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Exercise and Immune Function
Recent Developments

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Abstract

Comparison of immune function in athletes and nonathletes reveals that the adaptive immune system is largely unaffected by athletic endeavour. The innate immune system appears to respond differentially to the chronic stress of intensive exercise, with natural killer cell activity tending to be enhanced while neutrophil function is suppressed. However, even when significant changes in the level and functional activity of immune parameters have been observed in athletes, investigators have had little success in linking these to a higher incidence of infection and illness.

Many components of the immune system exhibit change after prolonged heavy exertion. During this 'open window' of altered immunity (which may last between 3 and 72 hours, depending on the parameter measured), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. However, no serious attempt has been made by investigators to demonstrate that athletes showing the most extreme post-exercise immunosuppression are those that contract an infection during the ensuing 1 to 2 weeks. This link must be established before the 'open window' theory can be wholly accepted.

The influence of nutritional supplements, primarily zinc, vitamin C, glutamine and carbohydrate, on the acute immune response to prolonged exercise has been measured in endurance athletes. Vitamin C and glutamine have received much attention, but the data thus far are inconclusive. The most impressive results have been reported in the carbohydrate supplementation studies. Carbohydrate beverage ingestion has been associated with higher plasma glucose levels, an attenuated cortisol and growth hormone response, fewer perturbations in blood immune cell counts, lower granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response. It remains to be shown whether carbohydrate supplementation diminishes the frequency of infections in the recovery period after strenuous exercise.

Studies on the influence of moderate exercise training on host protection and immune function have shown that near-daily brisk walking compared with inactivity reduced the number of sickness days by half over a 12- to 15-week period without change in resting immune function. Positive effects on immunosurveillance and host protection that come with moderate exercise training are probably related to a summation effect from acute positive changes that occur during each exercise bout. No convincing data exist that moderate exercise training is linked with improved T helper cell counts in patients with HIV, or enhanced immunity in elderly participants.

Publications on the topic of exercise immunology date from late in the 19th century, but it was not until the mid-1980s that a significant number of investigators worldwide devoted their resources to this area of research endeavour. From 1900 to 1997, just under 900 papers on exercise immunology were published, with 75% of these appearing in the 1990s.[1] Despite this plethora of research on the relationship between exercise, the immune system, and host protection, many questions and unexplored issues remain. In this article, we provide commentary on 4 topics that have received much attention among exercise immunologists, and have practical application to athletes and the general public. They are as follows:

- the contrast in immune function between athletes and nonathletes
- acute immune changes that occur following prolonged and intensive exercise
- the role of nutritional supplements in attenuating exercise-induced changes in immunity
- the influence of moderate exercise training on host protection and immune function, with attention given to the role of exercise as a countermeasure against immunosuppressive conditions such as HIV infection and aging.

Comments on future directions for research are given within each section.

1. Immune Function in Athletes and Nonathletes: More Similar Than Disparate

Several clinicians and epidemiologists have indicated that athletes are at increased risk of upper respiratory tract infection during periods of heightened training or following competitive race events.[2-5] On the other hand, athletes often report in surveys that they experience decreased rates of infection compared with nonathletes during normal-intensity training.[6] However, attempts thus far to compare resting immune function in athletes and nonathletes have failed to provide compelling evidence that athletic endeavour is linked to clinically important changes in immunity. The adaptive immune system (resting state) in general seems to be largely unaffected by intensive and prolonged exercise training.[7-9] The innate immune system appears to respond differentially to the chronic stress of intensive exercise, with natural killer cell (NK) activity tending to be enhanced while neutrophil function is suppressed.[8,10-13]

Even when significant changes in the level and functional activity of immune parameters have been observed in athletes, investigators have had little success in linking these to a higher incidence of infection and illness.[13-16] Pyne and colleagues,[13] for example, reported that elite swimmers undertaking intensive training had a significantly lower neutrophil oxidative activity at rest than age- and gender-matched sedentary individuals, and that function was further suppressed during the period of strenuous training prior to national-level competition (fig. 1). Nonetheless, upper respiratory tract infection rates did not differ between the swimmers and sedentary control individuals.

Two studies indicate that salivary immunoglobulin (Ig) A level warrants further research as a marker of potential infection risk in athletes. In a small study of elite squash and hockey players,

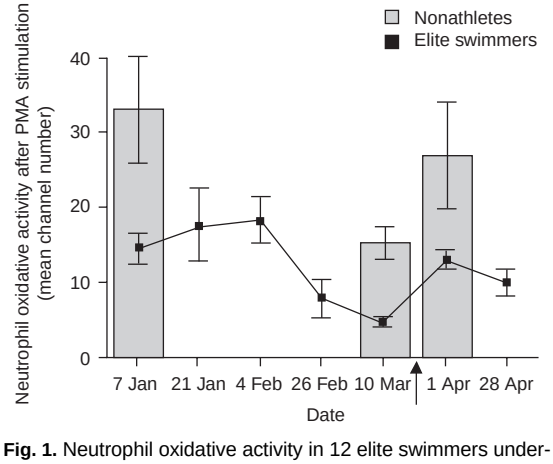

Fig. 1. Neutrophil oxidative activity in 12 elite swimmers undertaking intensive training compared with 11 age- and gender-matched sedentary individuals. The swimmers had a significantly lower neutrophil oxidative activity at rest, which was further suppressed during the period of strenuous training before the national championships on 22 March 1993 (indicated by the arrow).[13] **PMA** = phorbol myristate acetate.

Mackinnon et al.[17] demonstrated that low salivary IgA levels preceded upper respiratory tract infection. Gleeson et al.[18] have also established a link between salivary IgA levels and upper respiratory tract infection. Salivary IgA levels measured in swimmers before training sessions showed significant correlations with infection rates, and the number of infections observed in the swimmers was predicted by the preseason and the mean pretraining salivary IgA levels.

In general, the immune systems (resting state) of athletes and nonathletes appear to be more similar than disparate. Of the various immune function tests that show some change with athletic endeavour, only salivary IgA has emerged as a potential marker of infection risk. Future research should concentrate on this immune measure, using large groups of athletes and nonathletes to demonstrate its clinical usefulness.

2. Acute Immune Response to Heavy Exertion: Update on the 'Open Window' Theory

In light of the mixed results on the effect of long term intensive training on resting immune function and host protection, several authors have suggested that prolonged cardiorespiratory endurance exercise leads to transient but clinically significant changes in immune function.[5,15,19-21] During this 'open window' of altered immunity (which may last between 3 and 72 hours, depending on the immune parameter measured as well as the type, duration and intensity of exercise), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. Although this is an attractive hypothesis, no serious attempt has been made by investigators to demonstrate that athletes showing the most extreme immunosuppression following heavy exertion are those that contract an infection during the following 1 to 2 weeks. This link must be established before the 'open window' theory can be wholly accepted.

As described in several recent reviews,[19-23] and summarised in table I, many components of the immune system exhibit change after prolonged heavy exertion. The increases in blood granulocyte and monocyte phagocytosis and interleukin-6 suggest a strong pro-inflammatory response, whereas the increases in cortisol and interleukin-1 receptor antagonist show that anti-inflammatory forces are also at work.

Table I. Changes in immune system components after prolonged heavy exertion[19-23]

Neutrocytosis and lymphopenia, induced by high plasma cortisol
Increase in blood granulocyte and monocyte phagocytosis, but a decrease in nasal neutrophil phagocytosis
Decrease in granulocyte oxidative burst activity
Decrease in nasal mucociliary clearance
Decrease in natural killer cell cytotoxic activity
Decrease in mitogen-induced lymphocyte proliferation (a measure of T cell function)
Decrease in the delayed-type hypersensitivity response
Increase in plasma levels of pro- and anti-inflammatory cytokines (e.g. interleukin-6 and interleukin-1 receptor antagonist)
Decrease in *ex vivo* production of cytokines (interferon-γ, interleukin-1 and interleukin-6) in response to mitogens and endotoxin
Decrease in nasal and salivary IgA level
Blunted major histocompatibility complex II expression in macrophages

Taken together, these data suggest that the immune system is suppressed and stressed, albeit transiently, following prolonged endurance exercise. Thus it makes sense (but still remains unproven) that the risk of respiratory infection may be increased when the endurance athlete goes through repeated cycles of heavy exertion, has been exposed to novel pathogens, and has experienced other stressors to the immune system including lack of sleep, severe mental stress, malnutrition or bodyweight loss.[19,20]

The cytokine response to strenuous exercise has some similarities to that of sepsis and trauma. Data from the Copenhagen Muscle Research Center in Denmark indicate that after strenuous exercise tumour necrosis factor-α, interleukin-1β, interleukin-6 and interleukin-1 receptor antagonist are released in a sequential manner comparable to that observed in physical trauma.[22,24-27] The exercise-induced destruction of skeletal muscle fibres appears to trigger local production of interleukin-6 that

stimulates the production of interleukin-1 receptor antagonist from circulating blood immune cells.[27] Could the immune system's involvement in the inflammatory response following heavy exertion divert attention and resources away from host protection against upper respiratory tract infection? This is an interesting hypothesis that warrants further investigation.

Several studies have shown that, despite altered immunity following prolonged and intensive exercise, the ability of the immune system to mount an antibody response to vaccination over the 2- to 4-week post-exercise period is not affected.[28-30] In a study by Bruunsgaard et al.[28] comparing male triathletes with sedentary control participants, the athletes had normal antibody production to pneumococcal, tetanus and diphtheria vaccines following a half-ironman triathlon competitive event. However, the skin test response to 7 recall antigens applied after the race and measured 48 hours later was suppressed when compared with controls (fig. 2). These data suggest that the short term but complex immunological reaction to the delayed-type hypersensitivity skin test is negatively affected by prolonged and intensive exercise, whereas the longer term antibody titre response to vaccination is not affected. Although these data lend support to the 'open window' theory, additional research is needed to establish a link with infection risk.

3. Role of Nutritional Supplements in Attenuating Exercise-Induced Immunosuppression

Although endurance athletes may be at increased risk for upper respiratory tract infections during heavy training cycles, they must exercise intensively to compete successfully. Athletes appear less interested in reducing training workloads and more receptive to ingesting nutrient supplements that have the potential to counter exercise-induced immunosuppression.

Investigators have measured the influence of nutritional supplements, primarily zinc, vitamin C, glutamine and carbohydrate, on the immune response to intense and prolonged exercise.[31-46] Several double-blind placebo-controlled studies of South African ultramarathon runners have demonstrated that vitamin C supplementation (about 600 mg/day for 3 weeks) is associated with fewer reports of symptoms of upper respiratory tract infection.[38-40] This has not been replicated, however, by other research teams, and the method of reporting symptoms resulted in unrealistically high incidence rates. A double-blind placebo-controlled study was unable to establish that vitamin C supplementation (1000 mg/day for 8 days) had any significant effect in altering the immune response to 2.5 hours of intensive running.[31]

Glutamine, a nonessential amino acid, has attracted much attention.[32-37] Glutamine is an important fuel, together with glucose, for lymphocytes and monocytes, and decreased amounts have a direct effect in lowering proliferation rates of lymphocytes. Reduced plasma glutamine levels have been observed in response to various stressors, including prolonged exercise.[32,35,37] Whether exercise-induced reductions in plasma glutamine levels are linked to impaired immunity and host protec-

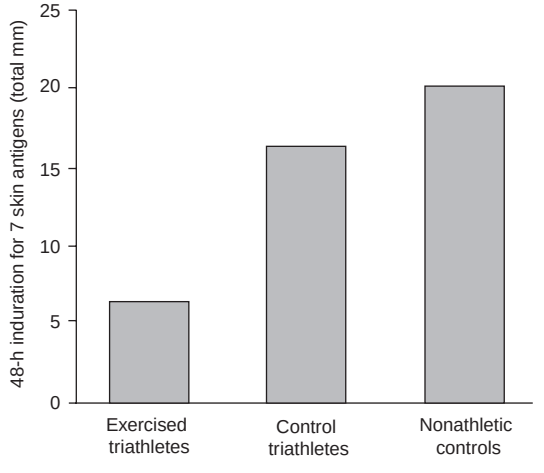

Fig. 2. Skin test response to recall antigens in 22 male triathletes 48 hours after competing in a half–ironman triathlon competition compared with 11 nonexercising triathletes and 22 moderately trained control individuals. A reduced delayed-type hypersensitivity response was observed in the competitors compared with both control groups ($p < 0.05$).[28]

tion against viruses in athletes is still unsettled, but the majority of studies have not favoured such a relationship.[34-36]

The most impressive results have been reported from studies of carbohydrate supplementation.[23,41-46] Earlier research had established that a reduction in blood glucose levels is linked to hypothalamic-pituitary-adrenal activation, an increased release of adrenocorticotrophic hormone and cortisol, increased plasma growth hormone, decreased insulin and a variable effect on blood adrenaline (epinephrine) levels.[23] Given the link between stress hormones and immune responses to prolonged and intensive exercise,[24] carbohydrate ingestion should maintain plasma glucose levels, attenuate increases in stress hormones and thereby diminish changes in immunity (fig. 3).

This hypothesis has been tested experimentally. First, a double-blind placebo-controlled randomised study investigated the effect of carbohydrate ingestion on the immune response to 2.5 hours of running in a group of 30 experienced marathon runners.[41-43] In a subsequent study of 10 triathletes, the effect of carbohydrate ingestion on the immune response to 2.5 hours of running and cycling was studied.[44-46] During 4 sessions, participants ran on treadmills or cycled using their own bicycles on electromagnetically braked tripod trainers for 2.5 hours at approximately 75% $\dot{V}O_{2max}$. In both studies, ingestion of carbohydrate-containing beverages before, during (about 1 L/h) and after 2.5 hours of exercise was associated with higher plasma glucose levels, an attenuated cortisol and growth hormone response, fewer perturbations in blood immune cell counts, lower granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response. Overall, the hormonal and immune responses to carbohydrate ingestion suggest that physiological stress was diminished. Some immune variables were affected slightly by carbohydrate ingestion (for example, granulocyte and monocyte function), whereas others were strongly influenced (for example, plasma cytokine levels and blood cell counts).

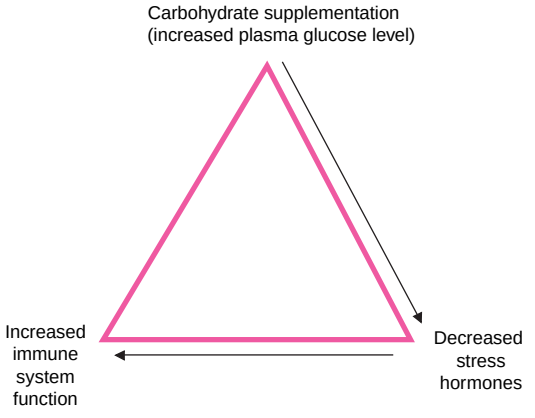

Fig. 3. Carbohydrate supplementation during prolonged and intensive exercise maintains or elevates plasma glucose levels, attenuating the usual rise in stress hormones and thereby countering negative immune changes.

The clinical significance of these carbohydrate-induced effects on the endocrine and immune systems awaits further research. At this point, the data indicate that athletes ingesting carbohydrate beverages before, during and after prolonged and intensive exercise should experience decreased physiological stress. Research to determine whether carbohydrate ingestion will improve host protection against viruses in endurance athletes during periods of intensified training or following competitive endurance events is warranted.

4. Moderate Exercise Training: Beneficial for Host Protection and Immune Function?

A common belief among fitness enthusiasts is that regular physical activity is beneficial in decreasing the risk of respiratory infection.[4,5,20] However, very few studies have been conducted in this area, and more research is certainly warranted to investigate this interesting question. At present, there are no published epidemiological reports that have retrospectively or prospectively compared the incidence of upper respiratory tract infection in large groups of moderately active and sedentary individuals.

A number of randomised experimental trials have provided important preliminary data in support of the viewpoint that moderate physical activity may reduce upper respiratory tract symptomatology (table II). All 3 studies indicated that near-daily brisk walking reduced the number of sickness days by nearly half over a 12- to 15-week period when compared with inactivity.[11,47,48] It should be noted, however, that in none of the 3 studies did exercise training cause any significant changes in resting immune function. Thus, it has been suggested that any beneficial effects on immunosurveillance and host protection that come with moderate exercise training are probably related to a summation effect from acute positive changes that occur during each exercise bout.[20]

Can moderate exercise training be used as a method to delay the progression from HIV infection to AIDS? Few investigators have published results in this area. Short term bouts of exercise enhance the number of CD4+ cells, neutrophils and cells mediating natural immunity in HIV-seropositive patients.[49] However, no convincing data exist that long term exercise training is associated with improved resting levels of T helper cell counts in HIV patients.[50-53] Exercise training does not appear to adversely affect HIV–infected individuals, and several potential benefits of both aerobic and strength training include improvement in psychological coping and maintenance of health and physical function for a longer period. Improved quality of life is perhaps the chief benefit of regular exercise by HIV-infected patients.

Immune senescence or age-associated immune deficiency appears to be partly responsible for the afflictions of old age. Can regular physical activity attenuate the decrease in immune function with increase in age? Very few studies on humans have been conducted in this area, with the most interesting results coming from cross-sectional studies of highly active and lean elderly individuals and their sedentary peers.[11,54,55] Natural killer cell activity and mitogen-induced lymphocyte proliferation have been reported to be significantly higher in elderly athletes compared with sedentary control individuals.[11,54] However, in a randomised study of elderly women, 12 weeks of moderate cardiorespiratory exercise training did not result in any improvement in natural killer or T cell function relative to sedentary control participants.[11] Similarly, 12 weeks of progressive resistance strength training also failed to affect immune function in healthy elderly individuals or those with rheumatoid arthritis.[55]

Although the relative importance of physical activity, nutrient intake, self-selection and other confounders is difficult to determine, the data taken together do suggest that exercise training may need to be long term (i.e. for a number of years) and of sufficient volume to induce changes in bodyweight and fitness before any change in immunity can be expected in old age.

Table II. Effect of moderate exercise training on upper respiratory tract infection (URTI)

Study	Participants	Method of determining URTI	Major finding
Nieman et al.[47]	36 mildly obese inactive women, California, USA	Daily logs of self-reported, precoded, URTI symptoms for 15 weeks during winter season	Walking group reported fewer days with URTI symptoms than control group (5.1 *vs* 10.8)
Nieman et al.[11]	42 elderly women (30 inactive, 12 athletes), North Carolina, USA. Inactive individuals randomised to 12 weeks walking or sedentary controls	Daily logs of self-reported, precoded, URTI symptoms for 12 weeks during autumn (fall) season	Incidence of URTI 8% in athletes, 21% in walkers, 50% in sedentary controls
Nieman et al.[48]	90 overweight and 30 normal-weight women, North Carolina, USA	Daily logs of self-reported, precoded, URTI symptoms for 12 weeks during winter season	Number of days with URTI symptoms: 9.4 ± 1.1, 5.6 ± 0.9 and 4.8 ± 0.9 in overweight controls, overweight walkers and normal-weight controls, respectively

5. Conclusions

The immune system is influenced acutely, and to a lesser extent chronically, by exercise. Epidemiological and experimental data suggest that moderate exercise enhances immunosurveillance and host protection from upper respiratory tract infection while heavy exertion by endurance athletes leads to transient immunosuppression and increased risk of infection. Additional research should provide athletes with a clearer understanding of underlying mechanisms, and the clinical applications and development of appropriate countermeasures against this immunosuppression.

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