Arquivos de Asma, Alergia e Imunologia

Review Article

Relationship between exercise and the immune system

Relação entre exercício físico e sistema imunológico

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ABSTRACT

The human body always tends to seek a homeostasis state, trying to balance all systems. Physical exercise is present in the routine of individuals even with different goals, but the influence in the immune system isnt a relevant factor. The immune system is responsible for protecting the human body against some infections and diseases, and could be modulated in response by some regular physical exercise. At the moment there is a greater concern to keep efficient immunity, a practice of regular and moderate exercise can contribute to a better effectiveness of this system, thus, it can be considered a form of protection to the human body. The objective of this review was to synthesize some data from any studies presented in the literature that demonstrate the influence of physical exercise on the immune system response. Making it possible to understand the molecular mechanisms, physiological, metabolic and cellular changes that turn to a specific type of response in the human body.

Keywords: Immune system, exercise, inflammation, leukocytes.

RESUMO

O corpo humano tende sempre a procurar um estado de homeostase, buscando o equilíbrio entre todos os sistemas. O exercício físico está presente na rotina diária de indivíduos, mesmo com objetivos diferentes, porém a influência no sistema imunológico não é muitas vezes abordada como fator relevante. O sistema imune é responsável por proteger o organismo contra infecções e doenças, podendo ser modulado perante a resposta de exercícios físicos regulares. Tendo em vista que, atualmente, existe uma preocupação maior em tornar e manter a imunidade eficiente, a prática regular e moderada do exercício pode contribuir para uma maior eficácia desse sistema, dessa forma, podendo ser considerada uma proteção ao corpo humano. O objetivo dessa revisão foi sintetizar os dados de estudos presentes na literatura que demonstram a influência do exercício físico na resposta do sistema imunológico, tornando possível compreender as alterações moleculares, fisiológicas, metabólicas e celulares que levam a um tipo específico de resposta do organismo humano.

Descritores: Sistema imunológico, exercício físico, inflamação, leucócitos.

Introduction

Nowadays, sedentary lifestyle has been a habit among human beings. The increase in hours in front of computers, video games and television contributes to the increase in this population, which, consequently, reduces the time spent in physical activity, causing countless damages to health.[1] The benefit of exercise has been evident for a long time. In the fifth century BC, the physician Hippocrates already stated: "All parts of the body, if used sparingly and exercised in the work to which each one is accustomed, become healthy and well developed and age slowly; but if they are not used and are left idle, they become subject to disease, grow defective, and age rapidly." Unfortunately, in the 21st century, the belief in the value of exercise for health has faded, so much so that lack of exercise now represents a major public health problem.[2] It is of paramount importance that the population come back to believe in the benefits of physical exercise, as it is an ally to improve health and even has the ability to promote immune responses, benefiting the

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health of the individual as a whole. According to the World Health Organization (WHO), to have the health benefits, more than 300 minutes of weekly physical exercise at moderate intensity are recommended for healthy adults, or 150 minutes of weekly physical exercise at vigorous intensity, or a combination of moderate and vigorous intensity exercises.[3]

This article aims to carry out an integrative literature review relating the role that physical exercise plays on the immune system.

Immune system

The immune system is made up of several organs, cells and molecules with the purpose of adapting the organism to defend against infectious or non-infectious agents, and maintain body homeostasis.[4] Many physical stressors, such as surgery, trauma, burns, sepsis and physical exercise, induce a pattern of similar immune responses.[5] Faced with these physical stressors, our bodies mount this immune response that includes two stages: innate immunity and adaptive immunity. The first comprises physical and chemical barriers, in addition to the action of cells such as macrophages, dendritic cells (DCs), natural killer cells (NKs) and neutrophils. At this stage, several cytokines and interleukins (ILs) can also be mentioned, in addition to nitric oxide (NO). The second stage has T lymphocytes (TCD4 + and TCD8+) and B lymphocytes and their products, such as antibodies and cytokines, as a mechanism of action. This response, called adaptive, it can be subdivided into cellular immunity (mediated by cells) and humoral immunity (mediated by antibodies).[6,7] To facilitate the understanding between physical exercise and its influences on the immune system, we will present below the main soluble cells and molecules of the innate and adaptive immune system, influenced during physical exercise.

Neutrophils

Neutrophils represent about half of the total amount of circulating leukocytes, thus becoming the most abundant leukocytes in the blood, and being one of the first cells to reach the site of infection and activate the inflammatory process. This set of cells is part of the innate immune system and is essential for the host's defense, in addition to participating in several inflammatory conditions. For this response to happen, neutrophils are attracted by chemical mediators to the injury site, and this migration occurs in four steps: first, the neutrophils marginally approach the endothelium, then they roll over so that neutrophils can adhere to the endothelium and change the shape, in this way transendothelial migration takes place, and finally neutrophils leave the vessels and reach the inflamed tissues.[4] They are also important in phagocytosis, and this process is stimulated by the binding of receptors present on neutrophils to opsonins, IgG Fc, complement molecules such as C3b and Toll-like receivers(TLRs).[8] It is noted, then, that several elements are involved in the behavior of these cells, such as neuroendocrine mediators, steroid release, cytokine production and oxidation-reduction processes associated with the production of free radicals, all of these factors are influenced by physical exercise.[4]

One of the most pronounced characteristics of physical activity in immunological parameters is prolonged neutrophilia after acute exercise, of moderate intensity and long duration.[9] A study was carried out on males who underwent an indoor cycling class. In this research, acute variations in the levels of neutrophils present in the blood were verified, in which, immediately after exercise, the neutrophil count increased by 12%, and in a 24-hour recovery period the number was reduced to 19.8% and 11, 3% within 48 hours.[4] This increase in neutrophil levels is closely related to the increased expression of cell adhesion molecules after exercise, which may contribute to the extravasation of neutrophils into damaged tissue, including skeletal muscle (Figure 1).[10] A reduction in L-selectin (CD62L) expression has been reported immediately after exercise, followed by an increase during recovery.[11] The expression of CD11b also occurs in response to physical exercise.[12]

Macrophages and monocytes

Macrophages are tissue cells that bridge the gap between the innate immune system and the adaptive immune system. They act by producing cytokines, phagocytizing microorganisms, presenting antigens via MHC molecules and initiating the tissue repair process.[4,6] Exercise stress has a stimulating effect on most macrophage and monocyte functions.[13] The action of catecholamines released during exercise causes transient monocytosis, but exhaustive exercise in those individuals who have an adjacent inflammatory condition can reduce the number of macrophages recruited to the inflammatory site.[14] It

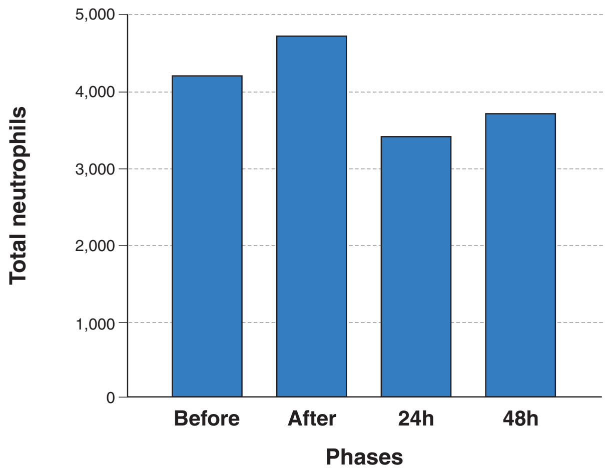

Figure 1
Total neutrophil counts at moments before, immediately after, 24h after and 48h after exercise.

has been shown that during and soon after exercise, chemotaxis, phagocytosis and cytotoxic activity are increased, possibly associated with increased secretion of cortisol, prolactin and thyroxine.[15,16] Prolonged and strenuous aerobic exercises decrease the expression of Toll-like receptors (TLRs) in macrophages and compromise the presentation of antigens to T lymphocytes, preventing, above all, the Th1 inflammatory response. This anti-inflammatory effect prevents tissue damage caused by inflammatory mediators and reduces the risk of chronic inflammatory diseases, but increases the susceptibility of infections by intracellular microorganisms.[17,18]

Dendritic cells

Dendritic cells have the ability to internalize antigens and express a large number of costimulatory molecules, being an important antigen-presenting cell for T cells, stimulating their clonal expansion.[19] They are also considered a bridge between the innate immune system and the adaptive immune system,[20] being one of the first cells to reach the site of infection.[4,6] Chiang et al. observed in rodents that, after five weeks of training on a treadmill with increments in speed and incline over the weeks, there was an increase in the number of dendritic cells, in their class II MHC expression and IL-12 production, suggesting the capacity of induction of cellular immune response.[21]

Natural killer cells

Natural killer (NK) cells are a heterogeneous population of T lymphocytes that express characteristic markers, such as CD16 and CD56,[22] and that are responsible for the recognition and lysis of cells infected by viruses, bacteria, protozoa and tumor cells, in addition to act against the spread of the tumor.[23] The cytolytic activity of these cells is increased by interferon-alpha (IFN-α)[24] and interleukin-2 (IL-2), while certain prostaglandins and immune complexes negatively regulate the function of NK cells.[22,25] This cell type is very responsive to the stimulus of physical exercise, exhibiting an increase of up to 6 times in its serum levels after physical effort.[26] This is mainly due to the responsiveness of these cells to increased levels of adrenaline and noradrenaline, which are released during exercise. This release, and consequently, the increase in serum NK cells, depends on the intensity and duration of physical exercise.[27] On the other hand, it was shown that after intense and long-term exercise, the concentration of NK cells and cytolytic NK activity tend to decrease below pre-exercise values. The maximum reduction in NK cell concentrations and, therefore, their lowest activity, occurs 2-4 h after exercise, probably due to the action of prostaglandins.[28]

Cytokines and chemokines

Cytokines are soluble glycoproteins that, in general, have a low molecular weight (between 5,000 and 30,000) and play a central role in mediating and regulating immune responses when launched at the site of inflammation.[29-31] Chemokines comprise a family encompassed by cytokines, responsible for mediating and moving leukocytes to areas of inflammation.[4] These substances have the ability to act as messengers between the cells of the immune, hematopoietic and neuroendocrine system.[32] These molecules can act as pro- or anti-inflammatory substances. The main anti-inflammatory cytokines are IL-10 and TGF-beta (transforming growth factor β) which can inhibit the production of pro-inflammatory cytokines. Among the pro-inflammatory cytokines we can mention IL-1, IL-2, IL-12, IL-18, IFN-γ and TNF-α. The production of anti-inflammatory cytokines, especially IL-10, can be regulated by a variety of factors, such as catecholamines, glucocorticoids and prostaglandin E2 (PGE2), which are produced during physical exercise.[32] IL-6, which is currently being called myokine, is a cytokine that can trigger several modulating functions due to the change in its physiological levels, inducing pro-inflammatory, anti-inflammatory effects or even both, depending on the body and/or cell group in which they are synthesized.[9,34] IL-6, during prolonged exercise, is released in high concentrations by skeletal muscles.[35-37] The plasma concentration of IL-8 chemokine may increase in response to inflammation resulting from a physical exercise session in which eccentric muscle contractions occur.[38,39]

Lymphocytes

Lymphocytes are divided into T and B lymphocytes, in which the T cell is responsible for eradicating infections caused by intracellular pathogens and activating other cells. B cells, on the other hand, are responsible for secreting antibodies and creating memory, when transformed into plasma cells after their activation. These cells are also responsible for antigenic memory, that is, in a new exposure, a faster and more intense immune response is induced, which helps to eliminate the pathogen more effectively.[4] During moderate physical exercise, the concentration of lymphocytes increases in the vascular bed and, after strenuous exercise, it decreases to levels below the pre-exercise period.[40,41] This drop can be a consequence of an apoptosis mechanism or due to the release of adrenaline and cortisol, which inhibit lymphocyte function and are released during high-intensity exercise.[10] The ratio between CD4 + and CD8 + lymphocyte levels decreases as CD8 + T cells increase in blood relative to TCD4.[42,43]

Immunoglobulins

Immunoglobulins are products of B cells that are secreted after contact with the specific antigen.[27] After high and medium intensity exercise, an increase in serum immunoglobulins has been described. This information can be explained by the contraction of plasma volume that occurs after exercise.[13] The influx of proteins from the extra to the intravascular, mainly represented by immunoglobulin-rich lymph, could also explain the finding.[43] However, the IgA, present in the mucous membranes of the upper respiratory tract and, therefore, responsible for protecting this system, can significantly decrease after high-intensity exercise, which may explain the prevalence of respiratory diseases that affect the upper airways in athletes (URTI).[27,44]

Physical exercise

Physical activity is considered one of the main components of healthy living. It can be used to maintain health and well-being, as it is capable of modulating some neurological and endocrinological aspects in individuals who undergo regular training. The practice of physical exercise is currently used as a means of health promotion and has been proposed as a non-pharmacological intervention that brings several benefits to the individual's health.[45] In addition to the functions related to the prevention of excess body weight, systemic inflammation and non-communicable chronic diseases, it is suggested that physical exercise has a beneficial potential in reducing communicable diseases, including viral pathologies, due to the stimulation of cellular immunity.[46,47]

The ability to carry out training depends on the metabolic responses of the human body to convert chemical energy from muscle tissues in the form of adenosine triphosphate (ATP) subsequently cleaved into adenosine diphosphate (ADP) into mechanical energy, which causes it to occur muscle contraction.[48] Seeking to understand the relationship between metabolism and physical exercise, numerous studies have been carried out, with the aim of demonstrating which cellular responses would be triggered by training and which variables could interfere with this cellular response.[17] The most common variable found in the researched articles concerns the intensity of training, classifying physical exercise according to the level of effort, which can be light, moderate or intense. This classification takes into account physiological parameters of the body such as maximum heart rate, maximum oxygen consumption and exercise perception index.[50]

Physical exercise is capable of generating stress for the body. Physiologically, there is loss of homeostasis, that is, there is a systemic imbalance due to changes in blood volume, body temperature and maximum oxygen consumption.[51] Before and during exercise, some chemical, neural and hormonal agents undergo adjustments, with the objective of providing cardiovascular changes with an increase in the frequency and pumping strength of the heart, changing the blood flow in proportion to the intensity of the exercise. In response to changes, the body modifies metabolic and physiological parameters to maintain balance, thus the cellular responses in the acute phase, in the short term, are different from the chronic phase, in the long term.[49]

Acute phase

An exercise session performed in isolation can be characterized as an acute phase, and in this phase some physiological effects may already occur. These effects can be divided into immediate and late effects. The immediate effects happen right after the exercise and the late ones from 24 to 72 hours after the exercise. The immediate acute effects correspond to sweating, increased heart rate and pulmonary ventilation, and the late effects consist of improved insulin sensitivity and catecholamine secretion. At the blood level we can find a leukocytosis, and this increase in leukocytes happens due to the increase in catecholamines. These substances induce an increase in the amount of neutrophils and natural killer (NK) cells,and some experimental studies have already shown an increase in the number of macrophages and a decrease in the expression of MHC II.[52-55]

Chronic phase

The chronic phase of physical exercise occurs after numerous training sessions performed on a regular basis. In this phase, there is an adaptation, and the stimuli of the acute phase become more effective. In this phase, muscles are strengthened, cardiovascular conditioning and lipid profile improve. This regular exercise practice, especially in a moderate way, makes the individual to create tolerance to stressful stimuli. This tolerance also takes place in the immune system. It is noteworthy that these changes are related to the type of exercise, intensity and load, that is, each type of training results in the activation or inactivation of cellular and molecular mechanisms, which can directly interfere with the human immune system.[13,56]

Types of training

Resistance training

Resistance training consists of carrying out exercises with the use of weights and machines, with the objective of working against muscular resistance, generating an overload on the muscle,[56] which favors muscular resistance and, consequently, an increase in lean mass and a reduction in body fat. With the regular practice of resistance training, it also generates a reduction in fat mass, which improves the physical adaptation of the body, facilitating daily activities. Weight training and weight lifting are examples of resistance training.[57]

Aerobic training

Aerobic training consists of a greater number of repetitions, longer duration and moderate intensity. During this type of exercise there is a greater consumption of oxygen by the body, in the form of ATP to generate muscle work. The benefits for the body are increased heart efficiency, reduced fat weight, improved mental health, mood and immune system. Cycling, swimming, and walking are examples of aerobic training.[56-58]

Intensity

The exercise intensity is related to the respiratory capacity (VO_2max) and has as variables the training volume, the exercise complexity, the individual's capacity and the duration time.[58] Physical exercise is a metabolic stress for the body, intense training generates even greater stress, as it increases the intracellular formation of reactive oxygen species (ROS) promoting greater oxidative stress.[21] Moderate or low intensity physical exercise helps a healthy immune response and reduces oxidative stress after an exercise session, thus not overloading the immune system, becoming more efficient and improving the response.[59]

Intensity is directly related to immunity, as it is the main variable that defines the body's immune response to the type of training. Thus, low and moderate intensity exercises bring greater benefits related to the immune system. Immunosuppression induced by high exercise intensity has been studied since 1994, by Nieman, who proposed the J-curve, which shows the relationship between exercise intensity and the possibility of infection (Figure 2). Analyzing all parameters and variables found within the performance of physical exercise, it is noted that the frequency, intensity and volume of training are the main factors capable of influencing the individual's cellular adaptations and metabolism, which includes the immune response.[15,52,59]

Immune response to physical exercise

The immune system has a specific response to the type of stimulus that exercise provides and, along with changes in immune function, molecular, cellular and tissue changes are also noted. This difference in response is related to the level of stress that training generates, the individual's physical fitness and regularity of stimuli.[60] Considering that physical

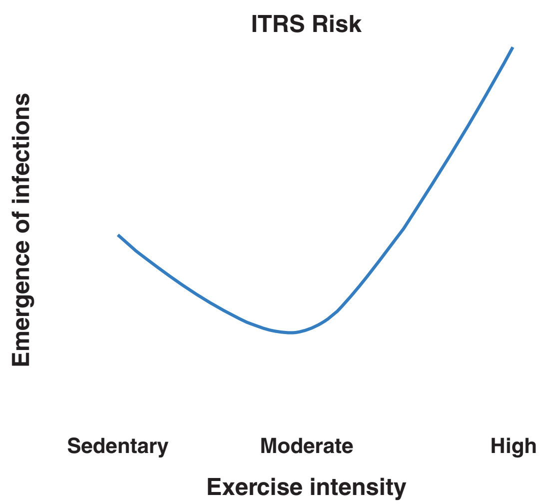

Figure 2
"J" curve model of the relationship between exercise load and the onset of upper respiratory tract infections (URTIs).

exercise induces inflammation (local and systemic), as well as tissue repair after trauma, physiological adaptations resulting from training can also be classified as acute and chronic.[61]

The acute response aims to adjust homeostasis for tissue repair right after a single or several exercise sessions. Furthermore, it can be subdivided into immediate or late, as mentioned in the previous topic.[28] Immediate acute adaptations are those that occur within a few minutes after the end of the exercise, such as increases in heart rate, blood pressure and body temperature. However, these values can change according to the type of exercise, static or dynamic, for example.[62,63] In static exercises, blood flow obstruction causes the metabolites produced during contraction to accumulate, activating muscle chemoreceptors, which promote a significant increase in sympathetic nervous activity, causing an increase in heart rate, with a decrease in systolic volume and a smaller increase in cardiac output.[28] On the other hand, blood pressure tends to increase, due to the increase in peripheral vascular resistance.[62] In dynamic exercises, there is high sympathetic nervous activity, which causes an increase in cardiac output, heart rate and stroke volume.[28] The release of muscle metabolites causes vasodilation in active muscles, which decreases peripheral vascular resistance.[62] In dynamic exercises, there is high sympathetic nervous activity, which causes an increase in cardiac output, heart rate and stroke volume.[28] The release of muscle metabolites causes vasodilation in active muscles, which decreases peripheral vascular resistance.[62]

A study in eight healthy men attempted to analyze the effects of three different types of exercise on white blood cell counts during and after exercise. The subjects were exposed to the following experiments: aerobic exercise of intensity equivalent to 90-97% of VO_2máx for 5 min, prolonged: two hours of exercise in cycle ergometry (long) completed at 60 to 65% of VO_2máx, and resistance: three sets of 10 repetitions at 60 to 70% of 1-RM strength (maximum repetition). Participants remained seated for a recovery period of 3 hours after each type of exercise, later compared with the control group, which was seated for 5 hours. During exercise, NK cells, T and B cells were recruited into the bloodstream, in addition to an increase in the amount of circulating neutrophils and monocytes. This leukocytosis occurred immediately after the exercises and persisted for 3 hours after the end.[63]

TCD3 and TCD4 lymphocyte counts showed a similar increase between aerobic and prolonged exercise. However, in the post-exercise period, after 3 hours of rest, TCD3 and TCD4 lymphocyte counts from aerobic exercise were below normal, characterizing lymphocytopenia. Circulating cells CD3 CD16+ CD56+ (natural killer) increased after aerobic exercise, a little less in prolonged exercise and even less in resistance exercise. However, all returned to baseline 3 hours later. Exercise induced few changes in B cell count (CD19+), which increased only at peak aerobics, immediately after exercise, and an increase after 3 hours in resistance exercise.[64]

The probable justifications for lymphocytopenia, caused after the end of exercise, may be related to the reduction in adrenaline levels, followed by an increase in the concentration of cortisol and growth hormone, leading to a redistribution of leukocytes and lymphocytes, thus presenting, an immunosuppressive effect.[27] On the other hand, the increase in natural killer cells is due to the greater secretion of catecholamines, especially epinephrine, and the release of some factors of the complement system, such as interferons (IFN-1), interleukins (IL-2) and beta-endorphin hormone as adjuvants in this process.[64] After 3 hours of exercise, NK cells returned to baseline values, considering the release of prostaglandins by neutrophils and macrophages together with hormonal factors such as cortisol, which has an immunosuppressive effect.[30] Over the 24 or 48 hours after an exercise session, the acute phase that used to be immediate becomes late, in which reductions in blood pressure and increased sensitivity are observed.[62]

Chronic adaptations, on the other hand, result from systematic and regular exposure to long-term exercise sessions, so the chronic phase is the sum of the effect of acute adaptations in the neuromuscular system over a few weeks, which generate morphofunctional changes in physiological systems. As an example, resting bradycardia, muscle hypertrophy, left ventricular hypertrophy and increased aerobic power.[28,63] In addition, there is an increase in blood flow to the skeletal muscles and to the cardiac muscle, as physical exercise promotes angiogenesis.[62]

A study carried out with 28 elderly individuals with a duration of six months of moderate training showed that the absolute number of CD4+ T lymphocytes (CD28+CD4+) increased, as well as that of IFN-γ (Th1) producing cells, while the T cells, responsible for IL-4 (Th2) production, did not undergo significant changes.[63] Some other studies support these data demonstrating that the total number of T lymphocytes, CD4+ T cells, and IL-2R expression in T cells increased in patients undergoing moderate intensity exercise combined with resistance and strength, or a training program exclusively for resistance. It was concluded that the increased expression is responsible for favoring the Th1 response, which prevents infections caused by intracellular microorganisms.[31,62]

The increase in interleukin-6, IL-6, is directly related to exercise intensity,[31] given the fact that it is found in abundance in muscle tissue, which makes it more sensitive to stimuli and intensity of physical exercise.[35] On the other hand, high-intensity activities generate increased concentrations of anti-inflammatory cytokines (Th2 pattern), which can result in increased susceptibility to infections, such as upper airway infection (URTI). Athletes with low plasma concentrations of IL-10 (low concentration also in the nasal mucosa), IL-1ra and IL-8 at rest are more likely to develop respiratory diseases.[65] These data demonstrate that the immune response can be modulated to different stimuli, that is, depending on the intensity of physical exercise (Figure 3).[62]

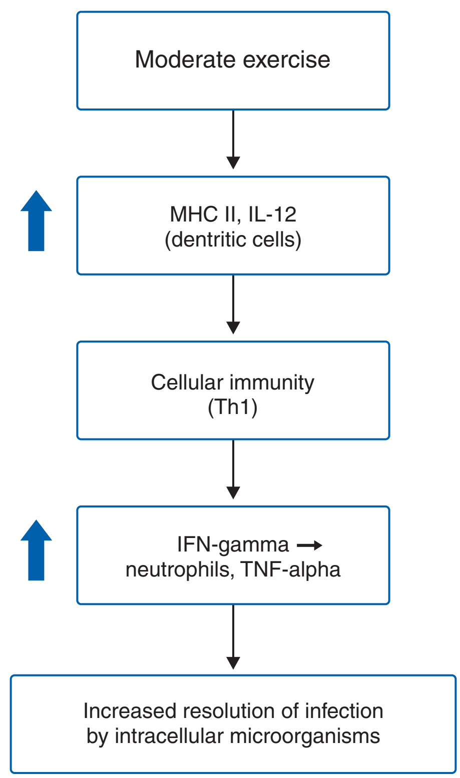

Figure 3
Summary of the effects of moderate-intensity exercise.

In summary, we can say that moderate-intensity exercise protects against infections caused by intracellular microorganisms, as it directs the immune response to the predominance of Th1 cells, in which the type of response is cellular.[62] It is associated with increased leukocyte function, helps chemotaxis, degranulation, phagocytosis and neutrophil oxidative activity one hour after physical exercise60. High-intensity exercise, on the other hand, generates an increase in the levels of anti-inflammatory cytokines (Th2 pattern), with the objective of reducing damage to muscle tissue due to the stress generated, making the individual more susceptible to infections (Figure 4).[62] After performing just one session of intense exercise, a temporary immunosuppression takes place, known as the "immune window", and can last from 3 to 72 hours.[60]

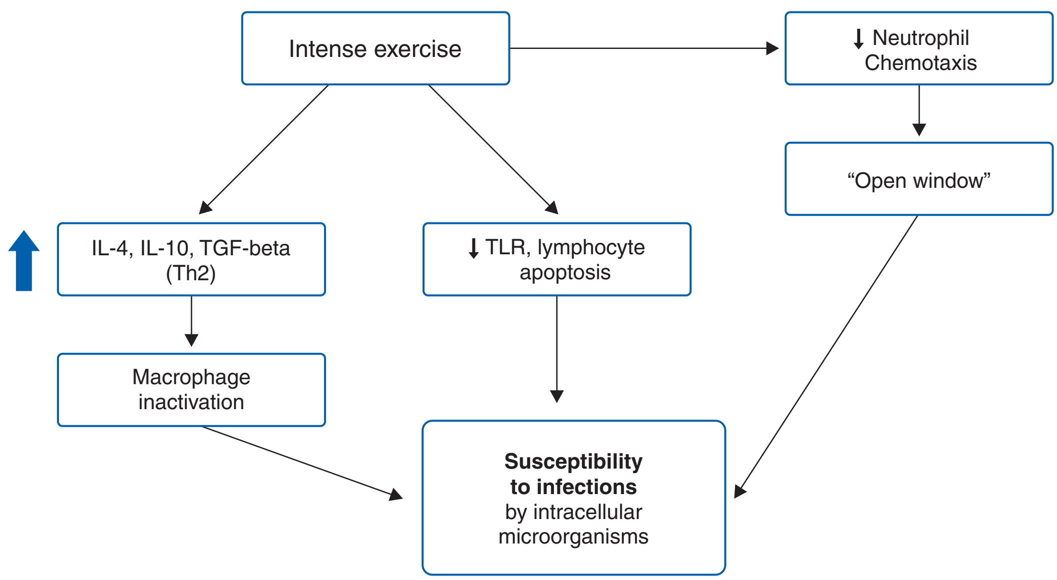

Figure 4
Summary of the effects of high intensity exercise.

Conclusion

The practice of regular physical exercise is essential for health maintenance, as it allows an adequate immune response, leads to the strengthening of the cardiovascular and respiratory system, in addition to improving the lipid profile of the individual who practices it. Science is rich in studies with evidence showing that physical exercise is capable of generating changes in the concentrations and functions of some cells of the immune system. Some aspects, such as exercise duration and intensity, influence how and what the immune response will be to the stimulus. An understanding of the immunological adaptations caused by physical exercise is necessary so that, in a future perspective, the best type of training for each person can be directed, taking into account the individuality of the practitioner.

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