

9



Clin Sports Med 2007, 21(4):310-319

CLINICS IN SPORTS MEDICINE

Exercise and the Immune System

P. Gunnar Brolinson, DO, FAOASM, FAAFP^{a,*},
Dan Elliott, DO^b

^aVirginia College of Osteopathic Medicine, Virginia Tech Sports Medicine,
112 Merryman Center, Blacksburg, VA 24061, USA

^bPrimary Care Sports Medicine, Virginia Center for Athletic Medicine,
Christopher Newport University, Newport News, VA 23606, USA

One of the most common reasons for poor performance at a major sporting event is an acute respiratory infection. A common perception among elite athletes and coaches is that heavy exercise may lower resistance and is a predisposing factor for upper respiratory tract infections (URTI) [1]. Many elite athletes have reported significant bouts with respiratory infections that have interfered with their ability to compete and train [1]. In juxtaposition to this concept is the common belief among many individuals that regular exercise is beneficial to the immune system and may confer some resistance to infection [1]. A 1989 *Runner's World* subscriber survey revealed that 61% of 700 runners reported fewer colds since beginning to run, whereas only 4% experienced more colds [2]. The National Center for Health Statistics reported that acute respiratory conditions (primarily the common cold and influenza) have an annual incidence rate of 90 per 100 persons, imposing substantial morbidity and economic burden on families [3]. The Centers for Disease Control and Prevention estimates there are 425 million colds and episodes of flu annually in the United States, with medical care and lost work costs estimated at \$2.5 billion annually [4]. Therefore, understanding the relationship between exercise and infectious disease has important potential implications for public health and for clinicians caring for athletes and athletic teams. What are the implications for practicing clinicians? Does exercise predispose to, or protect from, infectious disease? What are the effects of exercise on infectious disease? How does infection affect athletic performance? Are there guidelines for exercise during acute or chronic infections? Is there an immune link between exercise and cancer? What about exercise, aging, and immunity? Are there gender-specific issues regarding exercise and immunity? Is there a role for nutritional supplements? What is the role of drug (antibiotic) therapy?

*Corresponding author. E-mail address: techdo@vt.edu (P.G. Brolinson).

THE IMMUNE SYSTEM

The immune system is very complex and essential for maintaining health. Dysfunction can lead to a wide variety of diseases. The immune system comprises two basic components: the innate immune system and the adaptive immune system. Elements of the innate system include exterior defenses (such as the skin and mucous membranes), nonspecific phagocytic leukocytes, and serum proteins [4]. Pathogens that escape these initial outer barriers then come in contact with the adaptive system, which is made up of T and B cells. When this system is activated, cells with the ability to recognize specific microbes are generated. Unlike the innate system, the adaptive system develops gradually but exhibits memory and reacts quicker with subsequent exposure, which in turn results in a more comprehensive and efficient adaptive defense mechanisms with each repeated exposure to that specific pathogen. Together, these two elements provide a formidable obstacle to the establishment and long-term survival of infectious agents [5].

THE INNATE SYSTEM

The largest organ in the body, the skin, provides the initial blockade to infection. Many natural openings to body cavities and glands, however, provide entry for infectious agents. Protection at these sites is provided in the form of mucus, enzymes, and secretory immunoglobulins. Certain organs such as the lung and stomach also prevent entrance into the bloodstream. Characteristics specific for these organs, such as alveolar macrophages and low pH, respectively, provide protection from further invasion [5]. When these lines of defense are penetrated, the invading organism faces further compromise by the nonspecific fixed monocyte-macrophage system that lines the sinusoids and vasculature of organs such as the liver, spleen, and bone marrow. After a foreign substance enters the body, the inflammatory response begins generating an intricate cascade of events. Initially, circulating proteins and blood cells interact with the invading organism, initiating increased blood flow to the affected tissue. This, vasodilation in turn, results in the four classic signs of inflammation: rubor (redness), calor (heat), tumor (edema), and dolor (pain) [6]. This reaction essentially enhances the delivery of the immune system elements necessary to propagate the inflammatory response on a more microscopic level. These inflammatory mediators perpetuate the increased blood flow and result in increased capillary permeability, allowing diffusion of larger molecules across the endothelium. These molecules often play a role in eliminating the pathogen or in further enhancing the inflammatory response [5]. Such elements include the complement system, chemotactic factors, polymorphonuclear leukocytes, phagocytes, and components of the adaptive system such as immunospecific antibodies. Actual cell death then occurs with the extracellular release of inflammatory mediators such as free radicals and granular enzymes. Lysis of bacterial, viral, and cancer cells is also accomplished by natural killer cells. These large granular lymphocytes also prevent growth and establishment of foreign pathogens. It must be remembered that these systems are

described separately, but in vivo, these systems are intricately interwoven and only function appropriately when linked with the other system [5,7].

THE ADAPTIVE SYSTEM

The adaptive system provides its skill of fending off invaders by three unique methods. The first is the ability to recognize antigenic markers on specific pathogens. The second is the ability to supply a cellular and molecular assault on the invading organisms. The final aspect of this destructive triad is the capability of recalling previous invaders, which in turn accelerates and potentiates subsequent responses to the same agent or antigen. The cells that compose the adaptive system are antibodies, T cells, and B cells. Respectively, these cells are responsible for the recognition, effector, and memory functions of the adaptive system [7]. For this complex cascade to occur, an initial activation must occur, termed clonal selection. After a specific antigen has been recognized by a B cell's receptor, a progeny of B and T lymphocytes (specific for the inducing antigen) are created. These daughter B cells may proliferate into plasma cells capable of generating antibodies or into memory cells that function as the recognizing sentinel cell. As the number of these specific cells increases, so does the ability to react and respond to a future invasion, providing resistance to clinical disease [5]. This memory response is the fundamental basis for the use of vaccinations against certain diseases such as influenza, polio, varicella, measles, meningitis, and so forth. When the body is exposed to one of these pathogens, two possible responses may occur: cellular or humoral. As mentioned earlier, the T cells and B cells, respectively, carry out these responses. Cellular immunity is accomplished by a variety of T cells [6]. These cells do not secrete antibodies but create certain types of cells programmed with specific responsibilities. The helper T cell suppresses or activates certain immunologic mechanisms of other cells, whereas the cytotoxic T cell directly lyses pathogens, resulting in cell death. The activated T cell also provides the ability to secrete cytotoxic or immunomodulating cytokines such as tumor necrosis factor and interleukin 2 [5,7]. In contrast to the rapid onset of biologic response seen with the B-cell line, the T-cell activation is usually not recognized until 24 to 48 hours after the initial antigen challenge. An example of this reaction is the delayed-type hypersensitivity, such as the tuberculin purified protein derivative test. T cell-mediated immune response is also responsible for the rejection of transplant tissue grafts and the suppression of neoplastic cells. Deficiency of the T-cell progeny can lead to serious life-threatening disease such as seen in patients who have AIDS [6]. The humoral response is dictated by the versatile B cell that can proliferate into plasma cells or memory cells, as described earlier. Plasma cells have the ability to create antigenic-specific antibodies. The antibodies, or immunoglobulins, can be found in a variety of body fluids conveying external (saliva) and internal (serum) protection. There are different classes of immunoglobulins based on the molecular structure, size, and function. Immunoglobulin (Ig)G is the most prevalent antibody in serum and is responsible for induced immunity against bacteria and other

microorganisms. IgA is considered a secretory immunoglobulin due its protein being synthesized in the epithelium, allowing its secretion into the saliva, tears, colostrum, and mucus. This allows it to be secreted into the saliva, tears, colostrum, and mucus. IgM is unique, in that is the first immunoglobulin to be released after the initial antigenic challenge, thus providing resistance early in the course of an infection. Finally, IgE is an important player in the allergic response because it preferentially binds cells that store and release mediators of allergy and anaphylaxis, such as mast cells and basophils. The allergic response varies, from hives, rhinitis, and asthma to severe and sometimes fatal anaphylaxis. In contrast to the delayed response of the T cell, the antibodies can induce an immediate immunologic response known as an immediate hypersensitivity reaction. A specific example of this reaction is an anaphylactic reaction in which an antibody that is fixed to a mast cell binds to its specific antigen, generating an acute inflammatory reaction [5]. The mast cell degranulates, releasing certain mediators of the allergic response, including histamine (a potent vasodilator) and leukotrienes (smooth muscle contractors). Immune complexes that activate the plasma complement system cause other immediate reactions. The complement system comprises numerous distinct circulating proteins that, when activated, result in edema, chemotaxis (influx of activated phagocytic cells), and local inflammatory changes [7]. Overall, the combination and the intricate interaction between the innate and adaptive immune systems provide an extensive system to prevent and destroy pathogenic organisms.

SPORTS IMMUNOLOGY

Sports immunology is a relatively new field that examines the interaction of physical, psychologic, and environmental stress on immune function. Over the last 100 years, there have been more than 600 articles published in this area. Most (>60%) have been published since 1990. As late as 1984, some investigators believed that "there is no clear experimental or clinical evidence that exercise will alter the frequency or severity of human infections" [4]. More recently, clinicians and scientists have begun to understand the complex interaction between exercise and immune function. For the purposes of this review, the authors define *exercise* as the leisure-time application of physical activity. *Training* is the result of repetitive bouts of exercise, and *fitness* is the result of consistent training.

IMPACT OF EXERCISE ON THE IMMUNE SYSTEM

A large bank of scientific, clinical, and epidemiologic data supports the concept of positive and negative impacts of exercise on the immune system, including the American College of Sports Medicine position papers and the Surgeon General's report on physical activity and health. These effects are highly variable, depending on the nature and intensity of exercise. Currently, the authors define vigorous exercise as 5 to 60 minutes at 70% to 80% aerobic capacity and moderate exercise as 5 to 60 minutes at 40% to 60% aerobic capacity.

THE CELLULAR EFFECTS OF EXERCISE

The specific cause for the difference in URTI incidence has been demonstrated on a microscopic level. Cellular response to physical activity is seen with natural killer cell activity, neutrophil function, and lymphocytic response. Several studies have reproduced this concept; however, few have related the actual cellular response to the presence of clinical disease. There has been a great deal of research into the effects of exercise on secretory immunoglobulins, specifically IgA. As described earlier, IgA is the predominant antibody contained in secretions of the mucosal immune system and, therefore, one of the body's first lines of defense against invading upper respiratory pathogens. Since the late 1970s, researchers have demonstrated a disappearance of immunoglobulins in athletes [1,8]. Mackinnon and colleagues [9] reported an inverse relationship in URTI and secretory IgA presence. This finding has led to further investigation not only in the concentration of IgA but also in the rate of mucosal IgA secretion. Recent research has been more clinically relevant, searching for a direct relationship between cellular change and disease. A longitudinal study by Fahlman and Engels [10] reported that one year of American football resulted in a significant decrease in secretory IgA and the secretion rate of IgA. These investigators also related these findings to an increase in URTI. This drop in IgA effectiveness has also been shown to occur with only 1 hour of intensive activity. Novas and colleagues [11] also demonstrated that secretion rate and IgA concentration were directly associated with the amount of training during the previous day and week. It must be noted that these previous studies examined intensive activity. Other recent studies have investigated the effects of moderate exercise on IgA production, with the hypothesis that moderate activity would improve the body's immune function. Klentrou and colleagues [12] used an aerobic exercise program comprising three 30-minute sessions per week at 75% maximal heart rate. Salivary IgA concentration and secretion rates at rest were significantly increased in the group undergoing regular, moderate exercise. It appears that the level of intensity is the important factor in affecting the concentration and the secretory rate of IgA, which is a primary deterrent of clinical URTI. Another important player of innate immunology is the natural killer cell. Most studies reveal enhanced natural killer cell activity in athletes versus nonathletes [13]. Improved natural killer cell function was also shown to improve within the same athlete during periods of greater intensity. This study, however, did not account for the change of season (summer versus winter) [14]. It appears that exercise must be intensive and extensive to provide a demonstrable protective effect among exercise subjects. In contrast to natural killer cells, exercise seems to decrease the functionality of an important innate immune system component—the neutrophil. Hack and colleagues [15] demonstrated a decrease in the phagocytic properties of neutrophils in athletes during periods of intensive activity compared with light activity. This effect has also been demonstrated in elite swimmers during times of intensive training. The oxidative activity of neutrophils was shown decrease in these athletes compared with age- and sex-matched sedentary control subjects [16]. It is evident

that suppression of these effective phagocytes from intensive exercise plays a crucial role in respiratory disease potential. Studies of the adaptive immune system are not as clear in unveiling a direct relationship between exercise, URTI, and T- and B-cell response. T-cell function appears to be suppressed for several hours after high-intensity running [17]. A theorized mechanism of action relates to the change of T-cell activity with exposure to cortisol and epinephrine [18]. These findings, however, were not related to clinical expression of disease [1].

CANCER AND EXERCISE

Over 100 epidemiologic studies suggest that routine exercise is associated with a reduction of cancer, specifically colon and breast cancer [19]. Simple moderate activity such as mowing the lawn has shown a primary preventive protective benefit compared with activities of less intensity [20]. The evidence regarding secondary prevention is not as compelling but reveals some benefit associated with risk of death from breast cancer. Again, breast and colon cancer patients who exercise appear to decrease their relative risk (up to 40%) of cancer recurrence and cancer-related deaths. Although it appears that regular physical activity provides some protective benefit against cancer-related mortality and morbidity, additional large randomized controlled trials are necessary to fully uncover the specific mechanism of this beneficial observation in cancer patients.

AGING, GENDER, EXERCISE, AND IMMUNITY

As the body ages, disease is able to establish a foothold more easily than in the younger years. The body's innate ability to respond to and recover from foreign insult begins to waiver. A number of studies have revealed decreased T-cell response to pathogens in elderly subjects compared with young subjects [21,22]. It is difficult to isolate deconditioning from the ageing process as a primary cause of a dysfunctional immune system. This decremental progression is known to be multifactorial in cause, including nutritional deficiencies, psychologic stress, and decreased cardiorespiratory condition. Despite this complex interaction leading to immune system dysfunction, recent studies demonstrate that regular physical activity in the elderly may enhance the immune system. Neimen and colleagues [23] randomized a group of elderly women (aged 67-85 years) to a walking protocol or to a calisthenic program for 12 weeks. Natural killer cell activity and T-cell function were used as end points in evaluating the potential effect of physical activity. Although there was a significant increase in cardiorespiratory condition in the walking group, there was no demonstrable benefit to immune function compared with the less active arm. Superior baseline cardiorespiratory condition seemed to benefit NCK activity and T-cell function and to prevent the occurrence of clinical infection compared with lower baseline cardiorespiratory condition. URTI was less prevalent in elderly participants who had

a high baseline condition compared with the moderate exercise and calisthenic groups. No benefit was found with 12 weeks of moderate exercise in previously sedentary women.

IMMUNOLOGIC NUTRITIONAL CONCERNS

It has been proposed that nutrient supplementation may enhance the immune system, benefiting the transient immunosuppression seen from intensive training. This detrimental effect on the immune system may be related to the increased oxygen use during stressful activity, leading to the excessive production of free radical production. Therefore, research has been directed at antioxidant therapy such as vitamin C and vitamin E. In addition, data have been collected regarding the effect of nutritional supplementation with beta-carotene, zinc, iron, carbohydrate ingestion, and vitamins B₆ and B₁₂. Two South African studies have revealed encouraging results regarding vitamin C supplementation. One study analyzed athletes supplemented with 600 mg of vitamin C 3 weeks before a 90-km ultramarathon. These runners experienced fewer URIs than nonsupplemented athletes during a 2-week period following the competition [24,25]. Results from additional studies evaluating high-dose supplementation have not been as promising as those for lower dose therapy and may create more gastrointestinal side effects. In contrast to vitamin C supplementation, treatment with excessive vitamin E and beta-carotene appears to be detrimental to the immune system, increasing the oxidative stress on cells. This effect was demonstrated in a review of over 14,000 Scandinavian men supplemented with vitamin E and beta-carotene, which increased their risk of URIs while undergoing heavy exercise [26]. Several studies have also examined the function and levels of minerals in exercising subjects. Particular research has focused on zinc, iron, and glutamate supplementation and their effects in athletes. There is no compelling research recommending specific preventive therapy for certain elements. Iron deficiency appears to have little effect on antibody generation, whereas research is conflicting regarding its effect on cell-mediated immunity. Small studies on glutamine supplementation showed no benefit in enhancing immune cell levels or function in exercising patients [27]; however, it is known that excessive intake can have a deleterious effect on the immune system [28]. At present, athletes should obtain their nutritional supplementation from a well-rounded diet. In addition, taking a simple multivitamin is prudent because there is no evidence that this will cause excessive vitamin or mineral levels in the body. Training with optimal stores of carbohydrate not only appears to provide the necessary fuel for activity but also seems to negate some of the immunosuppressive effects of exercise. One study indicated that carbohydrate ingestion positively influenced blood cortisol, lymphocyte counts, and natural killer cell activity during the exercise recovery period [29]. No analysis of clinical disease relationship was evaluated in this study. Overall, good dietary carbohydrate replacement that matches the training session appears to support and boost the immune system.

SUMMARY

What does this mean for one's patients? All patients must be considered athletes because everyone undergoes various stressors of daily living that most likely affect the immune system in ways similar to intensive exercise. We must continue to appreciate the impact of stress and the environment on immune system function. When counseling patients, attention should be given to that patient's mental, social, and physical stress levels. It is prudent that emphasis be given to the role of moderately intensive exercise and nutrition as part of a comprehensive prevention program.

References

- [1] Nieman DC. Risk of upper respiratory tract infection in athletes: an epidemiologic and immunologic perspective. *J Athl Train* 1997;32(4):344-9.
- [2] Delhagen K, Miller B. Running from colds. *Runner's World* 1990;25:18-21.
- [3] Adams PF, Benson V. Current estimates from the National Health Interview Survey, 1990. National Center for Health Statistics. *Vital Health Stat* 1991;10(181):1-212.
- [4] Simon HD. The immunology of exercise, a brief review. *JAMA* 1984;252:2735-8.
- [5] Medical physiology. In: Rhoades RA, Tanner GA, editors. *The immune system*. Little, Brown, and Company: Boston; 1995. p. 220-4.
- [6] Haynes BF, Gauci AS. Harrison's principles of internal medicine. In: Fauci AS, Braunwald E, Isselbacher K, et al, editors. *Disorders of the immune system, connective tissue, and joints*. McGraw-Hill: New York; 1998. p. 1753-72.
- [7] Goronzy JJ, Weyand CM. Cecil Textbook of Medicine. Arends WP, Armitage JO, Drazen JM, et al, editors. 22nd edition. *The innate and adaptive immune systems*. W.B. Saunders: Philadelphia, PA; 2004. p. 161-5.
- [8] Pershin BB, Geliev AB, Tolstov DV, et al. Reactions of immune system to physical exercises. *Russ J Immunol* 2003;7(1):1-20.
- [9] Mackinnon LT, Chick TW, As AV, et al. The effect of exercise on secretory and natural immunity. *Adv Exp Med Biol* 1987;216A:869-76.
- [10] Fahlman MM, Engels HJ. Mucosal IgA and URTI in American college football players: a longitudinal study. *Med Sci Sports Exerc* 2005;37(3):374-80.
- [11] Novas AP, Rowbottom DG, Jenkins DG. Tennis, incidence of URTI and salivary IgA. *Int J Sports Med* 2003;24(3):223-9.
- [12] Klentrou P, Cieslak T, MacNeil M, et al. Effect of moderate exercise on salivary immunoglobulin A and infection risk in humans. *Eur J Appl Physiol* 2002;87:153-8.
- [13] Nieman DC, Buckley KS, Henson DA, et al. Immune function in marathon runners versus sedentary controls. *Med Sci Sports Exerc* 1995;27:986-92.
- [14] Tvede N, Steensberg J, Baslund B, et al. Cellular immunity in highly-trained elite racing cyclists and controls during periods of training with high and low intensity. *Scand J Med Sci Sports* 1991;1:163-6.
- [15] Hack V, Strobel G, Weiss M, et al. PMN cell counts and phagocytic activity of highly trained athletes depend on training period. *J Appl Physiol* 1944;77:1731-5.
- [16] Pyne DB, Baker MS, Fricker PA, et al. Effects of an intensive 12-wk training program by elite swimmers on neutrophil oxidative activity. *Med Sci Sports Exerc* 1995;27:536-42.
- [17] Nieman DC, Simandle S, Henson DA, et al. Lymphocyte proliferative response. *Int J Sports Med* 1995;16:404-9.
- [18] Cray B, Borysenko M, Sutherland DC, et al. Decrease in mitogen responsiveness of mononuclear cells from peripheral blood after epinephrine administration in humans. *J Immunol* 1983;130:694-9.
- [19] Haydon AM, Macinnis R, English D, et al. The effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut* 2005;1:62-7.

- [20] Lee IM. Physical activity and cancer prevention—data from epidemiologic studies. *Med Sci Sports Exerc* 2003;35:1823–7.
- [21] Canonica GW, Ciprandi G, Caria M, et al. Defect of autologous mixed lymphocyte reaction and interleukin-2 in aged individuals. *Mech Ageing Dev* 1985;32:205–12.
- [22] Krishanaraj R, Blandford G. Age-associated alterations in human natural killer cells. Increased activity as per conventional and kinetic analysis. *Clin Immunol Immunopathol* 1987;45:268–85.
- [23] Nieman DC, Henson DA, Gusewitch G, et al. Physical activity and immune function in elderly women. *Med Sci Sports Exerc* 1993;25(7):823–31.
- [24] Peters IM, Bateman ED. Ultramarathon running and upper respiratory tract infections. *S Afr Med J* 1983;64:582–4.
- [25] Peters EM, Goetzsche JM, Grobbelarr B, et al. Vitamin C supplementation reduces the incidence of post-race symptoms of upper respiratory tract infections in ultramarathon runners. *Am J Clin Nutr* 1993;57:170–4.
- [26] Hemila H, Virtamo J, Albanes D, et al. Physical activity and the common cold in men administered vitamin E and beta carotene. *Med Sci Sports Exerc* 2003;35(11):1815–20.
- [27] Krzywkowski K, Petersen EW, Ostrowski K, et al. Effect of glutamine supplementation on exercise-induced changes in lymphocyte function. *Am J Physiol* 2001;281:1259–65.
- [28] Speich M, Pineau A, Ballereau F. Minerals, trace elements and related biological variables in athletes and during physical activity. *Clin Chim Acta* 2001;312(1,2):1–11.
- [29] Henson DA, Nieman DC, Blodgett AD, et al. Influence of exercise mode and carbohydrate on the immune response to prolonged exercise. *Int J Sport Nutr* 1999;9:213–28.

