Physical exercise as immune adjuvant: review

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Summary

The use of adjuvants in order to enhance the effect of vaccines has been the focus of several research studies. However, some substances with the potential of being used as adjuvants may exhibit high toxicity and side effects. In this sense, new methods which are less invasive and more effective to perform this function are being developed. Thus, several studies have investigated the effects of exercise on immune parameters. It is suggested that physical activities can improve the immune response and may even act as exogenous adjuvants, increasing the host's immune response efficiency after vaccination. Therefore, the objective of this study was to review the literature in order to find out how different types, intensities and duration of exercise can act as adjuvants for immunization. To this end, studies that investigated the effects of different exercise modalities or protocols were selected, all of them investigating the effectiveness of immunization after vaccination, both in humans and in animal models. Regarding exercise intensity, there is a consensus that moderate activities increase the efficacy of vaccines, while light intensities do not cause any effect. Acute sessions of resistance exercise for upper limbs demonstrated to be effective for immunization of young people, while for the elderly, such efficacy was observed with the regular practice of aerobic exercise at a moderate intensity. In conclusion, from what has been observed in the literature, it seems to exist some evidence that physical exercise can be used as a complement to vaccination, especially when it comes to immunization of the elderly.

Key words:
Physical activity.
Immunology. Vaccines.
Immunomodulation.

El ejercicio físico como coadyuvante inmunológico: una revisión

Resumen

El uso de coadyuvantes para aumentar el efecto de vacunas ha sido el foco de varios estudios de investigación en el campo de la salud. Sin embargo, algunas sustancias con potencial coadyuvante pueden tener efectos secundarios con una alta toxicidad por lo que son necesarios métodos menos invasivos y más eficaces para realizar esta función. Varios estudios, investigando los efectos del ejercicio físico sobre diversos parámetros inmunológicos, han mostrado que la práctica de ejercicio físico de ciertas intensidades provoca mejoras en la respuesta inmune y que incluso puede actuar como coadyuvante exógeno inmunitario, por lo que puede ser una herramienta importante para aumentar la eficacia de la respuesta inmune después de la vacunación. El objetivo de este trabajo es revisar los estudios que demuestran cómo diferentes tipos, intensidades, y duración de ejercicios físicos pueden actuar como coadyuvantes inmunitarios. Para ello se seleccionaron estudios que investigaron los efectos de diferentes protocolos o modalidades de ejercicio sobre la eficacia de la inmunización después de la vacunación, tanto en humanos como en modelos animales. En cuanto a la intensidad del ejercicio, hay un consenso de que las actividades con intensidad moderada aumentan la eficacia de las vacunas, mientras que las intensidades ligeras no tienen tal efecto. Entrenamientos únicos de ejercicio de fuerza de los miembros superiores han demostrado ser eficaces para la inmunización de jóvenes, mientras que para las personas mayores, tal eficacia se observó con la práctica regular de ejercicios aeróbicos a una intensidad moderada. La literatura estudiada permite afirmar que hay evidencia de que el ejercicio físico se puede utilizar como un complemento de la vacunación, especialmente en la vacunación en ancianos.

Palabras clave:
Actividad física.
Inmunología. Vacunas.
Inmunomodulación.

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Introduction

The regular practice of physical exercise has been used as an effective method for disease prevention and also as a therapeutic method in some cases[1]. Several studies have investigated the effects of exercise on immune parameters[2-4]. Certain intensities of exercise may improve the immune response, resulting even in protection against certain autoimmune diseases[5].

Usually, the most effective method for protecting against some pathogens is the immunization through vaccination, as it provides protection to the host without manifesting the same disease[6]. However, some vaccines may have limited effectiveness, which instigate the use of adjuvants to potentiate their effect. Previous studies have indicated that the practice of different types of exercise can function as an exogenous adjuvants, increasing the efficiency of the host immune response after vaccination[7-9].

However, there is still some controversial issues regarding the ideal intensity and protocols that should be used in order to reach immune protection. Thus, the objective of the present review was to demonstrate how different types, intensity and duration of exercise can act as adjuvants for vaccination.

Physical exercise

Physical Exercise is characterized as a planned and repetitive structured physical activity with the purpose of improving or maintaining physical abilities[10,11]. The classification of the type of exercise is related to the bioenergetic pathway used for energy production. There may be a predominance of oxidative metabolism, thus characterizing aerobic exercise, or may occur predominantly lactic glycolytic metabolism, which is characterized as anaerobic exercise[12]. The determinant factors for energy pathway use during exercise are time and intensity. Exercises of short duration and high intensity culminate in lactic glycolytic metabolic pathway, whereas those of long duration and low intensity lead to oxidative metabolism[13].

Moreover, one can classify exercise as chronic or acute, according to the number of sessions. Acute exercise is characterized by a single session that is capable of producing metabolic and cardiovascular effects which persist only a few minutes/hours. On the other hand, chronic exercise is characterized by the accumulation of exercise sessions performed repeatedly over weeks or months (featuring training), leading to physiological and metabolic adaptations more durable, improving the physical fitness of the practitioner[11].

During exercise the body is taken out of its homeostasis, since there is an immediate increase in energy demand, requiring several physiological adaptations (cardiovascular, hormonal and metabolic) to reach this demand[14]. Additionally, exercise can change several parameters related to immune system responses, and these changes are related to the type, intensity and duration of exercise and/or physical training[15].

Vaccines

Vaccines are antigen compounds capable of stimulating a state of partial or total resistance against a particular infection[16,17]. The first vaccines were partially purified and consisted of a live attenuated virus, obtained by cultivation of microorganisms with subsequent attenuation, which could be accomplished by: chemicals, heat, or passages in culture, and also as it is currently held by gene deletion[18,19]. The vaccine could also be made of inactivated whole microorganisms, using chemical methods such as formaldehyde and beta-prolactione[18,19]. Over time, new technologies were introduced, rising subunit vaccines (second generation) consisting of purified antigens from natural or synthetic sources, such as purification and inactivation of a toxin to form a toxoid protein[20] and the use of purified polysaccharides (e.g., vaccines against pneumococcus). The use of genetic engineering has enabled the production of recombinant vaccines. In this case, the gene of a microorganism responsible for the production of an antigen is isolated, cloned, and then inserted into another microorganism (examples are: hepatitis B, human papilloma virus). The genetic vaccines have emerged with the introduction of fragments of genes encoding potentially immunogenic antigens in viral vectors or DNA plasmid without the need for adjuvants, which have been effective for tumors, allergy and infectious/autoimmune diseases[21,22].

Adjuvants

Some vaccines can present antigens with low degree of immunogenicity, which necessitates the use of substances that potentiate their action in the body, such as adjuvants[23]. Therefore, adjuvants are nonspecific substances, which can amplify the cascade of events that compose the immune response. Furthermore, they assist the formation of an early, high and lasting biologically active immune response[24,25].

The classic examples of the best components used as vaccine adjuvants include bacterial wall extracts (especially mycobacteria), paraffin oils, metalic salts (calcium or aluminum), endotoxin, mineral oil, saponins and emulsions[26]. Currently, liposomes, interferons, cytokines and immune stimulating complexes are being investigated as potential adjuvants because they share some of the following properties: protective antigen degradation, ability to sustain the release of antigen over a long period of time, and intracellular delivery of antigen, which contributes to the stimulation of cytotoxic T cells by targeting antigen-presenting cells[24].

The efficacy of adjuvants can be elucidated by several mechanisms. Thus the adjuvants may: induce a local inflammation (which causes the recruitment of cells as macrophages and lymphocytes); stimulate cell mediated immunity; forming an antigen depot (causing this to be released slowly thus prolonging their interaction with macrophage); enhance antibody production, increase the speed and duration of the immune response; modulate the avidity, specificity, isotype and subclass distribution of antibodies (which stimulates cytotoxic T lymphocyte response); induce mucosal immunity and increase the response in immunologically immature individuals[26,27].

Several substances are being tested in order to assess possible adjuvant activity. However, some of them have demonstrated high power associated with high toxicity, which highlights a major problem, preventing its use for such purpose[28]. Thus, it becomes necessary to use less invasive methods to act as adjuvants for immunization.

Immunization and physical exercise

The frequent practice of exercise at safe intensities (mild to moderate) is closely related to factors such as well-being, reduced psychological stress and maintaining a healthy body[29]. Exercise operate in different organic systems, and one of the most important one for maintaining health is the immune system[30]. Several components of the immune system, especially Natural Killer cells and Interleukin-6 (IL-6), are changed by physical activities increasing the body's defense against pathogens[30,31].

The voluntary aerobic exercise at moderate intensity (60-70% VO_2max) significantly improved the proliferation of CD4+ T cells (collected in the spleen, mesenteric lymphnodes and in Peyer's patches), Tumor Necrosis Factor Alpha ovalbumin-specific (TNF-α OVA-specific), IL-5 OVA-specific as well as increased levels of IFN-γ and IL-2 from CD4 + T cells from C57BL / 6 mice that received vaccination with OVA subcutaneously and intranasally[32]. These results showed that this type of exercise increases the cell-mediated immune response in healthy mice after vaccination.

In a similar way, mice vaccinated against B hepatitis, who exercised at moderate intensity (approximately 70% VO_2max belt) increased the cellular immune response by increasing the production of Th1 cytokines that cause proliferation antigen-specific T cells for virus[33]. However, the same exercise protocol in high intensity (above 91% VO_2max) debilitated the immune response mediated by cells[33].

In a study conducted with 60 students, it was observed that a single session of progressive exercise on a ergometer bicycle increased antibody response, levels of IL-6 (which may be related to a fundamental mechanism in antibody response against strains A/Panama/2007/99 (RESVIR-17) influenza virus) in women, whereas in men there was no significant change[7].

A protocol of upper limb resistance training has been used by Edwards *et al.* (2007), which compared the effects of this type of exercise on the response to influenza vaccination in young students. Female subjects who underwent the exercise protocol showed increased antibody response compared to the control group, whereas men who exercised showed reduced antibody titers. The IFN-γ responses were higher in subjects who exercised and were more significant in men than in women[9].

Regarding the type of exercise adopted as an adjuvant to vaccination, positive results (increased immune response) were observed in acute resistance exercise for upper limbs[9,34], above moderate until high intensity aerobic exercise[8,35,36], and progressive cycle ergometer tests[7]. However, no adjuvant effects were found for influenza and pneumococcal vaccines in individuals who underwent walking exercise at 55% of predicted heart rate for age (considered moderate intensity)[33]. The authors found that the adjuvant effect of vaccination occurs in exercises performed at intensity levels above considered moderate[37]. Such intensity causes increased secretion of endogenous opioids, which causes the improvement in antibody response due to the involvement in the mechanisms of their synthesis[38]. Furthermore, it was shown that moderate regular exercise increases selectively antigen-specific cell mediated responses after vaccination[3]2. Another relevant factor is that exercise at moderate intensity provides an improvement in chemotaxis and phagocytic activity of neutrophils, indicating that this cell type migrates with greater speed to infection sites, being effective against pathogens[33]. Moreover, moderate exercise can stimulate the immune system inducing a T-helper type 1 (Th1) response[39], which is remarkable for the development of a protective response against intracellular pathogens (viruses), and Th2, which directs the response to extracellular antigens and microorganisms[40,41]. When investigating the effects of one session of resistance exercises at different times before the influenza vaccination, Campbell *et al*. (2010), observed that concentrations of IL-6 were slightly higher primarily in groups that were immunized immediately and 48 hours after the exercise session, and cytokine levels in the group that was vaccinated 48 hours after exercising was greater than that of the others. However, these results were not significant; leading the authors to hypothesize that in young people, acute exercise can be effective as an adjuvant to vaccination only in cases where the control of the immune response of these individuals is depleted[42].

The adjuvant effect of physical exercise and vaccination was not observed in elderly practitioners[43]. The practice of low intensity exercises for 20 weeks increased levels of antibodies against influenza in this population. However, protection levels were not significant according to the parameters established for evidence of hemagglutination inhibition[43]. Immunization may be impaired in the elderly due to changes in the immune system with age, thus decreasing the effectiveness of vaccines[44]. Elderly practitioners of physical exercise showed higher levels of IgM and IgG anti-influenza, high proliferation of specific for influenza lymphocytes and mononuclear cells in the peripheral circulation[35], as well as high activity of granzyme B which indicates cytotoxic T lymphocyte systemic influence[36]. The cardiovascular training performed three times a week for 24 weeks in moderate intensity resulted in the elderly previously sedentary, increased response to influenza vaccine, keeping the hemagglutination titers greater than 40 pfu/ml[45]. It was observed that the same amount of flexibility exercises and balance caused no changes with respect to this variable[45].

Moreover, vaccination against influenza does not always provide adequate protection for the elderly, which makes moderate physical exercise an important ally for improving the immune response against this pathogen[35]. Thus, several studies have investigated exercise as a method to improve the effects of the immune response also postvaccination for this population[35,45-48].

Regular exercise promotes a low-grade chronic systemic inflammation. It can generate in the long term an anti-inflammatory response induced by the production of IL-6 in the muscle, which stimulates the appearance of other anti-inflammatory cytokines (IL-1ra and IL-10) and inhibits the production of proinflammatory cytokines like TNF-α[30]. The initial local inflammation causes the recruitment of cells such as macrophages and lymphocytes, which capture and present the antigen from vaccines[26]. This fact may explain the role of adjuvant immunization provided by exercise.

Final considerations

Considering this literature review, there is evidence that physical exercise can be used as an adjuvant to vaccination, especially when it comes to immunization of elderly. Exercises at moderate intensities appear to promote positive effects. However, there are still conflicting results related to gender, the ideal intensity and the type of exercise.

The use of exercise protocols, in certain populations, aiming to optimize the immunization process, can become a tool of great importance, mainly because it is a less invasive.

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