4. Immune system

4.1 Exercise and the immune system

One of the most important factors for a team in football is to make sure that the team collectively stays healthy. Preventing injury and illnesses is key to success. However, especially at the highest level, where 2 and sometimes 3 matches are played in one week, with a lot of travel, crowded spaces and so on, this can be challenging. Unfortunately, hard exercise and limited recovery will compromise immune system and therefore it is common for upper respiratory tract infections to occur during the winter periods (in European season) when there is a congested fixture schedule.

It is important to make sure the immune system is prepared to fight potentially damaging (pathogenic) microorganisms such as bacteria, viruses, and fungi. Although many factors influence exercise-induced immune depression (e.g., physical, environmental, and psychological stresses), nutrition plays a critical role. Inadequate nutrition can result in deficiencies and suboptimal function of the immune system. With adequate nutrition strategies it is possible to optimize recovery and in this section we will explore the evidence that nutritional interventions can help prevent immunosuppression. First we will study the immune system and the effects of exercise on the immune system.

4.1.1 The immune system

> The immune system is involved in tissue repair after injury and in the protection of the body against potentially damaging (pathogenic) microorganisms such as bacteria, viruses, and fungi. In some circumstances, the immune system can become functionally depressed (known as immunodepression), which may result in an increased susceptibility to infection. Several forms of stress, including a heavy schedule of training and competition, can lead to immunodepression in athletes, which places them at greater risk for opportunistic infections, particularly upper respiratory tract infections (URTIs). (Jeukendrup & Gleeson, 2018, p. 365).

Nutritional deficiencies can impair immune function and will increase the risk of infection. It is also evident that "even medically harmless infections may significantly impair athletic performance" (Jeukendrup & Gleeson, 2018, p. 365).

Simply put, the immune system recognizes, attacks, and destroys things that are foreign to the body. In actuality, the functions of this homeostatic system are far more complex, involving the precise coordination of many cell types and molecular messengers. Yet, like any other homeostatic system, the immune system is composed of redundant mechanisms to ensure that essential processes are carried out.

The immune system has two broad functions, **innate** (natural, or nonspecific) immunity and **adaptive** (acquired, or specific) immunity, which work synergistically. The attempt of an infectious agent to enter the body immediately activates the innate system. This so-called first-line of defence comprises three general mechanisms that have the common goal of restricting microorganism entry into the body:

- Physical or structural barriers (skin, epithelial linings, and mucosal secretions).
- Chemical barriers (pH of bodily fluids and soluble factors).
- Phagocytic cells (e.g., neutrophils and macrophages or monocytes).

Failure of the innate system and the resulting infection activates the adaptive system, which aids recovery from infection. Adaptive immunity is helped greatly by T-lymphocyte and B-lymphocyte acquisition of receptors that recognize the foreign molecules (called antigens), engendering specificity and "memory" that enable the immune system to mount an augmented response when the host is reinfected by the same pathogen.

The components of the immune system comprise both cellular and soluble elements. The white blood cells (leukocytes) have diverse functions, despite their common origin from the stem cells of the bone marrow. Leukocytes consist of the granulocytes (60% to 70%), monocytes (10% to 15%), and lymphocytes (20% to 25%). Various subsets of the latter can be identified through specific proteins (clusters of differentiation or cluster designators [CD]) that are expressed on the cell surface of a particular cell type. For example, all T-

> lymphocytes express the protein CD3 on the cell surface. B-lymphocytes do not express CD3 but express CD19, CD20, and CD22. A particular subset of T-lymphocytes called helper T-cells specifically express the CD4 protein, whereas the cytotoxic T-cells express CD8. T-cells recognize short peptide sequences from antigens only if they are held on the surface of the cell and complexed with a major histocompatibility complex (MHC) molecule. The ability of the immune system to distinguish self from nonself depends largely on the MHC, a group of protein markers that is present on the surface of every cell and is slightly different in each person. (Jeukendrup & Gleeson, 2018, p. 366).

4.1.2 Effect of exercise on immune function

"Athletes engaged in heavy training programs, particularly endurance events, appear to be more susceptible to infection than the general population. For example, sore throats and flulike symptoms are more common in athletes." (Calder & Yaqoob, 2013, p. 653). Nowadays, many athletes who participate in elite sports "are exposed to high training loads and an increasingly saturated competition calendars" (Soligard et al., 2016, p. 1030). Emerging evidence indicates that inappropriate load management is a significant risk factor for both acute episodes of illness and the overtraining syndrome.

> The International Olympic Committee (IOC) [recently] convened an expert group to review the scientific evidence for the relationship of load ([including] rapid changes in training and competition load, competition calendar congestion, psychological load and travel) and health outcomes in sport. (Soligard et al., 2016, p. 1030).

They concluded that there is evidence that changes in external load (increased volume and intensity of training) and internal training load (the physiological and psychological responses to external load in each individual) are associated with an increased risk of illness and that participation in competitions (single or multiple) is associated with an increased risk of illness. However, they also recognized that it is not yet possible to quantify the magnitude of the training load increase that is related to increased risk of a specific illness in any given sport. Also that the factors responsible for increased illness risk as a result of intensive training and competition are likely to be multifactorial and need to be further explored in future studies. (Schwellnus et al., 2016)

However, "some convincing evidence suggests that this increased susceptibility to infection arises because of a depression of immune system function" (Calder & Yaqoob, 2013, p. 653). (For detailed reviews, see: Gleeson, February, 2016; Gleeson & Walsh, 2012; Gleeson & Williams, 2013; Walsh et al., 2011).

The main component of the immune system consists of the white blood cells, or leukocytes.

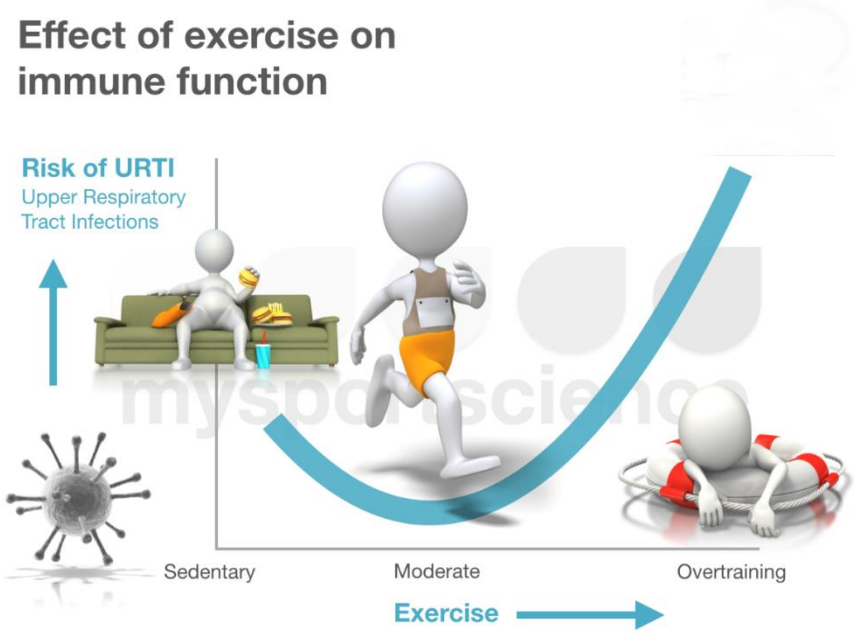
> The circulating numbers and functional capacities of leukocytes may be decreased by repeated bouts of intense, prolonged exercise... The cause may be increased levels of stress hormones (e.g. epinephrine and cortisol) and anti-inflammatory cytokines [e.g. IL-6 and IL-10] during exercise and entry into the circulation of less mature leukocytes from the bone marrow. (Calder & Yaqoob, 2013, p. 653).

Increased free radical production during exercise is another potential Inhibitor of several immune cell functions. "Drops in the blood concentration of glutamine have also been suggested as a possible cause of the immunodepression associated with heavy training, although the evidence for this is less compelling." (Calder & Yaqoob, 2013, p. 653). Inflammation caused by muscle damage may be another factor.

> The relationship between exercise and susceptibility to infection has been modeled in the form of a J-curve (Nieman, 1994)... This model suggests that, whereas engaging in moderate activity may enhance immune function above sedentary levels..., excessive amounts of prolonged, high-intensity exercise [may] induce detrimental effects on immune function. Although the literature provides strong evidence in support of the latter point, relatively little evidence is available to suggest any clinically significant difference in immune function between sedentary and moderately active people. (Calder & Yaqoob, 2013, p. 653).

Thus, the portion of the J-curve representing this part of the relationship should perhaps be flattened out, as shown in Figure 1.

Figure 1: The J-curve model implies that risk of upper respiratory tract infection (URTI) is reduced by moderate activity but progressively elevated by heavier training loads



Source: Jeukendrup, September 26, 2016, https://goo.gl/o1XtLy

> [C. E.] Matthews et al. (2002) reported that the regular performance of about 2 hours of moderate exercise a day was associated with a 29% reduction in risk of URTI compared with a sedentary lifestyle. Similarly, in a study of over 1,000 participants, Nieman et al. [Nieman, Henson, Austin and Sha] (2011) observed that doing moderate exercise on 5 or more days per week was associated with a 30% lower risk of URTI than doing 1 day or fewer days of exercise per week. This finding emphasizes that the benefit of regular, moderate exercise in improving resistance to infection is quite small [although there are, of course, substantial benefits to cardiovascular and metabolic health with a more active lifestyle]. (Jeukendrup & Gleeson, 2018, p. 381).

Congested competition schedules in combination with lots of travel, press events, large crowds, etc. increase the susceptibility to infection and need to be managed carefully. The factors that increase the chances of illness are discussed below.

4.1.3 Causes of illness in players

> The most common illnesses in athletes (and in the general population) are viral infections of the upper respiratory tract (i.e. the common cold and influenza), which are more common in the winter months. Adults typically experience between two and four episodes of respiratory illness per year. Athletes can also develop similar symptoms (e.g. sore throat [runny nose, dry cough]) due to allergy or inflammation [affecting the mucosal lining of the upper respiratory tract] caused by the inhalation of cold, dry or polluted air... [In themselves,] these symptoms are generally trivial, but no matter whether the cause is infectious or allergic inflammation, they can cause an athlete to interrupt training, under-perform or even miss an important competition. (Gleeson, 2015, p. 1).

"Prolonged bouts of strenuous exercise [usually in excess of 90 minutes and of a continuous rather than Intermittent nature; like a fairly typical training session in football] have been shown to result in transient depression of white blood cell (leukocyte) functions" (Gleeson, 2015, p. 2), which consequently can impair defense against infectious pathogens including both, viruses and bacteria. It has been suggested "that such changes create an 'open window' of decreased host protection" (Gleeson, 2015, p. 2), during which time pathogens "can gain a foothold, increasing the risk of developing an infection" (Walsh et al., 2011, as cited in Gleeson, 2015, p. 2). Other factors including "psychological stress, lack of sleep and inadequate nutrition (particularly deficiencies of protein and essential micronutrients) can also depress immunity" (Walsh et al., 2011, as cited in Gleeson, 2015, p. 2) and lead to increased risk of infection.

> There are also some situations, such as proximity to large crowds, coming into close contact with people suffering from infections and being exposed to environments with poor hygiene, in which an athlete's exposure to infectious agents may be increased. Thus, the degree of exposure to pathogens in the athlete's environment and the status of the athlete's immune system are the two important determinants of infection risk. Various strategies, including behavioral and nutritional ones, can be employed to reduce these risk factors. Of course, in many professional sports that attract large numbers of spectators, the competitors' exposure to large crowds is unavoidable. Air travel to foreign countries may also increase the risk of picking up infections. Recently,

international travel was shown to be associated with significantly more upper respiratory illness symptoms (URS) in professional rugby players travelling across multiple time zones (Fowler, Duffield, and Lu 2016; Schwellnus et al., 2012). International travel was an independent risk factor for illness in another prospective study among elite cross-country skiers (Svendsen et al. [Svendsen, Taylor, Tonnessen, Bahr, & Gleeson] 2016).

During dynamic exercise, exposure of the lungs to airborne bacteria and viruses increases because of the higher rate and depth of breathing. However, URS can also arise due to allergy and inflammation of the airways caused by breathing cold, dry or polluted air; the URS which result from this are indistinguishable from the URS that result from a respiratory infection. Hence, the cause of the increased incidence of respiratory illness symptoms in athletes is most likely multifactorial. (Jeukendrup & Gleeson, 2018)

Acute illness can cause a reduction in exercise performance, an interruption to training, and even result in missing an important competition. Acute infective illness can affect a number of the body's organ systems causing a reduction in exercise performance through a number of mechanisms including: impaired motor coordination, decreased muscle strength and power, decreased aerobic capacity, and alterations in metabolic function. Furthermore, the presence of fever causes a decrease in the body’s ability to regulate body temperature and increases fluid losses through sweating, thereby impairing endurance performance. It has also been documented that a decrease in exercise performance after full recovery from a respiratory illness can last for 2 to 4 days and data from one study indicates that runners who start an endurance race with systemic symptoms of an acute illness are 2-3 times less likely to complete the race. It has also been reported, that in 33% of cases, an infection (most commonly of the respiratory tract) was the reason why elite Great Britain athletes from 30 different Olympic sports miss training sessions. Perhaps more importantly, an acute infective illness can also increase the risk of serious medical complications and even sudden death during strenuous exercise. (Gleeson, August 19, 2016, https://goo.gl/BGyJik).

Other common illnesses in athletes are those affecting the skin, digestive tract and genitourinary system. Ear infections

> are more common in aquatic sports. In contact sports, skin abrasions may occur… increasing the risk of transdermal infections. In some situations, food hygiene can be a problem, which increases the risk of gastrointestinal infections.
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> Forms of illness that are quite common in athletes but are non-infectious include dehydration and heat illness. An increase in gut permeability may allow entry of gut bacterial endotoxins into the circulation, particularly during prolonged exercise in the heat and this can increase the risk of heat illness. Other forms of non-infectious illness include allergies that involve the respiratory tract, skin or digestive system and are caused by a hypersensitivity of the immune system to certain molecules (often proteins) that are inhaled (e.g. pollen), come into contact with the skin (e.g. latex) or are eaten (e.g. wheat gluten). All of these involve the inappropriate activation of the immune system against a compound that is normally tolerated well by the majority of people. The inflammation caused by this hypersensitivity is the major cause of the illness symptoms. Similar symptoms may arise with intolerance to certain food items, although this does not directly involve immune system activation [as explained below]. (Jeukendrup & Gleeson, 2018, p. 377).

4.1.4 Nutrition to minimise immunodepression in players

> Poor nutritional practices may contribute to impaired immunity in athletes. Some athletes adopt diets that are extremely high in carbohydrate content at the expense of protein and fat. By avoiding foods high in animal fat, athletes are reducing their intake of fat-soluble vitamins and essential FAs. (Jeukendrup & Gleeson, 2018)

On the other hand, extreme low carb diets will increase the stress response to exercise, which may also increase immunosuppression.

> Anecdotal and media reports promote the supposed performance benefits of certain vitamins and minerals, but most athletes do not realize that micronutrient supplementation is only beneficial when correcting a deficiency and that excessive intake of individual micronutrients can be toxic or can limit the absorption of other

essential trace elements. Deficiencies or excesses of various dietary components have a substantial effect on immune function and may exacerbate the immunodepression associated with heavy training loads. (Jeukendrup & Gleeson, 2018)

How does nutrition influences immune function?

Nutrient availability potentially affects almost all aspects of the immune system because many nutrients are involved in energy metabolism and protein synthesis. Most immune responses involve cell replication and the production of proteins with specific functions (e.g., cytokines, antibodies, and acute phase proteins). Immune system functions that may be compromised include the humoral and secretory antibody production, cell-mediated immunity, bactericidal capacity of phagocytes, complement formation, and T-lymphocyte proliferative response to mitogens.

A nutritional deficiency is said to have a direct effect when the nutritional factor has primary activity within the lymphoid system and an indirect effect when the primary activity affects all cellular material or an organ system that functions as an immune regulator. (Jeukendrup & Gleeson, 2018).

For example, carbohydrate availability directly affects a number of leukocyte functions but also indirectly affects the lymphoid system through its influence on circulating levels of the catecholamines, adrenocorticotrophic hormone (ACTH), and cortisol. Changes in plasma levels of these stress hormones are probably mostly responsible for the observed changes in immune function after an acute bout of exercise.

The effect of a nutrient deficiency on the immune system depends on the duration of the deficiency as well as on the athlete's nutritional status as a whole. The severity of the deficiency is also a factor, although even a mild deficiency of a single nutrient can alter the immune response. Because the availability of one nutrient may enhance or impair the action of another, and nutrient deficiencies often occur together, nutrient–nutrient interactions on immune function are also an important consideration. Athletes who are training hard eat to satisfy their energy demands, consuming more macronutrients (carbohydrate, protein, and fat) and micronutrients (vitamins and minerals) than their sedentary counterparts. Therefore, they may ingest excessive amounts of some nutrients. Excessive amounts of specific nutrients (e.g., omega-3 polyunsaturated FAs, iron, and zinc) can have detrimental effects on immune function.

Athletes are generally advised to eat a well-balanced diet consisting of a variety of foods in sufficient quantity to cover their energy expenditures. But many athletes alter their diets. They may use diets high in protein or carbohydrate or fat, very low-energy diets, fasting, or megadoses of vitamins and minerals. Such dietary extremes may in fact compromise immune function. For example, diets that are excessively high in carbohydrate, favored by many athletes to keep glycogen stores high, are generally low in meat products and thus are low in protein (an important nutrient for immune function) and vitamin B_{12} (essential for DNA synthesis). Many athletes avoid dairy produce to minimize intake of saturated fat, but by doing so they are omitting from their diet major sources of vitamin D, B-group vitamins, and calcium, all of which play roles of varying importance in maintaining immune function. "If fat intake is a concern, then athletes should select nonfat or low-fat dairy products that provide the same (or higher) levels of calcium, vitamin D, and vitamin B_{12} as full-fat dairy products do" (Jeukendrup & Gleeson, 2018, p. 396). Only milk (regardless of fat content) is likely to be fortified with vitamin D.