

# ***Exercise and Immune Function***

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## Introduction

Over the past two decades, the response of the immune system to exercise and sport has evolved into a topic of significant interest to both health and sport professionals. Changes in immune parameters often correspond to the level of training stress an athlete is experiencing, and these changes may indicate potential illness and/or performance decrements. Previous studies have reported athletes participating in heavy training are at a greater risk for upper respiratory tract infection (URTI) than healthy, sedentary individuals (21, 22). URTI symptoms often decrease the quality of training and hinder performance during competition. Therefore a basic understanding of the immune systems response to acute exercise and training can benefit those competing, coaching, or providing health care to athletes.

## The Immune System—Simplified

The human immune system is a complex system that, when overly-simplified, consists of 5 different types of cells: basophils, eosinophils, lymphocytes, monocytes/macrophages, and neutrophils. Lymphocytes are comprised of several different subsets, and these consist of T cells, B cells, and natural killer cells (NK). T cells are responsible for cellular direction of the immune response by either activating cells within the immune system via helper T cells or by killing cells infected with viruses or other intracellular pathogens (cytotoxic T cells). B cells are responsible for humoral immunity by producing antibodies. These antibodies are responsible for binding extracellular pathogens and their toxins. Natural killer (NK) cells are responsible for destroying host cells that are infected with pathogens, primarily viruses.

Macrophages and neutrophils are primarily responsible for phagocytosis, or the act of capture, engulfment, and breakdown of microorganisms. Macrophages are derived from monocytes, are present in healthy tissues, and are responsible for clearing cell debris. In contrast, neutrophils migrate rapidly to sites of infection and induce the local state of inflammation. Inflammation refers to the accumulation of fluid accompanied by swelling, redness, and pain produced by an active immune response (40). Macrophages also secrete proteins called cytokines which mediate signals between various cells and systems of the body and are also involved in inflammatory signaling. Extremely strenuous and/or unaccustomed exercise is likely to induce an inflammatory response partially characterized by the release of pro- and anti-inflammatory cytokines. During and immediately following strenuous exercise, pro-inflammatory cytokines tumor necrosis factor alpha (TNF- $\alpha$ ), IL-1  $\beta$ , and “inflammation-responsive” IL-6 are released, followed by regulatory or anti-inflammatory cytokines IL-4, IL-10, and IL-1ra (24). Normally, pro-inflammatory cytokine levels are counterbalanced by anti-inflammatory cytokine levels promoting homeostasis; however if levels are unrestrained, incidences of post exercise infection may occur (24). It is important to note that although excess, unresolved inflammation can cause tissue damage and/or infection, it is a physiologically necessary component to properly functioning innate immunity (1). Therefore, the balance between pro- and anti-inflammatory cytokines is crucial in maintaining proper immune function.

Eosinophils and basophils are less numerous and contribute less to the immune response than the other leukocytes. These cells have traditionally been thought of as merely end-stage effector cells with functions primarily limited to allergic reactions. However, an emerging paradigm indicates that these cells appear to be active players in immunoregulation as well as in tissue remodeling and repair (6, 14). Typically, these cells contribute to the inflammatory response by releasing cytokines and chemokines, which increase tissue permeability and allow other leukocytes to gain access to the tissues.

## Immune Functioning and Exercise

The effects of exercise express characteristics of the phenomena hormesis. Hormesis is a dose-dependent relationship in which a low dose of a substance is stimulatory and high dose is inhibitory (13). The hormetic effects of exercise on immune function are well documented. Moderate exercise has been reported to produce an anti-inflammatory environment and thus reduce the risk of infection (13, 19, 25, 27, 30, 37). Conversely, continuous, intense exercise may increase oxidative stress (an overproduction of reactive oxygen species compared to the body's ability to detoxify), inflammatory responses, as well as the risk for infection (20, 26, 38). Nieman (18) has described this relationship as the “J” curve in which the risk of URTI may decrease below that of a sedentary person, but risk will most likely rise with excessive high-intensity exercise. If the intense exercise continues for an extended period, an athlete may develop overtraining syndrome (OTS), a clinical designation without a consistent biological marker which can result in physiological, psychological, biochemical, and immunological disturbances; including a persistent change in mood, performance decrements, and increased susceptibility to infection (5, 33). In short, this relationship follows the pattern demonstrated in the development of most training adaptations: ample training must be coupled with adequate rest.

## Upper Respiratory Infection in Athletes

As noted, a heavy schedule of training and competition can lead to immune impairment in athletes, which is associated with increased risk for infections, primarily URTI (7, 11, 20). Weidner et al. (39) reported that 5% of athletes missed competition and 18% of athletes missed training due to URTI symptoms during a single competitive season. The popular theory behind the relationship between increased incidence of infection in athletes and those with intense training regimens is called the “open-window” theory (19, 20, 23). While the theory has yet to be thoroughly substantiated, it suggests that following strenuous exercise, a window of 3 to 72 hours exists in which immune function is compromised and bacteria and/or viruses may gain an advantage. Several mechanisms have been proposed to account for the “open-window” following an acute bout of exercise. Among the most often reported factors are a decreased salivary IgA (sIgA) level (10, 16, 20) and an activation of the latent Epstein-Barr virus (12). Another proposed mechanism to explain the post-exercise immunodepression is the exercise-induced down-regulation of T-helper-1 cytokine production (32). Intense exercise increases glucocorticoids (GC) and catecholamines (CA) levels, thereby down-regulating T-helper-1 cytokines and suppressing cell mediated immunity and increasing the risk for post exercise infection (32).

Resting levels of sIgA have been reported to be significantly lower in athletes during a competitive season when compared to sedentary matched controls (8). Gleeson et al. (9) examined the impact of intense training over a 7-month period on sIgA levels in 26 elite swimmers and compared these results to 13 moderately active matched controls. The authors reported a monthly decrease in both pre- and post-training sIgA levels during training in swimmers and no change in sIgA levels in moderately active matched controls. The authors reported a significant difference in pre- to post-training changes in sIgA level in swimmers versus controls following a training session. The sIgA levels in swimmers generally decreased following each training session. Overall, the results of this study indicate exercise training may cause both an acute and chronic suppression of immunity.

In a similar study, Fahlman and Engels (4) investigated the effect of a competitive American collegiate football season on sIgA. The study revealed sIgA levels and sIgA secretion rate were lowest in football players during the months of heaviest training and months of competitive play. These levels were significantly lower when compared to matched controls. The highest percentage of URTI's reported by football players were during the months of heavy training and competition and these numbers were significantly higher than those reported by matched controls. Fahlman and Engels (4) concluded

decreases in sIgA levels and sIgA secretion rate along with increases in URTI were related to heavy training and competition. The authors suggested monitoring sIgA levels during training and competition may help reduce the incidences of illness in American football players.

Difficulty still remains, however, in solidifying the “open window” theory, as URTIs are primarily self-reported (17). In many cases, the purported URTI may simply be an upper respiratory illness (URI) of non-pathogenic cause in which increased airway hyper-responsiveness may be mistakenly reported as URTI. A recent study reported only 30% of URI illness episodes were caused pathogenically in elite and recreationally competitive triathletes, and sedentary controls (34). It is also difficult to determine if the athlete encountered the pathogen prior to, during, or after exercise (17).

### **Effects of Age, Gender, and Training Status**

To maintain proper immune functioning, several factors must be considered when determining optimal training volumes and recovery periods. These include the age, gender, and training status of the athlete. Among these, age is likely the most important. Aging is accompanied by a reduced efficiency of the immune system known as immunosenescence (28). These changes are partially due to thymus involution, reduced numbers of helper T cells, and possibly a reduced production of the hormone dehydroepiandrosterone (DHEA) (2). In addition, some amount of low-grade inflammation similar to that observed in sepsis seems to accompany aging (27). However, regular moderate exercise offers protection against this inflammation as well as infections (15). Older athletes must be more aware of the possible detrimental effects of overly strenuous exercise.

While older athletes may not respond to the stress of training in a manner similar to younger athletes, it must be remembered that training status plays a large role on inflammatory changes. Training status appears to be an important factor in the ability of the immune system to respond to exercise stressors. Training seems to have a protective effect by an up-regulation of endogenous antioxidant defense systems that prevents some level of cell damage in highly trained subjects (29). Previous studies have reported decreased cytokine levels in trained individuals after acute exercise following a period of exercise training (31).

A final consideration might be the gender of the athlete. Although evidence is far from conclusive, there is some evidence that females may need less rest per a given relative training volume than males due to the possible protective effects from estrogen. Several recent studies have noted the need to control for gender in immunological research as differences have been shown to occur in immune cells due to exercise (3, 35, 36). Timmons et al. (35) reported a greater NK cell response to exercise in girls as well as greater exercise-induced increases in total leukocytes and lymphocytes in 14 year-old girls versus 14 year-old boys. Interestingly, the latter study reported no differences between genders in immune cells of 12 year-olds. It is likely that the role of puberty and the rise in estrogen plays a part in this finding.

### **Conclusion**

Proper immune functioning is a critical component of proper training and optimal performance. A basic knowledge of immune functioning can aid coaches and athletes in developing training programs that assist in maintaining good health during training and competition. A primary goal should be to include adequate rest to prevent the development of OTS, which is accompanied by performance declines and/or illness. Currently, the open-window hypothesis is the best explanation for the increased incidence of URTI in athletes, and low salivary IgA levels may be an indicator of compromised immune function. Further research is needed to confirm this hypothesis and/or determine other relevant indicators of infection. Finally, an athlete's training program, just as it would be to improve performance, should be individually tailored with his/her body's physiology in mind to prevent infection.

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