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Exercise and Immunity

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1. Introduction

Epidemiological evidence suggests a link between the intensity of the exercise and the occurrence of infections and diseases. The innate immune system appears to respond to chronic stress of intensive exercise by increased natural killer cell activity and suppressed neutrophil function. The measured effects of exercise on the innate immune system are complex and depend on several factors: the type of exercise, intensity and duration of exercise, the timing of measurement in relation to the exercise session, the dose and type of immune modulator used to stimulate the cell *in vitro* or *in vivo*, and the site of cellular origin. When comparing immune function in trained and non-active persons, the adaptive immune system is largely unaffected by exercise.

Physical activity in combination with infections is usually associated with certain medical risks, partly for the person who is infected and partly for the other athletes who may be infected. The risk of infection is greatest in team sports, but also in other sports where athletes have close physical contact before, during and after training and competitions.

This chapter starts with a short introduction of the immune system followed by a description of free radicals' and antioxidants' role in the immune system and how they are affected by physical activity. The chapter will also focus on need of antioxidant supplementation in combination with physical activity. The different theories regarding the effect of physical activity on the immune system will be discussed, along with advantages and disadvantages of being active, and finally effects of physical activity on the immune system are described.

2. The immune system

The immune system is large and complex and has a wide variety of functions. The main role of the immune system is to defend people against germs and microorganisms. Researchers are

constantly making new discoveries by studying the immune system. There are several factors which influence or affect the daily functioning of the immune system: age, gender, eating habits, medical status, training and fitness level.

Bacteria and viruses can do harm to our body and make us sick. The immune system does a great job in keeping people healthy and preventing infections, but problems with the immune system can still lead to illness and infections. The immune system is separated in two functional divisions: the innate immunity, referred to as the first line of defense, and the acquired immunity, which, when activated, produces a specific reaction and immunological memory to each infectious agent.

2.1. The innate immune system

The innate immune system consists of anatomic and physiological barriers (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 [1] (Table 1). When the innate immune system fails to effectively combat an invading pathogen, the body produces a learned immune response.

| INNATE IMMUNITY | | ADAPTIVE IMMUNITY | |
|-------------------|---------------------------------------------------------------------|-------------------|-----------------------------------|
| Physical barriers | Epithelial cell barriers Mucus | Humoral | Antibody Memory |
| Chemical barriers | Complement Lysozyme pH of body fluids Acute phase proteins | Cell-mediated | Lymphocytes T cells B cells |
| White blood cells | Monocytes/macrophages Granulocytes Natural killer cells | | |

Table 1. Innate and adaptive immunity (Source: Modified after Mackinnon, 1999).

Leukocytes (also known as white blood cells) form a component of the blood. They are mainly produced in the bone marrow and help to defend the body against infectious disease and foreign materials as part of the immune system. There are normally between 4×10^9 and 11×10^9 white blood cells in a liter of healthy adult blood [2] (Table 2). The leukocytes circulate through the body and seek out their targets. In this way, the immune system works in a coordinated manner to monitor the body for substances that might cause problems. 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 remember and recognize previous invaders [1].

The granulocytes (a type of phagocyte that has small granules visible in the cytoplasm) consist of polymorphonuclear cells (PMN) which are subdivided into three classes; neutrophils,

basophils, and eosinophils (Table 2). The neutrophils are the most abundant white blood cells, they account for 65 to 70% of all leukocytes [2]. When activated, the neutrophils marginate and undergo selectin-dependent capture followed by integrin-dependent adhesion, before migrating into tissues. Leukocytes migrate 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 protect us against bacteria and other invading organisms, a process that is called phagocytosis (ingestion). Only cells participating in the phagocytosis are called phagocytes. The granulocytes are short lived. After they are released from the bone marrow they can circulate in the blood for 4 to 8 hours. Then they leave the blood and enter into the tissues and can live there for 3 to 4 days. If 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 neutrophil granulocytes are very important in the fight against infections. If a bacterial infection occurs, the neutrophils travel to the infected area and neutralize the invading bacteria. In those cases, the total number of neutrophil granulocytes is high. The eosinophil granulocytes do not phagocytize and are more important in allergic reactions. The same is the case with the basophil granulocytes; they contain histamine and heparin and are also involved in allergic reactions.

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 [2], and circulate in the blood for about 1 to 3 days before moving into tissues throughout 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 responsible 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.

| Cells | Amount (cell/ μ L) |
|--------------|------------------------|
| Leukocytes | 4 500 – 11 000 |
| -Neutrophils | 4 000 – 7 000 |
| -Lymphocytes | 2 500 – 5 000 |
| -Monocytes | 100 – 1 000 |
| -Eosinophils | 0 – 500 |
| -Basophils | 0 - 100 |

Table 2. Normal values of circulating blood cell levels. Rhoades, 2003.

2.2. The acquired immune system

The second kind of protection is called adaptive (or active) immunity [2]. This type of immunity develops throughout our lives. Adaptive immunity involves the lymphocytes and develops from early childhood. Adults are exposed to diseases or are immunized against 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 molecules (antibodies and cytokines) to regulate the immune response. T lymphocytes can also be engaged in direct cell-on-cell warfare (Table 1). Lymphocytes start out in the bone marrow where they reside and mature into B cells. Lymphocytes can also leave and travel 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 [1].

3. 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 bind 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 an important part of the innate immune system. The complement system has an important role in the fight against bacteria and virus infections.

A blood test is commonly used in the diagnosis of infections. The level of CRP rises when an inflammatory reaction starts in the body. Blood for analysis may be taken by a finger prick and can be analyzed quickly. The level of CRP increases 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 ($\frac{1}{2}$ h ~ 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.

Recent investigations suggest that physical activity reduce CRP levels. Higher levels of physical activity and cardiorespiratory fitness are consistently associated with 6 to 35% lower CRP levels [3]. Longitudinal training studies have demonstrated reductions in CRP concentration from 16 to 41%, an effect that may be independent of baseline levels of CRP, body composition, and weight loss [3].

The mechanisms behind the role physical activity plays in reducing inflammation and suppressing CRP levels are not well defined [4]. 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 [4]. A short-term increase in serum CRP has been observed after strenuous exercise [4]. 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.

The most common infections in sports medicine are caused by bacteria or viruses. Infections are very common, particularly infections in the upper respiratory tract [5]. Asthma/airway hyper-responsiveness (AHR) is the most common chronic medical condition in endurance trained athletes (prevalence of about 8% in both summer and winter athletes) [6]. Inspiring polluted or cold air is considered a significant aetiological factor in some but not all sports people [6]. The symptoms of infections are healthy, which means that the body is reacting normally. The common cold is generally caused by virus infections and is self-healing and most of the times free of problems, but sometimes bacteria will follow and cause complications (e.g. ear infections). Mononucleosis ("kissing disease") and throat infections are usually caused by various viruses. Infections in the heart muscle (myocarditis) can be due to both virus and bacteria and represent a problematic area within the field of sports medicine [7].

4. 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-1 β 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, TNF α) and anti-inflammatory (IL-1ra, IL-10) cytokines. Interleukin-6 (IL-6) is the most studied cytokine associated with physical exercise [8]. Many studies have investigated the effects of different forms and intensities of exercise on its plasma concentration and tissue expression [9-11]. The effects of physical exercise seem to be mediated by intensity [10] as well as the duration of effort, the muscle mass involved and the individual's physical fitness level [12].

Increases in IL-6 over 100 times above resting values have been found after exhaustive exercise such as marathon races, moderate exercise (60–65% $\text{VO}_{2\text{max}}$) and after resistance exercise, and

may last for up to 72 h after the end of the exercise [13]. 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 [14]. Free radical damaging effects on cellular functions are for IL-6 seen as a key mediator of the exercise-induced immune changes [13].

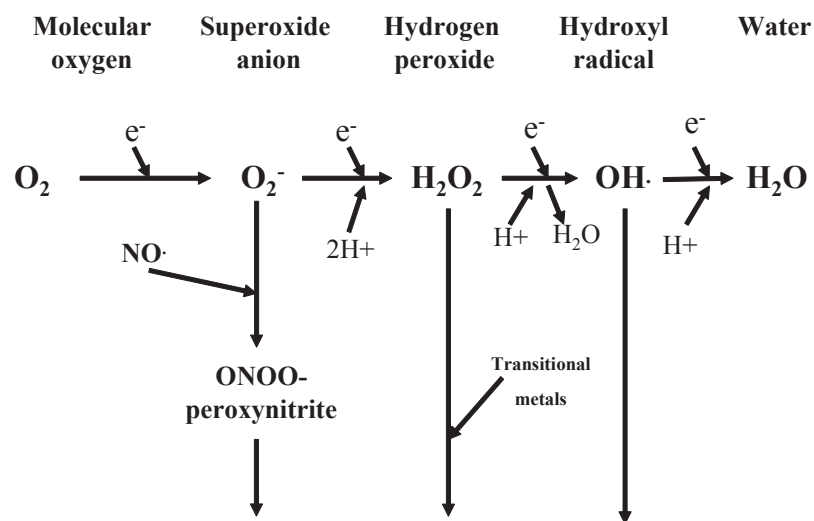
5. Free radicals

Free radicals are any atom with an unpaired electron. Reactive oxygen species (ROS) are all free radicals that involve oxygen. ROS formation is a natural ongoing process that takes place in the body, while the antioxidant defense is on duty for collecting and neutralizing the excess production of oxygen radicals. Many sources of heat, stress, irradiation, inflammation, and any increase in metabolism including exercise, injury, and repair processes lead to increased production of ROS [15]. ROS have an important function in the signal network of cellular processes, including growth and apoptosis, and as killing tools of phagocytising cells [15]. The granulocytes and the monocytes produce ROS like superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and hydroxyl radical (OH^\cdot).

Superoxide anion (O_2^-), an unstable free radical that kills bacteria directly, is produced through the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated oxidative burst reaction [16]. The superoxide anion also participates in the generation of secondary free radical reactions to generate other potent antimicrobial agents, *e.g.*, hydrogen peroxide [16]. Superoxide anion is generated in both intra- and extracellular compartments and when nitric oxide (NO) and O_2^- react with each other, peroxynitrite ($ONOO^-$) can form very rapidly [17]. Peroxynitrite is a strong oxidation which damages DNA, proteins and other cellular elements. The stability of $ONOO^-$ allows it to diffuse through cells and hit a distant target. Intracellular $ONOO^-$ formation will usually minimize by increased intracellular superoxide dismutase (SOD) activity [17] (Figure 1).

Regular physical activity and exercise at moderate levels are important factors for disease prevention [18]. Strenuous exercise leads to the activation of several cell lines within the immune system, such as neutrophils, monocytes, and macrophages, which all are capable of producing ROS [19]. During resting conditions, the human body produces ROS to a level which is within the body's capacity to produce antioxidants. During endurance exercise, there is a 15- to 20-fold increase in whole body oxygen consumption, and the oxygen uptake in the active muscles increases 100- to 200-fold [20]. This elevation in oxygen consumption is thought to result in the production of ROS at rates that exceed the body's capacity to detoxify them. Oxidative stress is a result of an imbalance between the production of ROS and the body's ability to detoxify the reactions (producing antioxidants). In the literature, there is disagreement whether or not oxidative stress and subsequent damage associated with exercise is harmful or not. This ambiguity may partly be explained by the methods chosen for

the different investigations [18]. Experimental and clinical evidence have linked enhanced production of ROS to certain diseases of the cardiovascular system including hypertension, diabetes and atherosclerosis [21]. Oxidized LDL inhibits endothelial ability to produce nitric oxide (NO). This is unfortunate since NO increases blood flow, allows monocytes to adhere to the endothelium, decreases blood clots and prevents oxidation of LDL. High amount of free radicals promotes the atherosclerosis process by oxidation of LDL. Free radicals react with substances in the cell membrane and damage the cells that line the blood vessels. This means that the fat in the blood can more easily cling to a damaged vessel wall. If there are sufficient antioxidants present, it is believed that the harmful processes in the blood vessels can be slowed down. On the other hand, free radicals are not always harmful, but can serve a useful purpose in the human body. The oxygen radicals are necessary compounds in the maturation process of the cellular structure. Complete elimination of the radicals would not only be impossible, but also harmful [22].



After Chabot, F. *et al.* (1998)

Figure 1. A simplified overview of the generation of ROS.

6. Antioxidants

An antioxidant is a chemical compound or a substance such as vitamin E, vitamin C, or beta carotene, thought to defend body cells from the destructive effects of oxidation. Antioxidants are important in the context of organic chemistry and biology: all living cells contains a complex systems of antioxidant compounds and enzymes, which prevent the cells by chemical

damages due to oxidation. There are many examples of antioxidants: e.g. the intracellular enzymes like superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, catalase, the endogenous molecules like glutathione (GSH), sulfhydryl groups, alpha lipoic acid, Q 10, thioredoxin, the essential nutrients: vitamin C, vitamin E, selenium, N-acetyl cysteine, and the dietary compounds: bioflavonoids, pro-anthocyanin.

The task of antioxidants is to protect the cell against the harmful effects of high production of free radicals. We can influence our own antioxidant defenses by eating food that contains satisfactory amounts of antioxidants (Table 3). A diet containing polyphenol antioxidants from plants is necessary for the health of most mammals [23]. Antioxidants are widely used as ingredients in dietary supplements that are used for health purposes, such as preventing cancer and heart diseases [23]. However, while many laboratory experiments have suggested benefits of antioxidant supplements, several large clinical trials have failed to clearly express an advantage of dietary supplements. Moreover, excess antioxidant supplementation may be harmful [22].

| Different types of antioxidants | Food with a high content of antioxidants |
|---------------------------------|---------------------------------------------------------|
| Vitamin C | Fruit and vegetables |
| Vitamin E | Oils |
| Polyphenols/flavonoids | Tea, coffee, soya, fruit, chocolates, red wine and nuts |
| Carotenoids | Fruit and vegetables |

Table 3. Examples of food with a high content of antioxidants.

Neutrophils are protected against ROS by SOD, catalase, glutathione peroxidase, and glutathione reductase. The exogenous antioxidants include among others vitamin E (α -tocopherol), vitamin C and coenzyme Q. The lipid-soluble α -tocopherol is considered the most efficient among the dietary antioxidants, because it contributes to membrane stability and fluidity by preventing lipid peroxidation. Coenzyme Q or ubiquinone is also lipid-soluble, and has the same membrane stabilization effect as vitamin E. Ascorbic acid or vitamin C (water-soluble) is, however, the predominant dietary antioxidant in plasma. The apprehension of increased rates of ROS production during exercise is part of the rationale why many athletes could theoretically profit by increasing their intake of antioxidant supplements beyond recommended doses. Table 4 shows an overview of the localization and function to the enzymatic antioxidants which protects the cell against oxidative stress.

Non-enzymatic antioxidant reserve is the first line of defense against free radicals (Table 5). Three non-enzymatic antioxidants are of particular importance. 1) Vitamin E, the major lipid-soluble antioxidant which plays a vital role in protecting membranes from oxidative damage, 2) Vitamin C or ascorbic acid which is a water-soluble antioxidant and can reduce radicals from a variety of sources. It also appears to participate in recycling vitamin E radicals. Interestingly, vitamin C can also function as a pro-oxidant under certain circumstances.

3) Glutathione, which is seen as one of the most important intracellular defense against damage by reactive oxygen species.

| Enzymatic antioxidants | Localisation | Function |
|------------------------|--------------------------------------|------------------------------------------------------|
| Superoxid oxidase | Mitochondria, cytosol | Superoxid anion |
| Glutathion peroxidase | Mitochondria, cytosol, cell membrane | Reduces H ₂ O ₂ |
| Catalase | Perisomes | Reduces H ₂ O ₂ |
| Glutaredoksine | Cytolsol | Protects and repair proteins and no-proteins thioles |

Table 4. An overview of enzymatic antioxidants and associated free radicals.

In addition to these "big three", there are numerous small molecules that function as antioxidants. Examples include bilirubin, uric acid, flavonoids, and carotenoids.

| Non-enzymatic antioxidants | Localisation | Function |
|----------------------------|-----------------------|-------------------------------------------------|
| Vitamin C | Aqueous | Scavenger free radicals |
| Vitamin E | Cell membrane | Reduces free radicals to less active substances |
| Carotenes | Cell membrane | Scavenger free radicals |
| Glutathione | Non- proteins thioles | Scavenger free radicals |
| Flavenoids/polyphenoles | Cell membrane | Scavenger free radicals |
| Ubuquinon | Cell membrane | Scavenger free radicals |

Table 5. An overview of non-enzymatic antioxidants and associated free radicals.

The optimal aim is an equal production of free radicals together with equal production of antioxidants (Figure 2). There is broad evidence suggesting that physical exercise affects the generation of ROS in leukocytes [3,15] which may induce muscle damage [12,23] and may explain phenomena like decreased physical performance, muscular fatigue, and overtraining [16]. Detrimental influences of free radicals are due to their oxidizing effects on lipids, proteins, nucleic acids, and the extracellular matrix. However, the available data to support the role of ROS in relation to physical exercise are highly inconsistent and partly controversial. These controversies are probably due to the different methodologies used to assess ROS, generally including time-demanding and laborious cell isolation procedures and subsequent cell culturing that most certainly affects the ROS status of these cells in an uncontrolled and unpredictable manner. The type of physical activity studied also varied considerably and probably influenced the results presented.

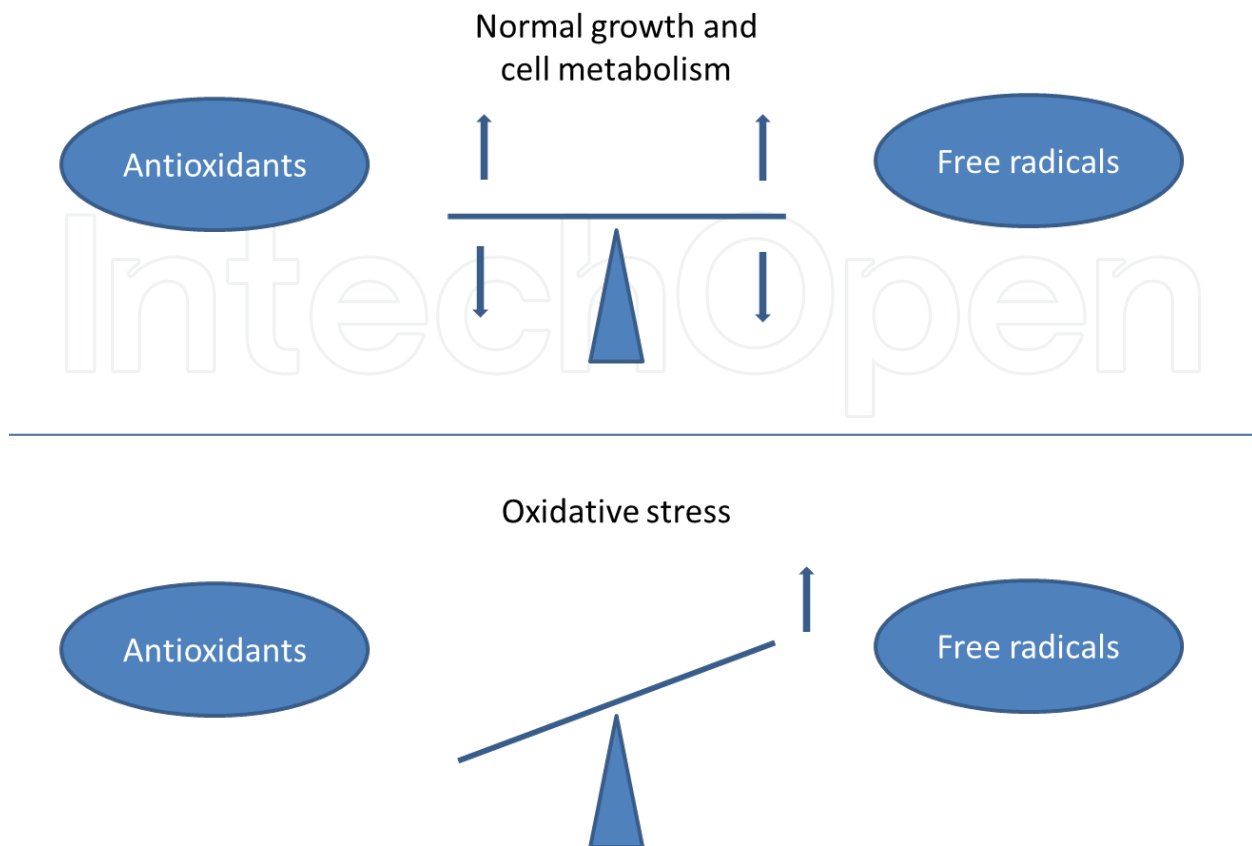


Figure 2. The balance between antioxidants and the amount of free radicals.

7. Physical activity and antioxidant supplementation

A very important question in this context is whether exercise-induced oxidative stress is associated with an increased risk of diseases. The great disparities as to whether ROS production increases or decreases after physical exercise should be considered when comparing different studies of antioxidant supplementation and exercise-induced oxidative stress; likewise the differences in antioxidant dosages used, the biological potency of different forms of the same antioxidant and the different manufacturers' products. The main explanations for the inconsistencies of the effect of antioxidant supplementation on oxidative stress seems to be due to the different assay techniques used to measure in vitro neutrophil ROS production, the exercise mode [22], and the fitness levels of participants.

The human body has an elaborate antioxidant system that depends on the endogenous production of antioxidant compounds like enzymes, as well as the dietary intake of antioxidant vitamins and minerals. Still, there is not enough knowledge at present as to whether the body's natural antioxidant defense system is sufficient to counteract the induced increase of free radicals during physical exercise or if additional supplements are needed [27].

Until now, the majority of investigations address the effects of exercise on markers of oxidative stress, and not the occurrence of disease. However, most research points to a beneficial effect of regular moderate-to-vigorous physical activity on disease prevention [22] [27].

8. Different methods for detection of free radicals and antioxidants

The work of getting reliable and validated measures of both free radicals and anti-oxidants is still ongoing. The most common methods for detecting free radicals are: 1) Electron spin resonance (ESR) and “spin trapping”, which quantify and generate free radicals. This technique makes it possible to identify the cells in their own milieu. 2) Flow cytometry, which is a technique for counting, examining and sorting microscopic particles suspended in a stream of fluid, and 3) Chemiluminescence Luminol, which is a method used to detect free radicals with chemical reactions (Table 6).

| Method | Free radicals |
|-------------------------|-----------------------------------------------------------------------------------------------------------------|
| Electron spin resonance | Free radicals; O ₂ ⁻ ; OH ⁻ - intra cellular |
| Flow cytometry | Free radicals; O ₂ ⁻ ; H ₂ O ₂ , ONOO ⁻ - intra cellular |
| Cheluminiscence | Free radicals - extra cellular |

Table 6. An overview of some of the methods used for detection of free radicals.

Part of the problem with measuring free radicals is that cells are very reactive and short-lived. Most methods used today are not sensitive enough and it is not unusual to find false signals and interference from other substances. It is therefore difficult to compare various studies involving the use of different methods, because it is difficult to know if the different laboratories have measured the same substances (Figure 3).

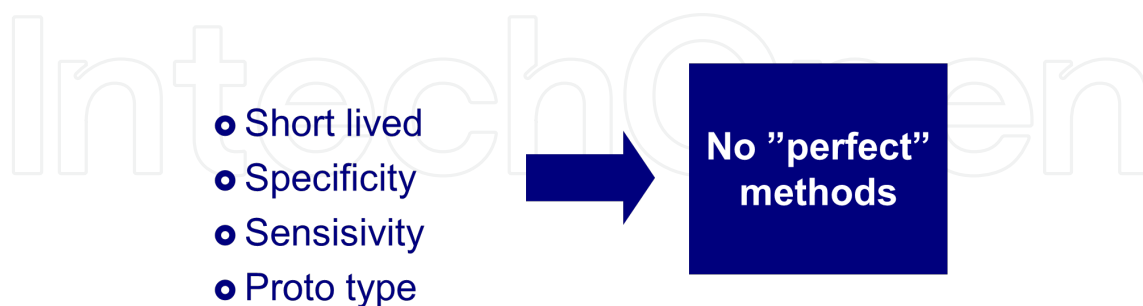


Figure 3. No “perfect” methods.

Several methods have been introduced to measure the plasma total antioxidant capacity (TAC) [24], and there are several techniques for quantifying TAC. The most widely used methods for TAC measurements are 1) the colorimetric method (a method for determining concentrations

of colored compounds in a solution), 2) the fluorescence method (a method for detecting particular components with exquisite sensitivity and selectivity) and 3) the chemiluminescence method (a method for observation of a light (luminescence) as a result of a chemical reaction) [24-26].

9. Effect of exercise on immunity

9.1. The J- curve

Although the consensus is lacking in some areas, there is sufficient agreement to make some conclusions about the effects of exercise on the immune system. Numerous publications before 1994 resulted in assumption that a J-shaped relationship [27] best described the relationship between infection sensitivity and exercise intensity. The hypothesis is based on cross-section analysis of a mixed cohort of marathon runners, sedentary men and women as well as longitudinal studies on athletes and non-athletes [28-30] that showed increased immunity with increased exercise training. However, one study [31] observed a lower risk for upper respiratory tract infections (URTI) in over-trained compared with well-trained athletes. Previous infections, pathogen exposure, and other stressors apart from exercise may also influence immune response and therefore interpretations of the results of such studies need to be made with care. According to the J-shaped curve, moderate amounts of exercise may enhance immune function above sedentary levels, while excessive amounts of prolonged high intensity exercise may impair immune function [13] (Figure 4).

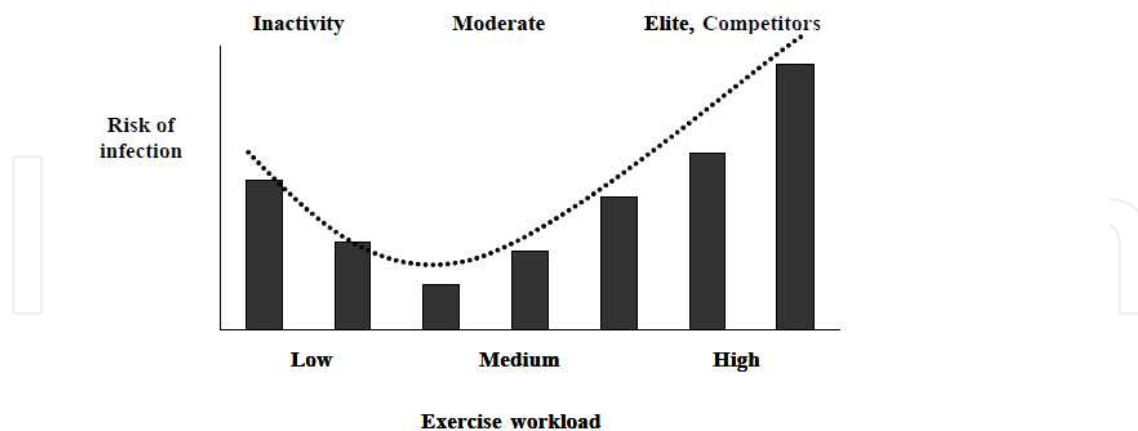


Figure 4. The risk of infection in relation to physical activity. Nieman et al., 1994.

9.2. The S-curve

With regard to induced infections in animals, the influence of any exercise intervention appears to be pathogen specific, and dependent on the species, age, and sex of the animals selected for

study, and the type of exercise paradigm. Individuals exercising moderately may lower their risk of upper respiratory tract infections (URTI) while those undergoing heavy exercise regimens may have higher than normal risk. When including elite athletes in the J-curve model, the curve is suggested to be S-shaped [30] (Figure 5). This hypothesis states that low and very high exercise loads increases the infection odds ratio, while moderate and high exercise loads decreases the infection odds ratio, but this needs to be verified by compiling data from a larger number of subjects [30].

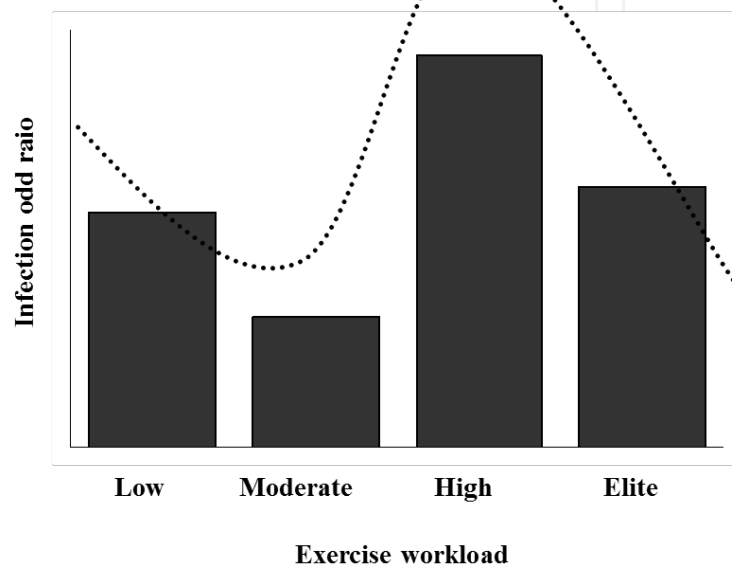


Figure 5. S-shaped relationship between training load and infection rate. Malm et al., 2006.

10. The open window theory

The J-curve relationship has been established among scientists, coaches, and athletes. However, the immunological mechanism behind the proposed increased vulnerability to upper respiratory tract infections (URTI) after strenuous physical exercise is not yet described [32]. The phenomenon is commonly referred to as the “open window” for pathogen entrance [33] (Figure 6). The “open window” theory means that there is an 'open window' of altered immunity (which may last between 3 and 72 hours), in which the risk of clinical infection after exercise is excessive [34, 35]. This means that running a marathon or simply engaging in a prolonged bout of running, increases your risk of contracting an upper-respiratory system infection. Fitch [6] reported that Summer Games athletes who undertake endurance training have a much higher prevalence of asthma compared to their counterparts that have little or no endurance training. Years of endurance training seems to incite airway injury and inflammation [6]. Such inflammation varies across sports and the mechanical changes and de-

hydration within the airways, in combination with levels of noxious agents like airborne pollutions, irritants or allergens may all have an effect [6].

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 [18]. 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 [18] [33], local release of proinflammatory cytokines [34], and activation of the complement, coagulation and fibrinolytic cascades [35]. Both physical and psychological stress have been regarded as potent suppressors of the immune system [36], which leaves us with many unanswered questions about whether or not physical exercise is beneficial or harmful for the immune system [37].

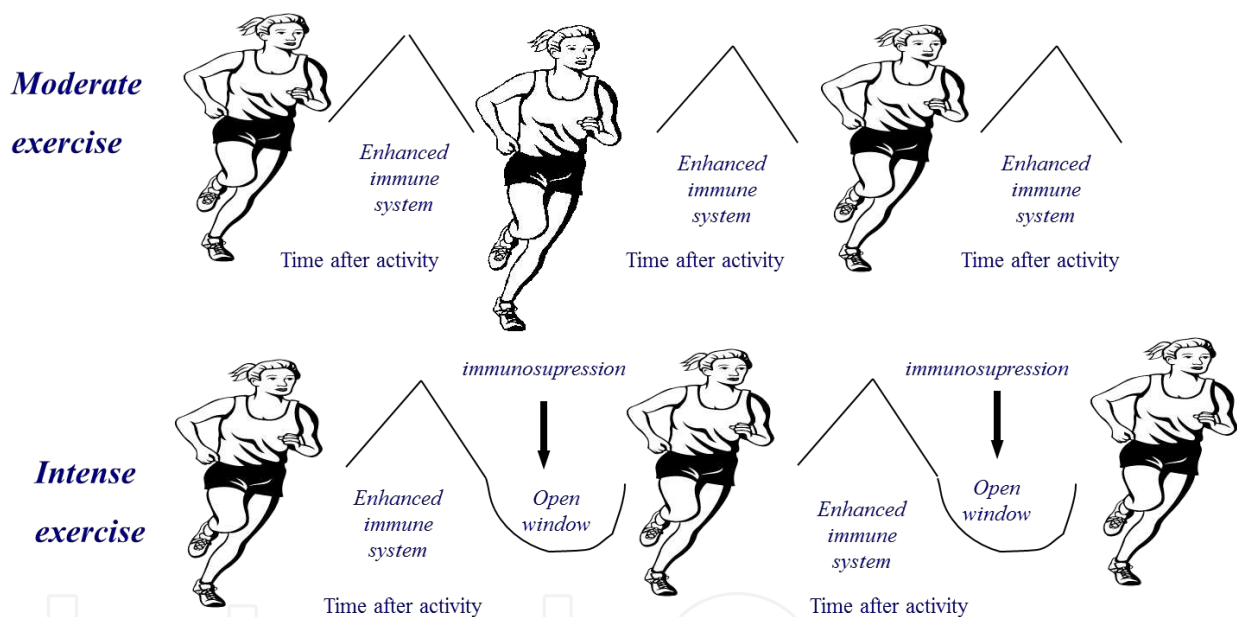


Figure 6. The open window theory. Pedersen & Ullum, 1994.

One of the most studied aspects of exercise and the immune system is the changes in leukocyte numbers in circulating blood [36-39]. 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 [2]. During exercise, the main source of circulatory neutrophils are primary (bone marrow) and secondary (spleen, lymph nodes, gut) lymphoid tissues, as well as margined neutrophils from the endothelial wall of peripheral veins [40, 41]. Fry *et al.*, [38] 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 [42-44]. One way to cure physical stress for the immune system is to increase the total number of leukocytes for fighting the infection and for normalizing the homeostasis. 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 [41].

11. Physical activity – A stimulator and an inhibitor to 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 [45]. 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 [46]. 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 [47]. This effect is seen in both untrained and trained individuals. How long this period lasts for is partly dependent of the intensity and duration of the exercise, and is very individual. The “open period” can last from a few hours up to a day. If such a long-term activity session happens too frequently, it can cause prolonged susceptibility to infections and increased risk of complications if an infection is acquired. Planning of training/activity/competition and rest periods is therefore very important and should be done on an individual basis.

12. Summary

The body's immune system fights all that it perceives as a foreign body. The immune system is separated in two functional divisions: the innate immunity, referred to as the first line of defense, and acquired immunity, which produces a specific reaction and immunological memory to each infectious agent.

Free radicals are any atom with an unpaired electron. Reactive oxygen species (ROS) are all free radicals that involve oxygen. ROS formation is a natural ongoing process that takes place in the body, while the antioxidant defense is on duty for collecting and neutralizing the excess production of oxygen radicals. Many sources of heat, stress, irradiation, inflammation, and any increase in metabolism including exercise, injury, and the repair processes lead to increased production of ROS.

An antioxidant is a chemical compound or a substance such as vitamin E, vitamin C, or beta carotene, thought to defend body cells from the destructive effects of oxidation. Antioxidants are important in the context of organic chemistry and biology: all living cells contain a complex systems of antioxidant compounds and enzymes, which prevent the cells death by chemical damages due to oxidation.

A very important question in this context is whether exercise-induced oxidative stress is associated with an increased risk of disease. The great disparities as to whether ROS production increases or decreases after physical exercise should be considered when comparing different studies of antioxidant supplementation and exercise-induced oxidative stress; likewise the differences in antioxidant dosages used, the biological potency of different forms of the same antioxidant and the different manufacturers products. The main explanations for the inconsistencies as to the effect of antioxidant supplementation on oxidative stress seems to be due to the different assay techniques used to measure the ROS production, the exercise mode, and the fitness levels of participants.

The J-curve theory describes that moderate exercise loads enhance immune function above sedentary levels, while excessive amounts of prolonged high intensity exercise may impair immune function. However, the immunological mechanism behind the proposed increased vulnerability to upper respiratory tract infections (URTI) after strenuous physical exercise is not yet described. This phenomenon is referred to as the "open window". The "open window" theory means that there is an 'open window' of altered immunity (which may last between 3 and 72 hours) in which the risk of clinical infection after exercise is excessive. When including elite athletes in the J-curve model, the curve is suggested to be S-shaped. This hypothesis states that low and very high exercise load increases the infection odds ratio, while moderate and high exercise loads decreases the infection odds ratio, but this needs to be verified by compiling data from a larger number of subjects.

- Exercise has anti-inflammatory effects, which means that moderate amounts of exercise may enhance immune function above sedentary levels.
- Physical activity is associated with reduced resting C-reactive protein (CRP) levels.
- Heavy physical activity produces a rapid, transient increases in cytokine production and entails increases in both pro-inflammatory and anti-inflammatory cytokines.
- Physical exercise affects the generation of reactive oxygen species (ROS) in leukocytes, which may induce muscle damage, decreased physical performance, muscular fatigue, and overtraining.
- It is currently not known whether the body's natural antioxidant defense system is sufficient to counteract the induced increase of ROS during physical exercise or if additional supplements are needed.
- There are three main theories describing the effects of exercise on immunity: 1) the J-curve theory, 2) the "open window" theory and 3) the S-curve theory.

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