.[29]

Kapasi et al. tested secondary antibody production in older versus younger mice after bouts of physical exercise. The secondary antibody response appeared to be exercise-dependent, because older mice that received a bout of intense exercise demonstrated increased levels of antibodies compared to elderly mice that did not exercise. In addition, old mice that received booster doses of immunizers after single physical activity and intense exercise achieved antibody levels comparable to those seen in young mice.[30]

Recently, it was investigated whether regular physical training could improve the response of specific antibodies to the influenza virus in elderly seropositive for cytomegalovirus (CMV). Eighty elderly were divided into two groups: non-practitioners of physical activity ($n = 31$; age = 74.06 ± 6.4 years) and practitioners of regular combined physical training for at least 12 months ($n = 49$; age = 71.7 ± 5.8 years). Volunteer groups underwent influenza vaccination and blood samples were collected before and 30 days after vaccination. Regarding the influenza-specific antibody response, higher levels of specific immunoglobulin M (IgM) were observed in both groups post-vaccination compared to pre-vaccination values. Serum levels of anti-influenza and anti-CMV IgG, as well as interleukin 6 (IL-6) and IL-10, were similar between the evaluated times. However, the post-vaccination IL-10/IL-6 ratio was higher in the physical activity group than before vaccination.[31]

In addition, negative correlations between IL-10 and CMV-specific IgG were found in all pre- and post-vaccination groups of volunteers, while a positive correlation between IL-10 and influenza-specific IgG pre- and post-vaccination was observed in the group. physical activity practitioner, as well as showed significant reductions in the proportion of $CD8^+$ effector T cells to naive and increased levels of IL-10 post-vaccination. Thus, this study demonstrated that the improvement in the response to vaccination in elderly seropositive for CMV was related to an anti-inflammatory state and an increase in naive $CD8^+$ T cells, associated with the regular practice of physical activity.[31]

A case of a male individual with no history of comorbidities, who was followed up with graded bicycle exercise before and after SARS-CoV-2 infection, and again after receiving adenovirus vector-based COVID-19 vaccine, has recently been reported. Using whole blood SARS-CoV-2 peptide stimulation, IFN-γ ELISPOT assays, flow cytometry, virus-specific T cell expansion assays, exercise was shown to robustly mobilize SARS-specific T cells. CoV-2 (T $CD3^+$/$CD8^+$ and T $CD3^+$ double negative [$CD4^+$/$CD8^+$]) into the bloodstream and capable of recognizing the spike protein, membrane protein, and nucleocapsid antigen. Neutralizing antibodies to SARS-CoV-2 were transiently elevated during exercise after infection and vaccination. However, data are presented in only one individual and within controlled parameters.[32]

In view of all these findings and in the absence of prophylactic medication or effective treatment, the existence of vaccines and their association with exercise, particularly in populations at risk of immune dysfunction, such as the elderly, should be encouraged.

Finally, when the COVID-19 pandemic promoted changes in life habits due to quarantine, reducing the practice of outdoor activities, anti-SARS-CoV-2 vaccines emerge as a tool of hope for the gradual return to activities. The practice of exercises is presented as an important adjuvant of the immunological effects on vaccination, however, with the progress of global vaccination for SARS-CoV-2, studies with regular follow-up will be necessary so that we can evaluate the correlation between physical activity and the immune response to these immunizers.

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Corresponding author:
Sérgio Duarte Dortas-Junior
E-mail: sdortasjr@gmail.com