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Anti-inflammatory effects of exercise training. A systematic review

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Abstract

Introduction: The diseases number with a known inflammatory etiology is constantly increasing. Cardiovascular and neurodegenerative diseases, osteoporosis, cancer, asthma, atherosclerosis, type 2 diabetes and obesity are associated with chronic low-grade inflammation. There is evidence that individuals who engage in intense physical activity or who exercise regularly, shows changes in biomarkers associated with chronic inflammation. Physical exercise is useful in preventing many diseases, due to improved cardiorespiratory, metabolic, musculoskeletal function. All these improve the immunity and antioxidant capacity, thus reducing the incidence of acute and chronic inflammatory diseases.
Materials and Methods: In this study were included 90 bibliographic sources, of which the title contains the following keywords: exercise - 23, inflammation - 27, anti-inflammatory - 6, IL-6 - 13, IL-10 - 4, myokine - 3, IL-15 - 3, irisin - 6, obesity - 11, chronic inflammation - 7. This study discussed aspects of exercise, pro- and anti-inflammatory cytokines, immunological mechanisms, the dual role of IL-6 cytokine, and the anti-inflammatory effects of physical exercise.
Results: Physical exercise is an efficient clinical tool, that limits chronic inflammation activating the immune system that will increase the level of anti-inflammatory IL-6 myokine. There is a direct relationship between the volume and intensity of exercise and the amount of IL-6 myokine in the blood stream.
Conclusions: These studies contribute significantly to the understanding of the mechanisms of the anti-inflammatory effect of exercise. More studies on chronic low-grade inflammatory diseases are needed to understand their pathophysiology, and that will inspire the specialists improve long-term treatment strategies.
Keywords: *physical exercise, chronic low-grade inflammation, anti-inflammatory, IL-6, myokine,*

INTRODUCTION

An active lifestyle with regular physical activity and / or constant training exercise is an effective strategy for the prevention and treatment of many chronic diseases without medication. Current scientific evidence has established positive correlations between a active physically lifestyle and health benefits (1). According to the Physical Activity Guidelines for Americans, the benefits of physical activity are: reduce the risk of all-cause and mortality specific disease, improved physical function and improved quality of life for individuals with various chronic medical conditions; reduce risk of cancer; reduced gestational diabetes risk for pregnant women; reduce the risk of fall-related injuries for older adults (2). According to the guide, patients with chronic diseases should practice exercise with moderate-intensity at least 150 minutes a week, or at least 75 minutes a week of exercise with vigorous-intensity to improve health (2).
Physical exercise can be used as a primary non-pharmacological clinical tool, for the prevention of many afections, due to improvements in cardiorespiratory, metabolic, musculoskeletal function, and for the management of chronic pain (2-5). A constant training with moderate-intensity exercise improves the immunity and antioxidant capacity, reduces oxidative stress and increases energy efficiency, thus reducing the incidence of acute and chronic inflammatory diseases (6-8).
Inflammation is a complex biological response of the immune system that prevents, limits, protects and repairs the damage caused by invasion of the pathogens agents, irritating factors, diseased cells or endogenous biomolecules (8). Acute inflammation is a beneficial transitory response for the body, while a persistent inflammatory response is associated with pathology (8,9). Cardiovascular and neuro-degenerative diseases, osteoporosis, postmenopausal breast cancer, colon cancer, asthma, atherosclerosis, dementia, depression,

type 2 diabetes and obesity have the chronic inflammation response, from pathophysiological common point of view. This chronic inflammation diseases, are part from "the diseasome of physical inactivity", even if they are apparently unrelated. It is interesting that the disease of physical inactivity represents very different diseases, but they share pathogenetic mechanisms, and it seems that type 2 diabetes plays a central role (8-14).

METHOD

Systematic Search Strategy. To realize this systematic review, we searched for relevant open access articles in the fields of: medicine, biochemistry, exercise physiology, and physical education and sports. We use 6 international databases: Elsevier, ISI Web of Knowledge, PEDro, NCBI / PubMed, NCBI / PMC and Cochrane.

Considering the niche area of this systematic review, we cite 46 articles from the years 2021-2010, and 44 between 2010-1982. Keywords combinations searched in the context were: exercise, anti-inflammatory effect, cytokines, myokines, inflammation, anti-inflammatory, CRP, IL-6, IL-15, TNF-α, IL-10, myokine, irisin, obesity, type 2 diabetes and chronic inflammation. Eligible articles were analyzed in detail regarding exercise and its anti-inflammatory role.

Inclusion and Exclusion Criteria. The articles included in this systematic review are following the methodology presented above, with the all keyword combinations present in the title. Cross-sectional studies, non-randomized controlled trials, randomized controlled trials, and reviews were included. As exclusion criteria, the articles studied in the next phase do not meet the relevance criteria.

RESULTS

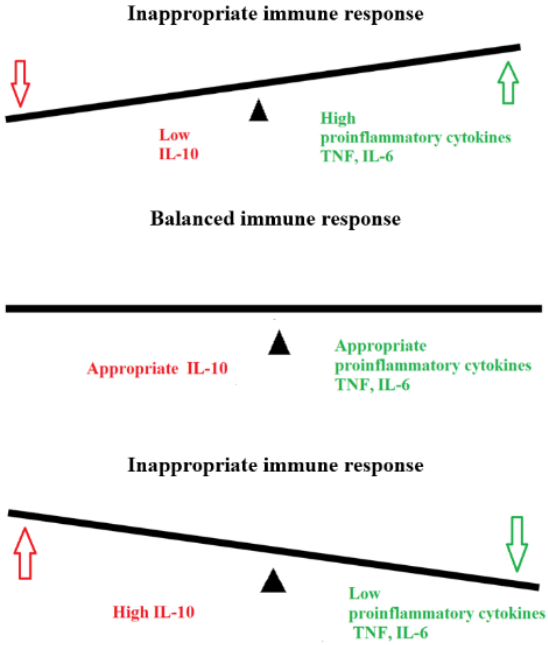
This study included 90 bibliographic sources, which were obtained after applying PEDro selection filters and removing duplicates from a total of 134. These 90 bibliographic sources passed the relevance criteria in the areas listed above and the keywords. This study discussed aspects of exercise, pro- and anti-inflammatory cytokines, immunological mechanisms, the dual role of IL-6 cytokine, and the anti-inflammatory effects of physical exercise.

Proinflammatory and anti-inflammatory cytokines

Physical exercise done regularly, guides the immune system to generate anti-inflammatory responses, which is there as a key factor in improving health condition, and controlling the persistent inflammation in chronic diseases (6,15). Activation of the immune system results in the release of cytokines, which are small proteins secreted and released by cells that have a specific effect on interactions and communications between cells. There are both proinflammatory and anti-inflammatory cytokines. Proinflammatory cytokines are: IL-1, IL-6, IL-8, IL-12, TNF-α, IFN-γ, VEGF and IL-1β. Anti-inflammatory cytokines are : IL-2, IL-4, IL-10, IL-11 and IL-13 (11-15).

Musculoskeletal, cardiovascular, diabetes and several other chronic diseases are associated with chronic inflammatory processes. Chronic diseases that have an low-grade inflammatory component, are specific to the elderly and sedentary individuals. It is proven that biomarkers of low-grade systemic inflammation in physically active or physically trained individuals are reduced, this being associated with the anti-inflammatory effects of the physical exercises (16-23).

Figure 1. IL-10 on the immune balance. When IL-10 production is low, inflammation increases, leading to tissue destruction (above). If IL-10 production is too high, the infection cannot be stopped and may result a chronic infection (below). If IL-10 is maintained in a state of equilibrium (adequate amount of IL-10) between immunopathology and chronic infection and thus both scenarios can be avoided (middle).



Circulating C-reactive protein (CRP) is an excellent biomarker of chronic and acute inflammation. CRP is an acute-phase protein which is synthesized by hepatocytes during inflammatory or infectious processes in response to pro-inflammatory cytokines.The increased concentration of CRP in serum levels, is correlated with increased body mass index (BMI), metabolic syndrome / diabetes, chronic infection, on smokers and individuals with below-normal high-density lipoprotein cholesterol (24-30).

Pro-inflammatory cytokines are used as biomarkers of chronic and acute inflammation. The proinflammatory cytokines TNF-α (Tumor Necrosis Factor-alpha) and IL-6 (interleukin-6) stimulate the liver release of CRP, and elevated serum or plasma levels are associated with low disease resistance, muscle loss, decline in physical function, and early death (31-35).

The anti-inflammatory cytokine IL-10, is the most studied and used in clinical practice, due to its clinical potential for applications. Due to this potential for clinical applications, extensive research on IL-10 has been conducted in both animal and human models to a better understanding of his activity. The dominant function of IL-10 is as an immunosuppressive cytokine, and can have an immunostimulatory effect on certain cell types. Immunologically, IL-10 levels are important in the management of inflammatory processes and destruction of pathogens. When a high level of inflammation is induced, the quantitative level of IL-10 increases to limit the immune response to avoid damaging the host. When IL-10 production is insufficient, the level of profinflammatory cytokines increases leading to damage to the host (Figure 1) (36).

The pro- and anti-inflammatory properties of the IL-6 cytokine

IL-6 is a cytokine with pro- and anti-inflammatory properties and its involved in inflammation and infection responses, and also in the regulation of metabolic and regenerative processes. IL-6 realizes the maintenance of bone homeostasis, and many neural functions. IL-6 is secreted by T cells and macrophages that promote immune system activation and inflammation, and is generally considered a proinflammatory cytokine. However, IL-6 has anti-inflammatory and immunosuppressive effects, when its derived from skeletal muscle, and that will decreas the proinflammatory response of the immune system (43-45). Pro- and anti-inflammatory differential effect of IL-6 has been shown to be induced by physical exercise intensity (figure 2). Muscle production of anti-inflammatory IL-6 is controlled by Ca^{+2} and glycogen stimuly activated by the muscle contraction. After the end of the physical exercise, IL-6 will reach the plasma peak, and will return to basal levels after a few hours, the values depending on the intensity and duration of the effort (45-47).

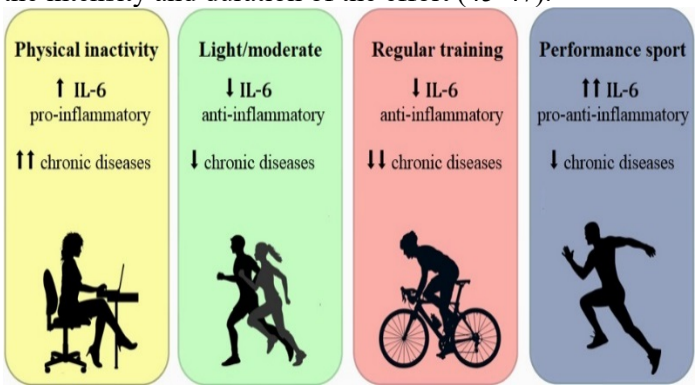


Figure. 2 The effects of physical inactivity and different intensities of exercise on the inflammatory response of IL-6 and on the outcome of health (chronic diseases).

The increase in IL-6 levels is closely related to muscle mass and muscle groups involved in contractile activity. The higher number of muscle groups are involved in contraction, the higher IL-6 plasma value. Another factor that increases the value of IL-6 post-exercise, is the increase in exercise intensity. Exercises with light-moderate intensity and intermittent exercise protocols of shorter duration, will generate modest increases values in IL-6 (48,49). In performance athletes who have an extended duration of exercises, more than 2.5 hours (marathon runners), the blood and muscle levels of IL-6 will increase up to 100 times, being accompanied by increased levels of anti-inflammatory inhibitors and cytokines (IL-1rα and IL-10) (50-52).

Anti-inflammatory effects of physical exercise

Anti-inflammatory cytokines, especially IL-10 and IL-6, belong to a group of regulatory mediators that govern the response of the proinflammatory cytokine TNF-α , IL-1β, IFN-γ, and others. Exercising with moderate intensity and regularity, ensures optimal control of the immune system, that will be able to decrease the chances of developing chronic diseases and to improve the defense against infections (figure 2) (3,53).

Another pathway that shows how exercise exerts its anti-inflammatory effect include: the release of IL-6 into the general circulation from contracting muscle fibres, that will subsequent increases IL-10 and IL-1 receptor antagonist in circulating levels. Physical exercise done regularly, increased the numbers of IL-10-secreting regulatory T cells circulating levels, which will lead to reduction of the pro-inflammatory monocytes. Another mechanisms is to limit the infiltration into adipose tissue of macrophages and/or monocytes (54-56).

Further anti-inflammatory effect of regular exercise is given by the interaction between the contracted muscle and the mediated cells, which receive signals transmitted by myokines (IL-8 and IL-15). Myokines are produced during muscle contractions and IL-1 receptor antagonists and sTNF-R are released, molecules that will generate anti-inflammatory effects (57).

General mechanisms by which exercise generates anti-inflammatory environment

Increased levels of circulating cortisol and adrenaline induced by the physical exercise. Secretion of the hormones cortisol and adrenaline is increased during physical exercise, through activation of the sympathetic nervous system (SNS) and the hypothalamic – pituitary – adrenal (HPA) axis. Cortisol is a steroid hormone secreted from the adrenal cortex in response to stress, and that has potent anti-inflammatory and catabolic effects. Adrenaline is a catecholamine secreted from the adrenal medulla in response to stress, that has effects on the cardiovascular system and metabolism. And it also has some immunosuppressive effects, that decrease the pro-inflammatory cytokines. Adrenaline its a fast-acting fighting hormone produced by the adrenal glands at direct signals from the brain under a stressful stimulus.

Cortisol is not released instantly like adrenaline, but rather lasts a few minutes because the amygdala is gradually activated. The levels of the two hormones increase during the physical exercise, and once released, adrenaline activates the sequential releases of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol. The increase in circulating cytokine concentrations is given by these hormonal responses, and the increase in plasma cortisol and adrenaline levels are related to the duration and intensity of exercises. Increased plasma cortisol levels appears to be mediated by exercise-induced IL-6, and after a viguros long term physical exercise the cortisol show an immunosuppressive action (58-62).

Effects of exercise on visceral adiposity. Visceral adipose tissue or white adipose tissue (WAT) is the „fuel storage" organ, and a key component of metabolic homeostatic mechanisms. WAT has a major role in lipid and glucose metabolism, being involved in a wide range of other biological processes. Hormones and adipokines and other biologically active agents are released from fat cells, and influence many physiological and pathological processes (63). Increased WAT deposition is a risk factor for the development of many chronic inflammatory conditions, including type 2 diabetes and obesity, cardiovascular diseas and chronic pain (14,23,64). WAT produces adipokines, including TNF-α, IL-6, IL-18, and leptin, and excessive WAT causes a reduction in plasma anti-inflammatory mediators, that leading to the development of systemic inflammatory conditions (13). Immune infiltration of macrophages and T cells in WAT, generates and maintains the inflammatory state and its correlates with a sedentary behavior and obesity (65-68). Exercising regularly decreases the activation of the immune system in WAT, and prevents the risk of type 2 diabetes and obesity. The volume of exercise is directly proportional to the anti-inflammatory effect. The higher the training volume and exceeding 45 min / workout, the greater the loss of WAT (69-71).

Increased levels of anti-inflammatory myokines (IL-6, IL-15 and Irisin) from skeletal muscles. Skeletal muscle contraction produces myokines, such as IL-6, IL-15 and irisin. Myokines exert either autocrine, paracrine or endocrine effects, mediating communication between muscles and other organs, including adipose tissue, bones, brain, liver, intestines, pancreas, muscle and skin. Myokines exert their effects on lipid and glucose metabolism, bone formation, etc.

Myokine IL-6 is plays multifunctional roles in the regulation of the immune system, nervous system, and glucose homeostasis. Myokine IL-6 mediates the anti-inflammatory effects associated with exercise both acutely with each workout and as a consequence of training adaptation, including reduced WAT. Blocking IL-6 signaling has been shown to compromise exercise-induced WAT reduction in obese individuals. Myokines can be considered useful biomarkers for monitoring the type and amount of exercise that is needed to prescribe exercise for individuals with diabetes, neurodegenerative disease, or cancer (67-74).

IL-15 play a significant role in lipid metabolism, preventing obesity. L-15 is an anabolic factor present in the muscle, and high expression of IL-15 prevents increasing of visceral fat, and its related to reduced WAT mass. IL-15 has been shown to be increased in trained human muscle (75-78).

Irisin is a myokin that induces thermogenic actions in adipose tissue in humans, being released into the circulation through physical exercise training. Irisin, expressed in a PGC-1α-dependent manner to produce FNDC5. Irisin is expressed in muscle and released into the bloodstream, through the control of the peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). Irisin has been involved in the downregulation of insulin resistance pathway, which is controlled by physical exercise. Irisin levels from circulation are lower in older than in younger subjects. Moderate / vigorous aerobic exercise like running and swimming, upregulates the expression of irisin at mRNA, protein, and plasma levels (79-87).

Toll-like (TRLs) receptors and immune regulation. TLRs receptors have a crucial role in the detection of microbial infection. Systemic inflammation is controlled by signaling TLRs. TLRs are highly conserved transmembrane proteins that helps on detection and recognition of microbial pathogens, that triggers the endogenous danger signals of tissue damage, such as heat shock proteins. Chronic exercise has been shown to decrease the cell surface expression of TLRs on immune cells, and inactivity correlates with the activation of TLRs, which are linked in the development of chronic diseases (88-90).

Summary and Future Directions

In this review, we present a number of key points of the physical exercise effects that represent an effective strategy for the prevention and treatment of many chronic inflammatory diseases without medication. The main benefits of physical exercise are: reducing the risks of diseases with high mortality, improving physical function and improving the quality of life; reduces the risk of cancer. In order to be effective in controlling chronic inflammation, a minimum of 150 minutes per week, moderate-intensity exercise is required, or at least 75 minutes per week of vigorous-intensity exercise.

Physical exercise is an efficient clinical tool, that limits chronic inflammation using complex mechanisms to activate the immune system that increase the level of anti-inflammatory cytokines, and limit pro-inflammatory cytokines from blood plasma and serum. TNF-α and IL-6 pro-inflammatory cytokines are used as biomarkers of

chronic and acute inflammation and stimulate the liver release of CRP. Elevated serum or plasma levels are associated with low disease resistance, decline in physical function, and early death. IL-10 is an immunosuppressive cytokine, with an important role in the management of inflammatory processes and destruction of pathogens.

The key player in this review is myokin IL-6. It is a cytokine with pro and anti-inflammatory properties that is involved in responses to inflammation and infection, as well as in the regulation of metabolic and regenerative processes. IL-6 is secreted by T cells and macrophages that promote activation and inflammation of the immune system and is generally considered a proinflammatory cytokine. However, IL-6 has anti-inflammatory and immunosuppressive effects when derived from skeletal muscle, and this will decrease the proinflammatory response of the immune system. The higher volume and intensity of the exercise, the higher the IL-6 levels are.

Identifying the mechanisms underlying the anti-inflammatory effects of exercise use is important, because they can serve as directions for future studies to improve pharmaceutical and physiotherapeutic treatments. Also a better understanding of the mechanisms that are responsible for the control and reduction of chronic inflammation will inspire specialists improve long-term treatment strategies. However, for new research directions it requires a comprehensive understanding of the relation between chronic low-grade inflammation and physical exercise.

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Author contribution

All authors have consistently contributed to this article

Declaration of conflict of interests

There is no conflict of interest for any of the authors regarding this paper

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