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Immune Biomarkers in Sports and Exercise

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Abstract

Aim: The aim of this article is to review immune biomarkers which are commonly used in sports and physical exercise. **Results:** Leukocytes (neutrophils, basophils and eosinophils), Monocytes, C- Reactive Protein (CRP) and Cytokines (TNF-α, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10) are commonly used as immune biomarkers in sports and exercise. **Conclusion:** Exercise changes in leukocyte numbers in circulating blood and the largest changes occur in the number of granulocytes (mainly neutrophils).Exercise intensity, duration and/or the fitness level of the individual may all play a role in regards to the degree of leukocytosis occurring. A short-term increase in serum CRP has been reported and increases in IL-6 over 100 times above resting values have been found after exhaustive exercise.

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Introduction

Blood biomarkers are measureable characteristics that reveal a particular physiologic state (Coriell institute 2016) and in the general population are important in risk evaluation and diagnosis of pathology, as well as in determining effectiveness of treatment. In sports and exercise, biomarkers may be used to assess an athlete's overall health or to determine positive/negative adaptations to training/environmental stimuli (San Millan 2013; Meyer and Meister 2011). Although limited, recent literature does provide evidence that monitoring specific blood biomarkers can lead to insights in immune biomarkers in sports and exercise. The present technological advances in mass spectrometry allowed system biology approaches (i.e. metabolomics, proteomics, lipidomics, and microbiome characterization) to be applied to sports and exercise immunology studies. The future of sports and exercise immunology will take benefit of these technologies to provide new insights on the interactions between sports and exercise and immune function. Moreover, these methodologies will improve mechanistic understanding of how sports and exercise-induced immune perturbations reduce the risk of common chronic diseases.

Immune system

The immune system is large and complex and has a wide variety of functions. The major role of the immune system is to defend the body against germs and microorganisms. Bacteria and viruses can do damage to our body and make us sick. The immune system does a great work in keeping individual healthy and preventing infections, but problems with the immune system can still lead to illness and infections. The immune system is divided into two functional divisions: the *innate immunity*, referred to as the first line of defense, and the *acquired (or adaptive) immunity*, which, when activated, produces a specific reaction and immunological memory to each infectious agent (Roitt and Male 2001).

Innate Immune System

The innate immune system consists of anatomic and physiological barriers (like skin, mucous membranes, body temperature, low pH and special chemical mediators such as complement and

interferon) and specialized cells (natural killer cells and phagocytes, including neutrophils, monocytes and macrophages (Mackinnon 1999).

Leukocytes

Leukocytes (also known as white blood cells) form a part of the blood. Leukocytes are chiefly produced in the bone marrow and help to defend the body against infectious disease and unfamiliar materials as part of the immune system. There are normally between $4x10^9$ and $11x10^9$ white blood cells in a liter of healthy adult blood (Roitt and Male 2001) (Table 1). The leukocytes travel throughout the body and search for their targets. In this way, the immune system works in a coordinated manner to check the body for substances that might cause harms. There are two basic types of leukocytes; the *phagocytes*, which are cells that chew up invading organisms, and the *lymphocytes*, which allow the body to memorize and recognize previous invaders (Mackinnon 1999).The *granulocytes* (a type of phagocyte that has small granules visible in the cytoplasm) consist of *polymorphonuclear cells* which are subdivided into three classes: **neutrophils**, **basophils** and **eosinophils**.

Table 1. Normal values of white blood cells

Cells	**Amount (cell/µL)**
Leukocytes	4500 – 11000
Neutrophils	4000 – 7000
Lymphocytes	2500 – 5000
Monocytes	100 – 1000
Eosinophils	0 - 500
Basophils	0 - 100

(Rhoades & David , 2003)

The *neutrophils* are the most abundant white blood cells, they account for 65 to 70% of all leukocytes (Roitt and Male 2001).Leukocytes move toward the sites of infection or inflammation, and undergo a process called chemotaxis. *Chemotaxis* is the cells' movement towards certain chemicals in their environment. Granulocytes along with monocytes shield us against bacteria and other invading organisms, a process that is called *phagocytosis* (ingestion).The granulocytes are short lived. After granulocytes are released from the bone marrow they can circulate in the blood for 4 to 8 hours. Thereafter they leave the blood and go into the tissues and can live there for 3 to 4 days. In case the body is exposed for serious infections, they live even shorter. The numbers of granulocytes in the blood depends on the release of mature granulocytes from the bone marrow and the body's need for an increased number of granulocytes (i.e. during infection).The neutrophils are very significant in the fight against infections. If there occurred a bacterial infection, the neutrophils move to the infected area and neutralize the invading bacteria. In such situation, the total number of neutrophils is high. The *eosinophil* do not phagocytize and are more significant in allergic reactions. The same is the case with the *basophil*; they contain histamine and heparin and are also involved in allergic reactions (Roitt and Male 2001).

Monocytes

Monocytes (another type of white blood cell) are produced by the bone marrow from hematopoietic stem cell precursors called *monoblasts*. Monocytes make up between 3 and 8% of the leukocytes in the blood (Roitt and Male 2001) and circulate in the blood for about 1 to 3 days before moving into tissues all over the body. Monocytes are, like the neutrophil granulocytes, effective phagocytes, and are responsible for phagocytosis of foreign substances in the body. When the monocytes leave the

blood barrier, they differentiate in the tissues and their size and characteristics change. These cells are named ***macrophages*.** Macrophages are accountable for protecting tissues from foreign substances but are also known to be the predominant cells involved in triggering atherosclerosis. Macrophages are cells that possess a large smooth nucleus, a large area of cytoplasm and many internal vesicles for processing foreign material.

Acquired (or *adaptive*) Immune System

The second kind of protection is called acquires (*adaptive* or *active*) immunity (Roitt and Male 2001). This type of immunity develops during our lives. Adaptive immunity involves the lymphocytes and develops from early childhood. Adults are exposed to diseases or are immunized against some diseases through vaccination. The main cells involved in acquired immunity are the lymphocytes, and there are two kinds of them: **B-lymphocytes** and **T-lymphocytes**; both are capable of secreting a large variety of specialized biomolecules (*antibodies* and *cytokines*) to regulate the immune response. T-lymphocytes can also be engaged in direct cell-on-cell fighting. Lymphocytes found in the bone marrow where they live and mature into *B-cells.* Lymphocytes can also leave and move to the thymus gland and mature into *T-cells*. B-lymphocytes and T-lymphocytes have separate functions: B-lymphocytes are like the body's military intelligence system, seeking out their targets and organizing defenses, while T-cells are like the soldiers, destroying the invaders that the intelligence system has identified (Mackinnon 1999).

C- Reactive Protein (CRP)

C-reactive protein (CRP) is an acute phase protein presented in the blood and rises in response to inflammation. Its physiological role is to tie to phosphocholine expressed on the surface of dead or dying cells to activate the complement system. The *complement system* is the name of a group of plasma proteins, which are produced by the liver, and is a significant part of the innate immune system. The complement system has an significant role in the battle against bacteria and virus infections. A blood test of CRP is commonly used in the diagnosis of infections. The level of CRP rises in many types of inflammatory reactions, both infections, autoimmune diseases and after cellular damage. After an infection, it takes almost half a day before the CRP increase becomes measurable. During the healing process the level of CRP decreases in a relatively short time (½h ~ 12-24 hours in the blood). The levels of CRP increase more during bacterial infections than viral and can thus be used to distinguish between these two types of infections. Bacterial infection can increase CRP to over 100 mg/L, while during viral infections the values are usually below 50 mg/L. This distinction between bacteria and viruses are often useful because antibiotics (such as penicillin) have no effect on viral infections, but can often be very useful in bacterial infections (Roitt and Male 2001). Recent investigations suggest that physical activity reduce CRP levels. Higher levels of physical activity and cardio-respiratory fitness are consistently associated with 6 to 35% lower CRP levels (Plaisance and Grandjean 2006). Longitudinal training studies have demonstrated reductions in CRP concentration from 41% to 16%, an effect that may be independent of baseline levels of CRP, body composition, and weight loss (Plaisance and Grandjean 2006). The mechanisms behind the role of physical activity plays in reducing inflammation and suppressing CRP levels are not well defined (Kasapis and Thompson 2005). Chronic physical activity is associated with reduced resting CRP levels due to multiple mechanisms including: decreased cytokine production by adipose tissue, skeletal muscles, endothelial and blood mononuclear cells, improved endothelial function and insulin sensitivity, and possibly an antioxidant effect (Kasapis and Thompson 2005).A short-term increase in serum CRP has been observed after strenuous exercise. This is due to an exercise-induced acute phase response, facilitated by the cytokine system, mainly through *interleukin-6* (*IL-6).* Exercise training may influence this response, whereas there is also a homeostatic, anti-inflammatory counter-acute phase response after strenuous exercise (Kasapis and Thompson 2005).

Cytokines

Cytokines are substances secreted by certain immune system cells that carry signals locally between cells, and thus have an effect on other cells. Cytokines are the signaling molecules used extensively in cellular communication. The term cytokine encompasses a large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin. A pro-inflammatory cytokine is a *cytokine* which promotes systemic inflammation, while an anti-inflammatory cytokine refers to the property of a substance or treatment that reduces inflammation. **TNF-α, IL-1β** and **IL-8** are some examples of *pro-inflammatory* cytokines. **IL-6** and **IL-10** belong to the *anti-inflammatory* category. IL-6 can be both pro-inflammatory and anti-inflammatory. Heavy physical activity produces a rapid transient increase in cytokine production and entails increases in both pro-inflammatory (IL-2, IL-5, IL-6, IL-8, TNFα) and anti-inflammatory (IL-1ra, IL-10) cytokines. *Interleukin-6* (IL-6) is the most studied cytokine associated with physical exercise (Chaar et al., 2011). Many studies have investigated the effects of different forms and intensities of exercise on its plasma concentration and tissue expression (Santos et al., 2007; Moldoveanu et al., 2001; Ostrowski et al.,1999). The effects of physical exercise seem to be mediated by intensity (Moldoveanu et al., 2001) as well as the duration of effort, the muscle mass involved and the individual's physical fitness level (Fischer 2006). Increases in IL-6 over 100 times above resting values have been found after exhaustive exercise such as marathon races, moderate exercise (60–65% VO_2max) and after resistance exercise, and may last for up to 72 hour after the end of the exercise (Gleeson 2007). One explanation for the increase in IL-6 after exhaustive exercise is that IL-6 is produced by the contracting muscle and is released in large quantities into the circulation. Studies have shown that prolonged exercise may increase circulating neutrophils' ability to produce reactive oxygen metabolites, but the release of IL-6 after exercise has been associated with neutrophil mobilization and priming of the oxidative activity (Santos et al., 2012). Free radical damaging effects on cellular functions are for IL-6 seen as a key mediator of the exercise-induced immune changes (Gleeson 2007).

Physical activities/or exercise and the immune system

Primarily physical activity stimulates the immune system and strengthens the infection defense. There are indications that untrained people who start exercising regularly get a progressively stronger immune system and become less susceptible to infections (Nash 1994). Intensive endurance training or competition which last for at least one hour stimulates the immune system sharply in the beginning, but a few hours after exercise/competition, a weakened immune system results (Friman et al., 1985). This means that the immune system in the hours after hard exercise/ competition has a weakened ability to fight against bacteria and viruses and the susceptibility to infection is temporarily increased (Waninger and Harcke 2005).It is well known that exhausting exercise can result in excessive inflammatory reactions and immune suppression, leading to clinical consequences that slow healing and recovery from injury and/or increase your risk of disease and/or infection (Williams et al., 2006).The argument that exercise induces an inflammation like response is also supported by the fact that the raised level of cytokines result in the increased secretion of adrenocorticotrophic hormone (ACTH), which induces the enhancement of systemic cortisol level. Monocytes and thrombocytes are responsible for the initiation of exercise induced acute phase reaction (Muir et al., 1984). Comparing the immune responses to surgical trauma and stressful bouts of physical activity, there are several parallels; activation of neutrophils and macrophages, which accumulate free radicals (Williams et al., 2006; Pedersen and Ullum 1994), local release of proinflammatory cytokines (Shephard 2001), and activation of the complement, coagulation and fibrinolytic cascades (Nieman et al., 1998). Both physical and psychological stress have been regarded as potent suppressors of the immune system (Ronsen 2003), which leaves us with many

unanswered questions about whether or not physical exercise is beneficial or harmful for the immune system (Pedersen and Hoffman-2000). One of the most studied aspects of exercise and the immune system is the changes in leukocyte numbers in circulating blood (Ronsen 2003; Pedersen and Hoffman-2000; Fry et al., 1992; McCarthy and Dale 1988). The largest changes occur in the number of granulocytes (mainly neutrophils). The mechanisms that cause leukocytosis can be several: an increased release of leukocytes from bone marrow storage pools, a decreased margination of leukocytes onto vessel walls, a decreased extravasation of leukocytes from the vessels into tissues, or an increase in number of precursor cells in the marrow (Roitt and Male 2001). During exercise, the main source of circulatory neutrophils are primary (bone marrow) and secondary (spleen, lymph nodes, gut) lymphoid tissues, as well as marginated neutrophils from the endothelial wall of peripheral veins (Van et al., 1999; Muir et al., 1984). Fry *et al.*, (1992) observed that neutrophil number increases proportionally with exercise intensity following interval running over a range of intensities. Exercise intensity, duration and/or the fitness level of the individual may all play a role in regards to the degree of leukocytosis occurring (Peake 2002 ; Nieman and Nehlsen 1992; Alessio et al., 1997).

Conclusion: Exercise changes in leukocyte numbers in circulating blood and the largest changes occur in the number of granulocytes (mainly neutrophils).Exercise intensity, duration and/or the fitness level of the individual may all play a role in regards to the degree of leukocytosis occurring. A short-term increase in serum CRP has been reported and increases in IL-6 over 100 times above resting values have been found after exhaustive exercise.

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