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Exercise induced modulation of immune system functional capacity

ABSTRACT

Exercise can have both positive and negative effects on the immune system. Regular moderate exercise seems to reduce the incidence of infection, while prolonged intense exercise causes a temporary suppression of many parameters of immune function, depending on the intensity and duration of exercise. The functional capacity of the immune system is necessary to be determined in order to get useful information about the immune system status of athletes and its impact on performance. In order to investigate the immunological status and depending on the purpose of each study, different laboratory techniques are used.

This study aims to review the exercise-induced modulation of immune system functional capacity in terms of cytokines production and WBCs differentiation, as described in the literature.

KEY WORDS: *cytokines, endotoxin stimulation, inflammation, physical activity, exercise.*

INTRODUCTION

In sports medicine, the term inflammation is often used to describe a se-
ries of signs and symptoms after soft tissue or bony injury. The cellular
processes of inflammation are regulated by a series of specific cell signals
that stimulate a variety of cell types, resulting in a cascade of events includ-
ing white blood cell (WBC) recruitment and activation. Physical activity may
cause specific changes which are also observed in infectious disease, sepsis
or trauma and include the acute phase response, the leukocyte mobilization
and activation, the release of inflammatory mediators (cytokines), the tissue
damage and cell infiltration, the production of free radicals, the activation of
the complement and the coagulation and fibrinolytic pathways. The variety of
the previous changes depends on the exercise intensity and duration.

Cytokines, WBCs and exercise

The acute phase response is stimulated by the release of cytokines such
as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-a (TN-
Fa) from macrophages and monocytes at the site of inflammatory lesions or
infection. Cytokines are proteins produced by human immune cells, regulating
inflammation and immunity and being responsible for host inflammatory re-
sponse to the invading microbes.The word cytokines derives from the greek
word "kytokin",meaning "to put cells into motion". All nucleated cells in the
body produce cytokines and similarly express cytokine receptors on their sur-
face membranes. Cytokines act at the surface of the target cells, principally
to alter cell function. Skeletal muscle continually produce cytokines in an ef-
fort to maintain homeostasis and to regulate function. Simple perturbations of
skeletal muscle, such as an active stretch during eccentric exercise, marked-
ly increase the expression of interleukin-1β (IL-1β) and tumor necrosis fac-
tor–α (TNF-α). The initial release of these pro-inflammatory cytokines is aug-
mented by their paracrine actions in causing further stimulation of cytokine
release and eventually results in a systemic release of cytokine.

These proinflammatory cytokines upregulate the expression of endothelial-
leukocyte adhesion molecules (E-selectin) within the endothelium of the adja-
cent blood vessels. Activation of the endothelium is site specific and can re-
sult in the release of additional IL-1β, as well as of additional proinflammatory
cytokines, including IL-6 and IL-8, both of which have been shown to attract
neutrophils. Endothelial activation serves two purposes, encouraging the ad-
hesion of neutrophils at the site of cell stress (margination) and assisting the
cell in recruiting additional neutrophils (2).

Shephard et al (23), mentioned that exercise can have both positive and
negative effects on the immune system and susceptibility to minor illnesses.

The production of cytokines by neutrophils as well as the resulting response from all WBCs subpopulations can be modified with long-term exercise. The exact mechanisms are not well known, but the low-level inflammatory response produced through regular exercise may blunt the cells' response to cytokines or inhibit their production and subsequent release. In this regard, regular exercise may suppress the release of proinflammatory cytokines, but prolonged and vigorous exercise is needed to suppress immune function. Prolonged exercise induces an inflammatory response that is expressed by an increase in circulating antiinflammatory and proinflammatory molecules. Thus, moderate activity may enhance the immune's functional capacity, while prolonged and intense exercise may impair the immune function, which finally, results in a decline in exercise performance and the ability to undergo heavy training (22).

The relationship between exercise and susceptibility to infection has been described as a J- Shaped curve (16) but there are only a few epidemiological studies showing that moderate exercise is associated with decreased infection incidence.

Gleeson (6) mentioned that there is little evidence to suggest that there are clinical differences in the immune function between sedentary and moderate active persons. One of the mainly suggested pathophysiological mechanisms of exercise–induced impaired immune function is the reduction of the circulating number and the functional capacities of circulating leukocytes,probably due to the elevated levels of stress hormones (catecholamines, cortisol and growth hormone) during repeated bouts of prolonged exercise (14) and the entry of less mature leukocytes into the circulation from the bone marrow (7).Reduction in glutamine levels has also been suggested as a possible cause of immune-suppression (7),while during exercise the production in oxygen reactive species is increased which in its turn may also impair the function of some cells (18). On the other hand, there is an increased exposure to pathogens during several exercise types. For instance, exercise demands in respiration result in a higher rate and depth of breathing, which may increase the risk to exposure to airborne pathogens, while prolonged intense exercise in the heat, may affect gut permeability, allowing entry of gut bacterial endotoxins into the circulation. Hence,the increased exposure to pathogens along with a variety of physical, psychological and environmental factors make athletes more susceptible to infections. (7).

Furthermore, exercise increases the production of T- lymphocytes, but can also influence balance of their different types. T- lymphocytes can be classified as type 1 and type 2 cells. Type -1 cells produce IFN-γ, and TNF-a and they activate macrophages and induce killer mechanisms, including T cytotoxic cells, providing so a cell mediated immune response and protection against viruses and other intracellular pathogens. Type-2 cells mainly produce IL-4, IL-5, IL-10, and IL-13, promoting so humoral immunity and activation of poten-

tially tissue damaging eosinophils. IL-4 and IL-13 help B cells differentiation and IL-4 together with Il-10 can inhibit Type-1 cell cytokine production. Strenuous exercise elevates circulating IL6, IL-10 and IL-1ra and decreases the percentage of type-1 T cells, without changing the percentage of type-2 T cells (12). IL-6 stimulates Type -2 cell production, whereas cortisol and epinephrine suppresses Type- 1 cell production. Additionally, IL-6 suppresses the production of TNF-a, a potent activator of inflammation (26).

Even if strenuous exercise works against Type -1 cells and cell mediated immune response, through cytokines production and hormonal changes(20), it should not be underestimated that it might also have positive effects by increasing the production of Type -2 cells and suppressing so the ability of the immune system to induce tissue damage and inflammation (7), which plays a beneficial role, especially in chronic diseases. It is known that exercise greatly affects the leukocyte subpopulations. Neutrophil concentration increases during exercise due to the increased concentration of catecholamines and growth hormone (20) and continues to increase after the end of exercise, due to the increased concentration of cortisol, while catecholamines and growth hormone return to resting values shortly after the cessation of the exercise (20). Lymphocytes concentration on the other hand, also increases during exercise, due similarly to the increased concentration of catecholamines, but in contrary the increase of cortisol production following exercise provokes lymphopenia even below the resting values (20). The magnitude of the changes in leukocyte populations depends on exercise characteristics such as intensity and duration (8).

Studies on the exercise induced inflammatory response

Taking in mind that reactions to exercise are generally much less pronounced than reactions during sepsis, any experimental studies of the inflammatory response need to be based upon patterns of exercise that maximise the immunological changes caused by physical activity. Possible approaches may include: (a) adoption of a certain type of exercise that has been shown to have the greatest effect on health outcome; (b) meta-analysis of circulating cell counts changes in order to determine the exercise pattern provoking the largest disturbance of normal values; (c) experimental comparisons of the response to different volumes of endurance training; (d) experimental comparisons of the response to different types of acute exhausting exercise.

In order to estimate the immune system status using the laboratory, the very first step is the full blood count and the differential white blood cell count. However, these blood tests cannot estimate the white blood cells sub-

populations effectiveness to respond to pathogens. Therefore, in order to examine the functional capacity, we need to determine both the number of white blood cells and their capacity to react to a stimulus.

The estimation of white blood cells functional capacity can be determined using two separate techniques. The first technique is the cellular stain for markers indicative of an activated status. These cell markers are molecules expressed on the cell surface, whenever a cell commits itself to react to a stimulus. The second technique measures the concentrations of cytokines that the cells secrete in response to a pathogen (15).This technique is widely used and often referred in literature, while the first one is employed in more recent studies examining the origin of cells that secrete cytokines.

According to the purpose of each study protocol, a specific antigen is chosen. Therefore, polyclonical mitogens are needed for the lymphocytes development in cultures(10) and endotoxin (LPS) stimulation is preferred for the study of monocytes. Monocytes are the major mediators of inflammatory responses triggered by the LPS component of Gram negative bacteria leading to pro- inflammatory (TNF-a, IL-6, IL-1) and anti- inflammatory (IL-10, TNF-RI-Tumor necrosis factor receptor I) cytokine production.Bacterial endotoxin (LPS) is the most potent stimulus for TNF-a production (15) and can induce cell proliferation but in much slower kinetics than the two other potential inducers the Con (Concanavalin A) and the PHA (phytohaemagglutinin) do. Under these terms, endotoxin stimulation may be considered closer to the natural environment and seems to be a better model to investigate complex regulatory effects (29).

A great number of studies were conducted, aiming to investigate the effect of different exercise patterns and intensity. Haahr et al (9), examined the effect of 60-minute cycling at 75% of VO2max on the production of IL-1, IL-6, IL-2, TNF-a, and IFN-γ. Blood mononuclear cells (BMNC) were stimulated in vitro with either LPS or PHA. The production of IL-6 increased significantly 2 hours after exercise while the production of IL-1a, and IL-1β slightly increased. TNF-a,IL-2, and IFN-γ did not change in response to exercise due to the decrement of the CD4+ subsets and the increment of CD16+. According to the investigators and also to the earlier observations of Cannon et al, the increased production of IL-6, IL-1a from a fixed number of WBC was attributed to the increased both percentage and absolute number of blood monocytes 2 hours after exercise. Furthermore, Kvernmo et al (11), studied the production of TNF-a and tissue factor activity in LPS stimulated blood before and after exercise of different intensities. They separated three groups of athletes, one consisting of twice daily trained (top athletes), a second one consisting of athletes trained 3-7 times a week and a third group including those practiced 4-5 times per month. TNF-a production after LPS stimulation at rest in the first group (2.7 ±1.1 ng/ml) was significantly lower than in the

other two groups, while, the highest values were measured in the third group (7.6 ± 1.6 ng/ml). Immediately after exercise cessation, the monocytes appeared to be less responsive to stimulation, resulting in a reduction of TNF-a production by 47% in the first two groups. In contrary, the tissue factor activity of monocytes was higher in the first and the second group after the end of exercise compared to the resting values, which was speculated to be the result of granulocytes and platelets increased activation. Thus, they concluded that strenuous exercise causes suppression of TNF-a production after LPS stimulation. Furthermore, Drenth et al (4), examined the impact of running 5 km on the cytokine production in whole blood. They showed that the production of CRP, TNF-a, IL-1β and the number of leukocytes were increased after the end of the exercise. LPS stimulation in whole blood caused a decrease in the concentration of TNF-a immediately after the exercise.

Baum et al have examined the effect of two different exercise protocols, moderate exercise and exhausting exercise on induced cytokine production. Production of interleukin (IL)-1beta, IL-6 and tumour necrosis factor (TNF)-alpha were induced with lipopolysaccharides (LPS), and that of IL-2 and interferon (IFN)-gamma with staphylococcal enterotoxin B (SEB) and phytohaemagglutinin (PHA). The lymphocyte subset distribution was observed to be unchanged after moderate exercise, but after exhaustive exercise, the CD16+ count was found to be significantly lower, whereas 24 h later the CD4+ count was significantly higher than pre-exercise counts. Moderate exercise influenced the IFN-gamma production (PHA-stimulated), which increased significantly, while after exhaustive exercise the IFN-gamma level in the supernatants (SEB-stimulated) was significantly decreased. The IL-1beta and TNF-alpha production per monocyte was also significantly reduced. (1). The IL-2 production remained unchanged after the end of intense exercise, result that is controversary to these of other studies (19, 28), showing that the production of IL-2 was upwards or downwards modulated after intense exercise. In a contemporary to the previous one study, 15 athletes were examined after an exhaustive exercise stress test,lasting 68 minutes(29). The exercise protocol was including 400 meters swimming, 25 km cycling and 4 km running. Cytokine production was examined in serum, urine and supernatants of whole blood cultures. The blood was stimulated with LPS, Con-A and PHA. The production of IL-6 and IL-2R was increased 1 hour after the end of exercise in both serum and urine samples. Serum TNF-a values were also increased, while urine IL-2 values decreased. LPS stimulation suppressed the production of TNF-a, and IL-1, but in contrary the concentration of IL-6 increased, 1 hour after the end of the exercise. When TNF-a and IL-6 were expressed per 1000 monocytes, their production was suppressed 1 hour after the end of exercise. Stimulation with Con-A and PHA caused a reduction on the production of IFN-γ and IL-2 accordingly. In addition, the study of Northoff

et al (19), noticed that LPS and Con- A stimulation in whole blood caused a reduction in cytokine production (IFN-γ, IL-1β, TNF-a) after intense exercise (1 hour triathlon), but IL-6 values remained stable in the post exercise measurements. Furthermore, absence of stimulation revealed increased cytokines production compared to resting values, except the one of INF-γ.

Apart from such studies examining the effect of prolonged and continuous exercise, other studies are focused on the influence of the intermittent exercise on the cells of the immune system. Fry et al (5), examined lymphocyte function after Con-A stimulation and mobilization of the peripheral blood leukocytes after incremental exercise test and series of interval training(15 exercise periods, 1 minute duration alternated with 2 minute recovery intervals). The exercise intensity for each of the different sessions was set at 30%, 60%, 90% and 120% of their maximal work capacity. The authors noticed significant decrease in lymphocyte subpopulations after maximal and supramaximal exercise. Also, there was a decrease in the peripheral lympocytes cultures response to Con-A. They speculated that the in vitro depressed response of T-cells to mitogens may be attributed to a redistribution of subpopulations of cells after exercise, related to the intensity.

Intense and short duration exercise or maximal exercise induce also transient changes to the cytokine production. Lewick et al. (13) have shown that maximal exercise in cycle ergometer caused temporarily immune suppression in highly trained athletes. A significant increase in Ts (suppressor, cytotoxic) and a moderate increase in Th (helper, inducer) and NK (natural killer) cell numbers were noted 3 min after maximal physical exercise. At the same time, a significant diminution of the Th/Ts ratio was observed. A significant increase of IL-1 production and a diminished IL- 2 production were observed at the same time. After a 2 hours recovery, there was a normalization of most of the parameters investigated.

The referred studies may present controversial results which could be explained by the different exercise protocols and the laboratory blood analysis, as well as by the different expression of the results (per monocytes, lymphocytes, whole blood etc). Referring to these controversies, we have to take in mind that the whole blood culture technique measures cytokine production by a known volume of blood. The main disadvantage of this technique is that the number of cells cultured is neither known nor controlled. So, variations in cytokine production either between individuals, or in different physiological and pathological states, could represent either changes in the numbers of cytokine producing cells (e.g. T lymphocytes, monocytes),an altered ability of those cells to produce cytokines, or both. In contrast, purified monocytes cultures include a precisely known number of cytokine-producing cells as monocytes are the principal source of TNF and IL-1b. In contrast, IL-6 released during inflammation is derived not only from monocytes, but also from noncirculating sources, such as endothelial

cells and fibroblasts. However, when using whole blood stimulated by LPS, monocytes are likely to be the principal source of IL-6.

A number of studies investigated the cytokines production by monocytes, supposing that monocytes is the major source of cytokine production.

Starkie et al (27) as well as Rhind et al (21), tried to show if the monocytes are the basic source of cytokines after stimulation with a pathogen. They have stained specific cells for cell markers and studied how these cells react to a pathogen. Rhind et al (21) studied the production of cytokines (IL-6, IL-10, TNF-a) from CD14 monocytes after a weekly training and they suggested that blood monocytes contribute to exercise-induced cytokinemia. Starkie et al (27, 25) mentioned further that the post-exercise reduced production of cytokines (IL-6, IL-10, TNF-a) from CD33 monocytes after in vitro stimulation with LPS could probably be attributed to the increased production of stress hormones.

Endogenous and exogenous glucocorticoids effect a variety of inflammatory cytokines. The influence of plasma cortisol fluctuations on the relative numbers of different circulating WBC has been well documented. The cytokines release and their modulation by dexamethasone in whole blood following exercise were studied by Smits et al (24). These changes were studied using LPS-induced cytokine release and the exercise was intermittent.It consisted of exercise periods of 3 minutes alternating with 30 second breaks. The mean exercise duration was 15 to 20 minutes depending on the physical condition of the subjects. Following exercise, significant decreases in LPS-induced release of IL-6, TNF-α and IL-10 were observed. In addition, the inhibitory effect of dexamethasone on both IL-6 and TNF-α secretion was significantly reduced following exercise, whereas that on IL-10 release was not affected. These changes were accompanied by an increase in adrenocorticotropic (ACTH) hormone immediately following exercise. The results from the present study suggested that glucocorticoids sensitivity of whole blood cytokine release can be regulated in a dynamic fashion and that this can be assessed using an ex vivo stimulation assay. The mechanisms that may explain the decreased production of cytokines are changes in specific leukocyte subsets and a decreased stability of mRNA encoding selected cytokines in leukocytes. Nieman et al (17) compared immune changes in terms of released cytokines and hormonal changes after two intensive exercise cycling protocols. The first protocol was continuous exercise at 64% Watts max, lasting 2 hours, and the second one was intermittent exercise with 3 minute rest intervals interspersed every 10 minutes, lasting 2 hours and 6 minutes. They observed that the two exercise protocols had similar effect on production values of cytokines (IL-6, IL-8, ILl-10), hormones (cortisol, epinephrine) and monocytes, suggesting the total work generated is the provoking factor for immune changes rather than the type of exercise.

CONCLUSIONS

Hundreds of studies have now been conducted that confirm both acute and chronic effects of exercise on the immune system, yet there are still very few studies that have been able to show a direct link between exercise-induced immune depression and increased incidence of confirmed illness in athletes. Strenious and/or prolonged physical activity leads to muscle and other tissue damage and, thereby, induces an inflammatory response characterized by secretion of proinflammatory cytokines, chemokines, and other cellular or hormonal mediators of inflammation. On the other hand, physical activity also induces counter-regulation of inflammation through secretion of immunosuppressant mediators, such as cortisol and antiinflammatory cytokines. Whether these changes have long-term negative effects on professional athletes health remains unknown.This is an important issue that needs to be addressed in future studies, although it must be recognized that this is a difficult task. Even among the general population, we do not know the impact of small changes in specific immune parameters on risk of infection.

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