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Physical exercise, inflammatory process and adaptive condition: an overview

Exercício físico, processo inflamatório e adaptação: uma visão geral

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Abstract – Physical exercise induces inflammation, a physiological response that is part of immune system activity and promotes tissue remodeling after exercise overload. The activation of the inflammatory process is local and systemic and is mediated by different cells and secreted compounds. The objective is to reestablish organ homeostasis after a single bout of exercise or after several exercise sessions. The acute-phase response involves the combined actions of activated leukocytes, cytokines, acute-phase proteins, hormones, and other signaling molecules that control the response to an exercise session and guide the adaptations resulting from training. This review provides an overview of the inflammatory process related to exercise and literature data regarding markers of inflammation in response to different experimental protocols. The results obtained indicate distinct inflammatory responses to acute and chronic exercise. In general, acute exercise induces a proinflammatory response characterized by transient leukocytosis (neutrophilia, monocytosis, and lymphocytosis), followed by a partial cellular immunosuppressive state. An increase in serum concentrations of creatine kinase, C-reactive protein and cell adhesion molecules is also observed, in addition to an increased secretion of cortisol and cytokines. In contrast, chronic exercise results in a local and systemic anti-inflammatory response that promotes tissue adaptation and protects the organism against the development of chronic inflammatory diseases and against the effects of non-functional overtraining, a condition in which a systemic and chronic proinflammatory and pro-oxidant state seems to prevail.
Key words: Adaptive condition; Cytokines; Inflammatory process; Overtraining; Physical exercise.

Resumo – *O exercício físico induz inflamação, evento que ocorre para promover o reparo e remodelamento tecidual após o trauma. A ativação do processo inflamatório é local e sistêmico, valendo-se para isso de diversas células e componentes secretados. O objetivo é restabelecer a homeostasia orgânica após uma única sessão ou após diversas sessões de exercícios. A resposta de fase aguda consiste de ações integradas entre leucócitos, citocinas, proteínas de fase aguda, hormônios e outras moléculas sinalizadoras que controlam a resposta tanto a uma sessão de exercícios como também direcionam as adaptações decorrentes do treinamento. Nessa revisão, apresentaremos um panorama geral sobre inflamação e exercício físico, e os dados na literatura sobre marcadores de inflamação em resposta a diferentes protocolos experimentais. Os resultados obtidos apontam respostas distintas sobre o processo inflamatório em relação aos efeitos agudos ou crônicos dos exercícios. De forma geral, uma única sessão de exercício físico intenso induz um estado pró-inflamatório, representado por leucocitose transitória, em decorrência de neutrofilia, monocitose e linfocitose, seguida de supressão parcial da imunidade celular. Também têm sido observados aumentos nas concentrações séricas da enzima creatina quinase, proteína C-reativa e moléculas de adesão celular, além do aumento na secreção de cortisol e citocinas. Já o treinamento físico sistematizado pode levar a um estado anti-inflamatório local e sistêmico. Esse ambiente anti-inflamatório viabilizaria a adaptação e, ao mesmo tempo, protegeria o organismo contra o desenvolvimento de patologias inflamatórias crônicas e dos efeitos nocivos do overtraining, quando parece prevalecer um estado pró-inflamatório e pró-oxidante crônico e sistêmico.*
Palavras-chave: *Exercício físico; Processo inflamatório; Adaptação; Sobretreinamento; Citocinas.*

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INTRODUCTION

The inflammatory process or inflammation is characterized as a body's defense response against an aggressive agent, whose goal is to promote healing / repair. The magnitude of this process is regulated by pro- and anti-inflammatory factors. Inflammation is considered a highly beneficial and necessary process when related to regular and systematic physical training, since together with the action of hormones and other signaling molecules, is responsible for regeneration and repair of injured structures[1]. In this context, the aim of this study was to characterize inflammation in the physical exercise context through a broad survey of original articles - including transversal and longitudinal studies - and reviews published in international journals with high impact factor (over 1.5) . To do so, PUBMED / MEDLINE electronic databases were used, giving preference to articles published since 2000, using as main descriptors terms such as inflammatory response, immune function, exercise training, overtraining syndrome, cytokines, acute phase response, injury, repair, and skeletal muscle. An average number of 116 articles in full were selected and analyzed, which components are part of this manuscript, giving priority to such a choice the inflammatory markers used.

OVERLOAD AND ADAPTIVE CONDITION

The overload principle is one of the training principles required to improve physical performance. It is assumed that progressive overloads should be applied during training sessions in order to cause a disturbance of cell homeostasis and the resulting response to this stress. Overloads can be manipulated through the following variables: load, duration, interval between stimuli, muscle action, movement execution speed, frequency of exercises per week, number of exercises per session, range of motion and the combination of exercises in the exercise session[2].

The application of overload causes tissue traumas of several degrees in skeletal muscle tissue, connective and bone tissue. These traumas are considered temporary and repairable damage, because they result in an acute inflammatory response triggered, among others, by neutrophils and macrophages[3], whose function is to clean, repair and develop tissues previously injured[3].

Especially in relation to skeletal muscle tissue, these traumas are dependent on effort intensity and include disruption of the extracellular matrix, basal lamina and sarcolemma. They may result in the release of intracellular proteins into the bloodstream such as myoglobin, lactate dehydrogenase, aspartate aminotransferase and creatine kinase (CK)[4]. It can also cause damage to the contractile material and to cytoskeletal proteins, as well as a disruption in the myofibrillar structure, rupture, enlargement or extension of the Z line with subsequent impairment of the anchorage of thin filaments and connection of adjacent fibers[4].

When the resting time required for recovery from the acute effects of physical exercise is respected, there is a positive adaptation of the skeletal muscle tissue and adjacent structures for a morphological and metabolic remodeling of myofibrils[5]. That is, the adaptive process involves the activation of intracellular signaling pathways and subsequent gene activation, which may result in changes in the muscle mass, in contractile properties and metabolic responses[6]. This signaling is dependent on the specificity of the exercises used, which reflects in increased performance of several physical capacities[2].

TISSUE TRAUMA AND INFLAMMATORY RESPONSE

The damage repair mechanism is highly synchronized, and can be basically divided into three phases: a degenerative phase followed by a regenerative phase, and a third phase of remodeling of the injured tissue[5]. Tissue trauma is a complex condition in which inflammatory cells promote both injury and regeneration. This is achieved through the combined action of reactive oxygen species (ROS), enzymatic antioxidants of low molecular weight, growth factors, hormones and cytokines that maintain a balance between pro- and antioxidant and pro- and anti-inflammatory activities[7,8].

The first phase of repair is triggered by the sarcolemma injury or damage. This injury favors the release of eicosanoids, particularly prostaglandins, prostacyclins, leukotrienes and thromboxanes[5]. These eicosanoids are derived from the arachidonic acid, a constituent of the phospholipids of cell membranes, especially of those of the immune system, playing a role in the vasodilation regulation, in the chemotactic activity and in the increase of the vascular endothelium permeability, which is inherent to tissue inflammation[5,7,8]. Together, these factors enable the influx of inflammatory cells into the injured site, which is a phenomenon known as diapedesis.

Neutrophils are the first subpopulation of leukocytes to migrate into the tissue[8]. They show a peak after 60 minutes of exercise, which can last for up to 5 days. At the same time, there is an increase in the transport of neutrophils from bone marrow into the bloodstream, mediated by the action of cortisol and interleukin-6 [8].

The main function of neutrophils is the removal, by phagocytosis, of undesirable elements related to tissue injury. This action is the starting point for subsequent responses of tissue repair and growth[8]. For this, activated neutrophils release lysosomal proteases that degrade local proteins. They also form ROS as a result of the action of the NADPH oxidase enzyme through a process known as respiratory burst and also by activating the myeloperoxidase enzyme[8]. The response mediated by neutrophils should be acute and very well regulated in order to preserve the integrity of cells and tissue around the inflammatory event and to avoid the exacerbation of the injury by increasing the production of ROS[6,8].

Monocytes form the second subpopulation of leucocytes to appear at the injured site. When these cells leave the circulation and migrate into the tissues begin to be called macrophages[8]. Recently, there is evidence that the role of macrophages that early invade the injured site (between 24-48h) is different from those that appear latter at this site (between 48-96h). The latter would have a more active role in muscle repair while the former would have the main function of removing the injured tissue[9].

In fact, *in vitro* and *in vivo* studies have confirmed that macrophages play an important role in growth and repair of injured tissue, probably by secreting pro-regenerative molecules[7,9]. Among these, some hormones such as insulin-like growth factor (IGF) and cytokines regulators of cell growth such as fibroblast growth factor (FGF) and transforming growth factor (TGF-β) stand out[10]. These cytokines act in the recruitment and activation of fibroblasts that secrete collagen molecules, thus contributing to tissue regeneration. Moreover, they signal activation, proliferation and differentiation of muscle satellite cells, which are important for tissue recovery[11]. Macrophages also secrete several other molecules such as chemokines, prostaglandins, and ROS[8].

Lymphocytes are also important in the process of tissue regeneration after exercise, when they respond in a biphasic manner. They show an increase during and immediately after exercise, especially of Natural Killer cells (NK), followed by decrease, which can last for several hours (primarily of T lymphocytes and NK cells), inducing a loss of their functional capacity. Such changes may lead to the development of transient immunosuppression[7]. This immunosuppression seems to be related to increased susceptibility to upper respiratory tract infections in athletes, an acute effect of exhaustive and prolonged exercise[11].

Acute immunosuppression may also be associated with decreased activity of neutrophils and monocytes, reduced secretion of cytokines, attenuated respiratory burst, lower chemotactic capacity of neutrophils and lower expression of Toll-like receptors (TL) by monocytes, responsible for the recognition of injured tissues[7,12,13]. Cortisol appears to play a role in this immunosuppressant environment, known in literature as the "immunological window" or "open window"[5]. The phenomenon of open window seems to be related to the greater possibility of the development of post-exercise infectious conditions[7,12].

ACUTE PHASE RESPONSE (APR)

An important point to be considered in relation to the inflammatory process is that the local response, described above, is usually followed by a systemic response, known as acute phase response[4]. The aim of the acute phase response is to adjust homeostasis for tissue repair. That is, within a few hours after the activation of the local inflammation, body can show a variety of physiological and behavioral systemic changes (also known as Sickness Behavior), which depend mainly on intensity and duration of the stress stimulus[14]. Some of them are presented in Picture 1.

One of the most important responses of the acute phase involves an increase in the hepatic synthesis, with consequent increase in blood flow, the so-called acute phase proteins[5]. Among these, C-reactive protein (CRP), a-1-acid glycoprotein, serum amyloid A a-2-microglobulin, haptoglobin, fibrinogen, transferrin and ceruloplasmin, stand out[15,16]. Each of these proteins has specific functions in the inflammatory context. On the other hand, there are some proteins that have decreased concentration in the acute phase in order to provide substrates for positive acute phase proteins. They are called negative acute phase proteins. Among them, albumin stands out[15].

In humans, studies classify positive acute phase proteins according to their potential to increase in the bloodstream during the acute phase (Picture 2)

or, according to proteins that signal their hepatic synthesis within this phase (Picture 3).

Picture 1. Major organic alterations that may occur during the acute phase response. Adapted from Ceciliane et al. (2002) 15; APP = Acute Phase Proteins, ACTH = adrenocorticotrophic hormone, GH = Growth Hormone.

ALTERAÇÕES	RESPOSTAS BIOLÓGICAS
BIOCHEMICAL	Increased protein catabolism
	Increased hepatic lipogenesis
	Increased gliconeogenesis
	Increased lipolysis in adipose tissue
	Drop in plasma [Zinc] and [Iron]
	Increase in plasma [cytokines]
	Increased hepatic synthesis of APP
	Increased synthesis of chemotactic factors
PHYSIOLOGICAL	Fever
	Increased secretion of ACTH, cortisol, glucagon, catecholamines, GH
	Change in hematopoiesis
	Development of anemia
	Leukocytosis
BEHAVIORAL	Somnolence
	Loss of appetite

Picture 2. Classification of acute phase proteins based on the magnitude of increase within the acute phase response. Adapted from Heinrich et al.[17]; Ceciliane et al.[15].

CLASSIFICAÇÃO	EXEMPLOS
APP that increases its concentration in up to 50%	Ceruloplasmin
APP that increases its concentration from 2 to 3x	Fibrinogen
	α1-acid glycoprotein
	Haptoglobin
APP that increases its concentration hundreds of times	C-Reactive Protein (CRP)
	Serum amyloid A

Picture 3. Classification of acute phase proteins based on proteins that induce their synthesis. Adapted from Heinrich et al.[17]; Baumann & Gauldie,[18]; Moshage,[16].

CLASSIFICAÇÃO	EXEMPLOS
TYPE I (IL1β, TNFα)	Serum amyloid A
	C-Reactive Protein (CRP)
	Haptoglobin
	α1-acid glycoprotein
TYPE II (IL6)	Fibrinogen
	α1-Antichymotrypsin
	α1-Antitrypsin
	α2-Macroglobulin

Positive acute phase proteins help holding the amplification of potentially lethal inflammation in various ways: by activating the complement system, action of proteases, removal of microorganisms and cellular metabolites, cellular remodeling, control of the gene expression, antithrombotic and hemostasis control, and control of the respiratory burst triggered by inflammatory cells and proteolytic enzymes, and activation of the local inflammation[15-17]. In addition, some of them scavenge reactive ions (Fe^{+2}, Cu^{+}) and ROS[15,17], thus modulating the inflammatory response. As an example, increased serum transferrin concentration has the function of holding secondary injuries to those generated by tissue injury via decrease in the plasma concentration of iron ion, which can participate in the generation of powerful cellular oxidants[15].

Regarding negative acute phase proteins, e.g., albumin, its decrease in plasma appears to occur due to a hepatic inhibition on the synthesis of its mRNA, mediated by other proteins related to inflammation such as IL-6, or due to the need of liver to increase the synthesis of positive acute phase proteins, requiring for this, a greater availability of amino acids obtained by the greater deterioration of albumin[19]. Also, an increased vascular permeability during the activation of the inflammatory process could trigger a greater efflux of albumin from plasma into the cell interstitium, causing the drop of its plasma concentration, thus contributing to the development of tissue edema, a peculiar feature of the inflammatory response[20]. Other compounds that have their plasma concentrations decreased during the acute phase are zinc and calcium[15].

INFLAMMATORY RESPONSE CONTROL

A group of glycoproteins collectively called as cytokines are the responsible for coordination, amplification and regulation of the magnitude and duration of inflammatory events and, consequently, their effects[3,20].

Cytokines are produced and released mainly by immune system cells, besides the active muscles and by a variety of tissues such as adipose tissue and endothelial cells[21]. Cytokines may have pro-inflammatory (IL-1β, TNF-α, IL-6), anti-inflammatory activity (IL-6, IL-10, IL-4, IL-5, IL-13 and IL-1ra) or even behave as inflammatory modulators (IL-6), regulating, besides inflammation, the activation of the energy pathways to support this process[21].

Cytokines are responsible for intercellular, inter-organ and intersystem communication[20], allowing different systems to be informed about the injury in a specific tissue. They enable the influx of neutrophils, monocytes, lymphocytes and other cells that participate in tissue regeneration and cleaning, indirectly indicating the increased permeability of blood vessels and hence an increase in the transition of fluids and proteins between intra and extra-cellular spaces[20].

Tissue trauma in muscle tissue induced by exercise can signalize through the action of cytokines other tissues such as brain, liver, kidney, endothelium, immune cells and endocrine system, especially the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonads axes to promote the combined action required to cure / repair the injury[3]. Thus, the balance between pro- and anti-inflammatory actions of different cytokines contributes to the complete recovery of the injured tissue[3,6].

PRO-INFLAMMATORY CYTOKINES

The main pro-inflammatory cytokines are Interleukin-1b (IL-1β) and Tumor Necrosis Factor-a (TNF-α). They are considered "alarm cytokines", since they are stimulated by events directly related to tissue injury, e.g., some intramuscular chemical mediators such as histamine, bradykinin, prostaglandins, leukotrienes and ROS[3,6].

IL-1β and TNF-α are produced by monocytes, macrophages, neutrophils, endothelial cells and smooth and skeletal muscle cells. They play the role of enhancing the migration of monocytes and neutrophils into the inflammation site[20]. This signaling is further reinforced both by inducing the secretion of other chemotactic cytokines, particularly interleukin 8 (IL-8), and by inducing the synthesis of cell adhesion molecules (selectins, integrins)[8], which promote the adhesion and subsequent infiltration of inflammatory cells into the injured tissue[3,20,] which is a phenomenon characterized by chemotaxis, followed by diapedesis.

IL-1β and TNF-α also have receptors in the hypothalamus. This interaction causes an increase in the synthesis of prostaglandins, which cause fever. They may also induce behavioral changes such as reduced appetite and thirst, decreased libido, depression and mood changes[5]. IL-1β and TNF-α induce the activation of hypothalamic-pituitary-adrenal axis and sympathetic nucleus, resulting in high plasma concentrations of stress hormones cortisol and catecholamines[3]. This physiological condition triggered by these cytokines is known as Sickness Behavior[20].

IL-1β and TNF-α also have receptors in liver, which binding indicates the synthesis of some acute phase proteins[3] (Picture 3). These cytokines also signal the increase in the production of Interleukin 6 (IL-6) by monocytes, macrophages, endothelial cells, epithelial cells, fibroblasts and skeletal muscle cells[20], which may also signal, when produced in high amounts, proteolysis of the skeletal muscle tissue and inhibition of anabolism pathways[22.]

ANTI-INFLAMMATORY CYTOKINES

IL-6 has already been called the exercise factor, in addition to Interleukin 8 (IL-8) and Interleukin 15 (IL-15) cytokines[21]. The regulatory activity of the inflammatory process of IL-6 has been considered in literature as the main agent regulating the acute phase response in exercise. This cytokine is produced in higher concentrations in skeletal muscle tissue, in leukocytes and in endothelial cells through signaling of pro-inflammatory cytokines and ROS, and its secretion is related to intensity, duration and the amount of muscle mass involved in physical exercise[21].

The anti-inflammatory activities of IL-6 are diverse and include inhibitory effects on the production and secretion of TNF-α, stimulating the synthesis of anti-inflammatory cytokines such as the antagonist receptor of Interleukin-1 (IL-1ra) and Interleukin-10 (IL-10), and also stimulating the release of soluble receptors for TNF-α[20,21].

Among some specific roles played by IL-1ra and IL-10, the blockade in presentation of antigens by macrophages, the inhibition in the production of IL-1β, IL-6, TNF-α and chemokines by macrophages and lymphocytes, and thus the completion of the inflammatory response stand out[20,21].

The hepatic synthesis of acute phase proteins is also controlled by IL-6 [14], which also has hypothalamic receptors that activate the hypothalamic-pituitary-adrenal axis and increase the secretion of cortisol by the adrenal cortex[3].

IL-6 activates the hepatic glycogenolysis[21] and lipolysis in adipose tissue via activation of the AMP-dependent kinase (AMPK). Increasing the oxidation rate of fatty acids is important to provide energy for tissue synthesis and repair processes[21]. IL-6 also controls the oxidative stress condition in the injured tissue through induction in expression of heat

shock proteins (HSPs) in both skeletal muscle tissue and immune cells[23], and regulates the migration of satellite cells in order to promote muscle tissue hypertrophy[24]. Finally, IL-6, along with Interleukin 4 (IL-4), Interleukin 5 (IL-5), IL-10, Interleukin 13 (IL-13) and IL-1ra seems to drive the inflammatory response pattern to an increased antibody production and a marked activation of **eosinophils**[25].

GLUCOCORTICOIDS: CORTISOL AND CORTICOSTERONE

Glucocorticoids, among them, cortisol (in humans) and corticosterone (in rats), are secreted by the adrenal gland cortex and also have anti-inflammatory function when at physiological concentrations. Their actions are contrary to the pro-inflammatory actions signaled by IL-1β and TNF-α.

Cortisol is involved in regulating the expression of endothelial adhesion molecules, thus controlling the migration of phagocytes into the injured tissue. This prevents the worsening of muscle injury state, for example, ~~of~~ a marked increase in respiratory burst[26]. Cortisol has the ability to stabilize lysosomal membranes, inhibiting the release of proteolytic enzymes that signal tissue inflammation, which may also reduce the permeability of capillaries, thus reducing the effect of tissue edema[26].

Glucocorticoids also induce increase in the transport of glutamine out of the muscle by stimulating the activity of Glutamine Synthetize enzyme and the mRNA expression of this enzyme[27], which is a fact that relates glutamine to the function of leukocytes. Glucocorticoids, when secreted in larger amounts during physical exercise, suppress the lymphocyte activation, especially T lymphocytes, thus contributing to the development of post-exercise immunosuppression, also suppressing fever through reduced secretion of IL-1β by immune system cells[26]. Another role played by glucocorticoids is to induce muscle proteolysis in order to provide a large amount of free amino acids for the synthesis of acute phase proteins in the liver.

INFLAMMATORY MARKERS AFTER ACUTE EXERCISE PROTOCOLS AND IN CHRONIC ADAPTATION TO SYSTEMATIZED PHYSICAL EXERCISE

Many authors have used inflammatory markers such as cytokines, leukocytes, cell adhesion molecules, cortisol, serum CK and acute phase proteins in the context of acute response and chronic adaptation to exercise. In general, the responses depend on factors such as: protocols used, intensity, frequency and volume of exercise, moments of data collection after exercise, number and fitness level of the sample subjects, markers investigated, tissues investigated and the type of sample used (animals or humans).

Studies that measured the acute effects of physical exercise on inflammatory markers commonly used blood collected before and immediately after exercise, and an average number of 25 patients considered physically active, submitted to exhaustive endurance protocols (half marathon, marathon, ultramarathon, treadmill test and stationary cycle ergometer).

Overall, experimental data have shown that acute exercise is associated with transient leukocytosis (especially due to neutrophilia, monocytosis and lymphocytosis), followed by partial suppression of cellular immunity by the reduced number and / or function of lymphocytes and Natural Killer cells[28]; it is still possible to find a reduction in the activity of neutrophils and monocytes and decreased secretion of antibodies such as salivary IgA[29]. There has been found significant increases in serum concentrations of CK, CRP, cell adhesion molecules and in cortisol secretion, and increases in muscle gene expression[30] and in the concentration of pro and anti-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10, IL-1ra, IL-8, IL-15) have also been observed in skeletal muscle tissue and blood[31-33].

Studies that measured the chronic effects of physical exercise on inflammatory markers are less common. Most of these studies used blood collected before and after the proposed protocols as a means of analysis, an average number of 34 subjects considered physically active, submitted to exhaustive endurance protocols (running, cycling and swimming).

The results indicate, as a chronic effect, a reduction in the local and systemic pro-inflammatory condition. Some studies have shown attenuation in the production and secretion of acute phase proteins, especially CRP[34], increased production and secretion of cytokines with anti-inflammatory function (especially IL-6 in skeletal muscle tissue and blood)[21] and improvement in the antioxidant power of cells[21,35]. However, the production of IL-1β and TNF-α remained unchanged and transient or, in many times, it is not even identified, being

dependent on the exercise type, intensity and duration[21]. Adipose tissue has also been investigated in chronic protocols and has shown the same anti-inflammatory pattern[36].

It is important to highlight that clear experimental evidence, showing adjustments related to the control of inflammatory condition by regular and systematic physical training is still incipient, although there are good review articles suggesting that this practice can lead to an anti-inflammatory protective environment[37,38]. That is, an increase in the pro-inflammatory organic condition by stimulus of acute exercise would be offset by the chronic anti-inflammatory environment, which would control the inflammatory magnitude and duration and would provide tissue regeneration and adaptation to the exercise loads[3,6]. On the other hand, the literature also suggests that the beneficial effects of physical training on the inflammatory modulation is dependent on the quality and quantity of stimuli, which are directly related to the rest time among stimuli, trying to avoid the appearance of the overtraining condition.

Overtraining (OT) is characterized by a continuous process of intensified physical training without adequate recovery, which may induce changes in the activation and regulation pattern of the inflammatory process[3]. According to the European College of Sport Science, in 2006, OT can culminate in two different states in relation to performance: short-term overreaching (functional overreaching - FOR) and extreme overreaching (non-functional overreaching - NFOR)[39].

The FOR state is characterized by a rapid drop in performance followed by an eventual improvement, in a process that resembles the super compensation theory [39]. In the NFOR state, the drop in performance has more prolonged recovery. In general, it is followed by fatigue and biochemical, immunological and physiological alterations, and even by behavioral disorders[39]. The NFOR state can lead to overtraining syndrome (OTS), which as the name implies, has features even more diffuse, negatively affecting various systems, presenting a very slow recovery feature[39].

There is a hypothesis that an increased chronic secretion of pro-inflammatory cytokines and pro-oxidant agents could lead to the NFOR state[3,6]. According to this hypothesis, what triggers this state in athletes undergoing intense training and insufficient recovery time would be a progression of the adaptive stage of trauma induced in the skeletal muscles and joints to a non-adaptive stage of sub clinical injury[3,6]. This would activate the circulating leukocytes and various tissues including skeletal muscle tissue to produce more pro-inflammatory cytokines and pro-oxidant agents[3,6]. However, this hypothesis has not yet been experimentally verified.

To investigate the relationship between physical training, overtraining, adaptation or non-adaptation conditions, and several biomarkers, including the inflammatory process, our research group has recently developed a model to induce OT in animals, which allowed the separation of animals into FOR and NFOR groups[40]. In the OT induction model, the animals were submitted to 11 weeks of treadmill training at a frequency of 1x/day from week 1 to week 8, 2x/day, with 4 hours rest between sessions, in week 9; 3x/day with 3 hours rest between them in week 10, and 4x/dia, with 2 hours rest between them in week 11. The data obtained from the group of animals in the FOR state showed an antioxidant and anti-inflammatory pattern, followed by increased performance at the end of 11 weeks of training.

FINAL CONSIDERATIONS

The studies presented in this review suggest that the follow-up of athletes in training / competition sessions or periods by inflammatory markers could contribute to define, with a lower degree of empiricism, the adaptation level of these subjects to the training loads imposed. In this sense, the control of the inflammatory condition resulting from the balanced action between pro and anti-inflammatory effectors in different tissues, especially in skeletal muscle tissue, seems to determine the adaptive success, either in acute or chronic forms.

However, to define the most sensitive markers to indicate FOR and NFOR states, further studies should be conducted to monitor the training protocol and its variables, the investigation period, size, trainability and diet used by the sample, the moments of collection and the inflammatory markers used, since the cross-talk between tissues involved in inflammation seems to determine the acute response and the chronic adaptation pattern found.

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