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Literature Review

How does the Immune Response to Exercise Differ from the Immune Response to Infection? How can this be Applied while Advising Athletes Regarding Return to Activity/Competition?

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Abstract

The initial response to infection always involves the innate immune system, which consists of a variety of cell types and factors.

The inflammatory response causes vasodilation thus increased vascular permeability. This facilitates the recruitment of cells with the bloodstream.

If the infection is not resolved, the second procedure of the immune system, the specific immune system recruits special cells and mediators to fight the infection.

Regarding the acute immune response to exercise, a variety of mechanisms are involved, including exercise-induced changes in stress hormone and cytokine concentrations, elevated body temperature, increases in blood flow and dehydration.

Following prolonged running at high intensity, cortisol concentrations are significantly higher than control levels for several hours. Glucocorticoids can cause increased neutrophils, low numbers of eosinophils, lymphocytopenia and a reduction of both NK and T-cells, all of which happen after prolonged, high-intensity cardiorespiratory exercise.

Athletes during periods of heavy training have low neutrophil counts. Neutrophils are an important component of the innate immune system, initiating the phagocytosis of many bacterial and viral pathogens and releasing immunomodulatory cytokines.

Moreover, two other environmental factors, improper nutrition and psychological stress can negatively influence the immune system.

Keywords: *Immune Response; Exercise; Infection; Athletes*

Introduction

The immune response to infection begins with the activation of the innate immune system, which constitutes the immediate first-line barrier and response mechanism to prevent microbial invasion [1]. The innate immune response combats pathogens through two ways. First, by acute inflammation, induced by the secretion of cytokines by tissue cells. Inflammation is characterised by the accumulation of leukocytes, plasma proteins and fluid derived from the blood at the extravascular tissue site of infection. Large numbers of neutrophils and macrophages are recruited to the site of infection to destroy microbes, mainly through phagocytosis. The second mechanism is the blocking of viral replication mechanisms and the direct killing of virally-infected cells. The major way by which viral replication is inhibited, is through the stimulation of type I interferons. If an infection persists, the adaptive immune system is activated to eliminate infectious agents [2].

The adaptive immune response requires time to develop but is stronger and more specific than the innate immune response. Two major types of cells mediate the adaptive immune response: B lymphocytes and T lymphocytes. There are two types of adaptive immunity: humoral immunity and cell-mediated immunity, each induced by different types of lymphocytes. Humoral immunity is mediated by molecules called antibodies, which are secreted by B lymphocytes. Antibodies recognize and bind to microbial antigens neutralizing their activity, target microbes for elimination by phagocytes and activate protein complement pathways. Humoral immunity is the main defence mechanism for extracellular infection by pathogens. Cell-mediated immunity is mediated by T lymphocytes and is the main defence mechanism against intracellular pathogens and microbes. This type of adaptive immunity promotes destruction of infected cells by cytotoxic T lymphocytes, eliminating reservoirs of infection [2,3].

Immune response to exercise

The immune response generated due to the impact of acute and chronic workload forms the basis of exercise immunology [4]. Neutrophils are the first cells to be recruited at the site of infection or at muscular tissue due to high intensity exercise [5]. However, the response of immune system to exercise is correlated with the intensity and duration of physical activity.

A single session of exercise markedly increases the composition of leukocytes in blood resulting in a transient biphasic change during the exercise period causing lymphocytosis. The mobilization of lymphocytes (natural killer cells, CD8+ T cells, B cells, CD4+ T cells, regulatory T cells) are driven by shear stress and the increased expression of β2-adrenergic receptors on the surface of lymphocytes due to the effect of catecholamines released during exercise [6].

The post exercise phase is characterized by a rise in neutrophils, which increases up to 6 hours in to the recovery period, especially in exercise bout lasting more than 2 hours. The glucocorticoids, growth hormone and IL-6 plasma levels which promotes the mobilization of myeloid cells, are the major factors affecting the prolonged neutrophilia. The neutrophil levels usually return to normal by 24 hours.

Additionally, a delayed monocytosis period is also noted 1-2 hours after intense exercise, which usually returns to typical levels, 6 hours post exercise [7].

Within 30 minutes post exercise cessation, the number of lymphocytes subsequently falls to below resting levels with the 'lymphopenia' usually corrected 24 hours into recovery. Natural killer cells and CD8+ T cells are the majorly reduced cells, which creates a hypothetical 'open window' for microbes to attack the host causing immunosuppression, making them particularly susceptible to upper respiratory tract infections (URTI) [6-8].

The mucosal immunity is usually unaffected with moderate level exercise; however, high intensity prolonged training is said to decrease the secretions of IgA in saliva, which provides the major first line immunity via the mucosal immune system. The reduction in the IgA secretion is associated with changes in hypothalamic- pituitary- adrenal axis and studies have linked it to increased URTI risk [8].

This systematic and complex mechanism can be influenced by multiple factors, however the relationship between URTI and the intensity of exercise has been justified in the form of a J- curve (Figure 1). This model explains that moderate level of exercise decreases the risk of URTI as compared to sedentary lifestyle; while high intensity workout raises the susceptibility to infection [10].

Vigorous continuous exercise without complete recovery can result in chronic immunodepression, muscle damage, oxidative stress and inflammation. Though intensity and duration of training is vital, it is essential to note that exercise induced nutritional dysfunction, particularly the decrease in the levels of glucose and amino acid levels could further impair the immune system [11,12].

Factors (stress, nutrition, travel, sleep and heat)

An athlete's immune response is dynamic: it can change as a consequence of the different types of stress placed on it. Around 3 - 72 hours following training, this change is evident [13]. Within this time frame the body is more susceptible to upper respiratory tract infections as a result of a decreased immune response [13]. Multiple factors can influence this 'open window' [13-15] such as sleep, nutrition, psychological stress, heat and travel [14].

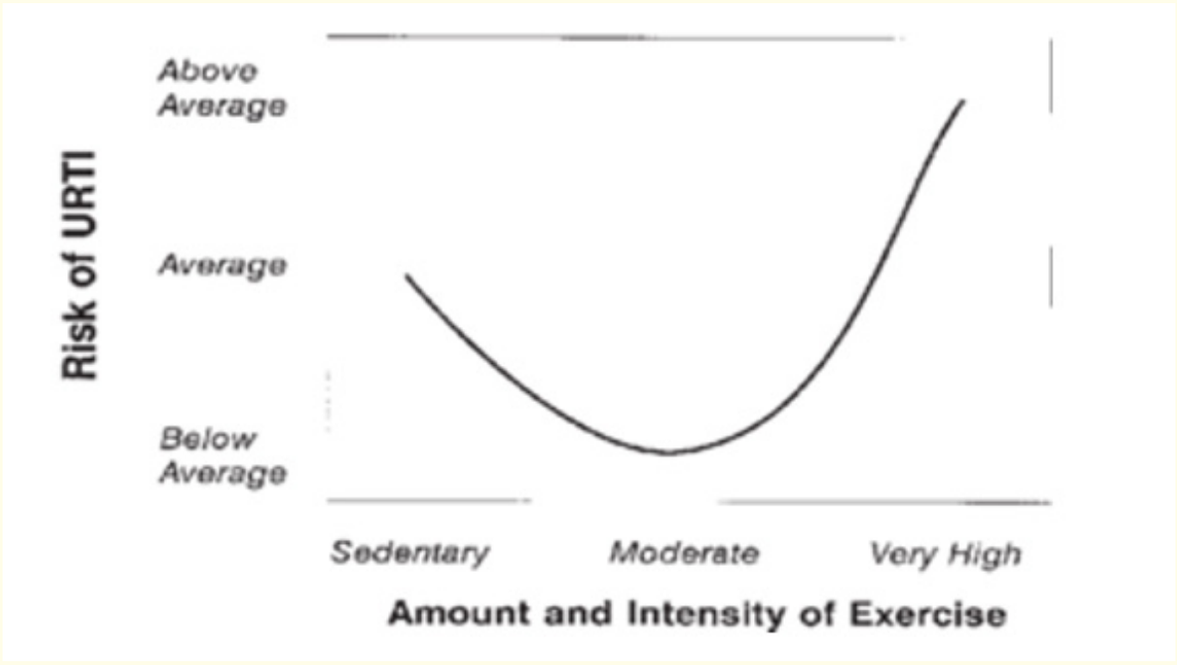

Figure 1: *Relationship between the risk of URTI and the intensity of exercise [9].*

Body homeostasis [13], cognitive and physiological function [16] can be influenced if an athlete does not get enough hours of sleep. Sleep is a crucial factor to study in regards to athletic performance, since athletes can be deficient in sleep, whether due to environmental stressors (e.g. light, noise) or even anxiety experienced before competing [16]. The optimal duration of sleep for athletes is approximately 9 hours [16]. Fullagar., *et al*. [16] explained that one main reason for the extended period is to obtain proper recovery. An athlete may experience sleep restriction or sleep deprivation. Sleep restriction is defined as "normal sleep wake cycle is partially disturbed" [16], while sleep deprivation is defined as "extreme cases of sleep loss, whereby humans do not sleep at all for a prolonged period (i.e. whole nights)" [16]. In regards to sleep restriction, Fullagar., *et al*. [16] suggests that exercising after a night of sleep loss can increase the athletes chances of developing inflammatory disease. The reason for his proposition is based on a study that demonstrated a rise in both pro-inflammatory cytokines IL6 and TNF-a after exercising on a night of sleep loss. Sleep deprivation has negative effects on the immune system. As mentioned in an article, "Inflammatory mediators increase due to constant sleep loss that alter CNS processes and behavior during immune feedback to infection, including sleep" [17]. Deficiency in sleep is associated with an increased risk of upper respiratory tract infections such that common colds are more common in those who sleep 6 hours and less [18].

Nutrients like carbohydrates, proteins, vitamins and minerals play a pivotal role in enhancing immunity to infections [14]. Gleeson and Bishop [14] mention that a deficiency in the above nutrients can change the normal immune response, thus expose the athlete to infection and negatively impact their athletic performance. A well-proportioned diet suitable for the majority of sports is composed of the following, "CHO is likely to contribute about 60 - 70% of the total energy intake and protein about 12%, with the remainder coming from fat" [14]. The direct effect of a nutritional deficiency on the immune system is when it plays an active role in the lymphoid system [14]. While an indirect effect is when a nutrient impacts an organ which regulates the immune system [14].

Immune system cells (lymphocytes, neutrophils, macrophages) rely on carbohydrates for energy since they have a high metabolic rate [14,15]. A study conducted by Gleeson and Bishop [14] analysing how low vs. high carbohydrate can alter the immune response to training deduced that neutrophilia can result from a diet with low carbohydrate levels. They further explain that although a well-balanced diet is the optimal goal to set for any athlete, some fail to eat enough protein in a day; compromising proteins for higher levels of carbohydrates [14]. T cells (CD8 + and CD4+) are specifically affected when protein requirements are not met [14]. In other cases, post-exercise glutamine levels can decrease due to diets containing high protein and low carbohydrates [14]. With that being said, the

beneficial role of glutamine is put at risk since it plays an important role in the immune system (e.g. macrophage function, nucleotide biosynthesis) [14]. As for vitamins, food is the only source of acquiring them, since the body lacks the ability to produce them. The products of free radicals produced from exercising can be deactivated by antioxidant vitamins (e.g. vitamin C and E) thus making them an important factor in maintaining the immune system's function [14]. Some harmful effects of free radicals include preventing T and B lymphocytes to divide and multiply and preventing neutrophils from getting rid of bacteria [14].

An athlete's performance can be impaired due to dehydration [19]. Sobana and Many [19] mention that inadequate water levels in the body can alter body homeostasis; rise in body temperature and a fall in the amount of sodium in the body. One of the risk factors of fluid loss is training in hot environments [19]. With that being said, exercising in Bahrain's hot temperatures, particularly in the summer, could expose local athletes to dehydration. Sweating is common in athletes and can lead to body mass loss [20]. Maughan and Shirreffs [20] mention that 1 - 2% loss of body mass due to sweating can alter athletic performance. They emphasize on proper rehydration to stop further reduction in body mass [20]. Although water itself can restore fluids that were lost after training, it is assumed that a better alternative to plain water are drinks with a small percentage of carbohydrates [20].

Athletes are often required to travel to participate in tournaments and to face other teams in their leagues, often across multiple time-zones. International travel by plane poses a risk for transmission of infection, as airline cabins are ventilated, closed environments that expose passengers to hypobaric hypoxia, dry humidity and close proximity to fellow passengers [21]. A study by Schwellnus., *et al.* [22] showed that international travel of elite athletes to a location greater than 5 time zones from their home country showed a 2 - 3 fold increase in the incidence of all illnesses, including: respiratory tract illness, gastrointestinal tract illness, and all infective illnesses.

Additionally, flights for an extended period of time may cause jet lag, which is a syndrome associated with long-haul flights, characterised by: sleep disturbances, daytime fatigue, reduced performance, gastrointestinal problems, and generalised malaise. The syndrome occurs due to disturbances to the body's circadian rhythms [23]. Furthermore, long flights result in reduced sleep for athletes. Wilder-Smith., *et al*. [24] reported that partial sleep deprivation resulted in a reduction of immune markers including impaired mitogen proliferation, decreased HLA-DR and variations of CD4 and CD8. That could be one possible explanation for the increased risk of respiratory tract infection due to disrupted sleep caused by travel.

Psychological stress is another factor to take into consideration when analysing the impact of stress on immunity of athletes. Personal life events (e.g. financial difficulties), physical trauma due to training or even competition are only some of the factors that can result in psychological stress [25]. Walsh., *et al*. [25] states that the immune response post-exercise is greatly modified when psychological stress is experienced previously and thus hypothesized to increase the risk of infection. As mentioned, more research into this field is needed, but for the time being, it is recommended to involve athletes in programs related to stress management [25].

As many sports are played outdoors, the negative impact of heat in Bahrain is a questionable aspect. Gulf news has reported in the year 2017, "Bahrain broke a record that had stood for 115 years for the hottest month of July" [26]. Keaney., *et al*. [27] mentions that when the temperature is extremely hot or cold, stress hormones rise more rapidly. She further explains that stress hormones' (e.g. catecholamines and cortisol) rise/fall is linked to the immune response; a rise in stress hormones suppresses the immune system. However, a study analysing the effect of heat on immune system cells concluded that exercising at a temperature of 35 degrees celsius elicited no changes in cytokines T1 and T2 [27].

Training while sick and return to play

Athletes with acute illness should be guided in order to maintain their health, so they realize what activity is appropriate during their sickness and when to return to play. As a general fact, athletes with above neck symptoms such as nasal congestion and rhinorrhoea are safe to exercise with mild -moderate intensity sports for 10 to 15 minutes/day once they feel able. If their health deteriorated they must stop.

Whereas for those with systemic symptoms such as fever or diarrhoea they should rest for a longer duration and return to their practice with caution once symptoms subside for 7 - 14 days [28,29].

In case of infectious mononucleosis (IM) it highly important to prevent splenic rupture as it one of the most frequently encountered complications that reaches its peak in the first 3 weeks of sickness .Therefore, athletes should be forbidden from participating in sport for a base time of three weeks counted from the first day of symptom onset. After resolving may continue noncontact sport at half of pre sickness level if the accompanying criteria are met:

- "Resolution of symptoms (including fever, fatigue, lymphadenopathy and pharyngitis)
- Normalization of all laboratory markers
- Resolution of splenomegaly, confirmed ideally by ultrasound
- Resolution of any and all complications (including fatigue, airway obstruction secondary to enlarged tonsils and hepatitis)".

If the competitors keep on improving without relapse in the first seven day, they are can resume playing, this includes contact sport [29].

In the event of concussion which is a mild traumatic brain injury [30], which often happens to the players despite the safety measures, in general 7 - 10 days are optimal for recuperation but athletes should follow a return-to-play protocol (Table 1) [31].

Furthermore, gender and athletes status (elite/non elite) should be considered, as a study in the United States shows that males recover faster than females and elite athletes improve in shorter period in contrast to non-elites [32].

However, it is essential to take into account infectious diseases with an early medical intervention in order to minimize their transmission to other athletes and it is important to educate the team members about the disease transmission pathways.

In order to send athletes to the field, they should be free of symptoms, with normal physical examinations, laboratory and image results [33].

Despite rest hydration should be retained, appropriate nutrition rich in vitamins, periodic sleep patterns and avoiding excessive alcohol consumption which weakens the immune system [34].

Conclusion

Athletes with acute illness should be guided in order to maintain their health, so they realize what activity is appropriate during their sickness and when to return to play. As a general fact, athletes with above neck symptoms such as nasal congestion and rhinorrhoea are safe to exercise with mild-moderate intensity sports for 10 to 15 minutes/day once they feel able. If their health deteriorated, they must stop.

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