

Exercise Immunology: Future Directions for Research Related to Athletes, Nutrition, and the Elderly

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This article examines three questions related to exercise immunology: 1) Can exercise attenuate changes in the immune system related to aging? The few research papers available suggest that the answer may be “yes”, but exercise training may have to be long-term and of sufficient volume to induce changes in body weight and fitness before any change in immunity can be expected in old age. 2) Is the athlete an immunocompromised host? For most athletes, probably not, although the answer may be ‘yes’ during certain periods when the athlete exceeds normal training limits or competes in endurance events. Most studies have reported that the immune systems of athletes and nonathletes in the resting state are more similar than disparate with the exception of natural killer cell activity which tends to be elevated in athletes. Infection risk may be more related to the acute changes in immunity that occur following heavy exercise, but this hypothesis has not been sufficiently studied. 3) Are nutrition supplements effective countermeasures to exercise-induced inflammation and immunosuppression? Except for carbohydrate, the answer at this time for all other nutrients studied is ‘no’. While data from the vitamin and mineral studies have been negative, and those involving glutamine conflicting, several investigations indicate that carbohydrate compared to placebo ingestion is associated with attenuated hormonal and immune responses.

Key words: Aging, lymphocyte, neutrophil, respiratory infection, carbohydrate, vitamin C, glutamine, cytokines.

Exercise as a Countermeasure to Immunosenescence

Immune senescence or age-associated immune deficiency (in particular, dysregulation of T cell function) appears to be partly responsible for the afflictions of old age [26,52,59,76,84,96]. Elderly persons are more susceptible to many infections, auto-

immune disorders, and cancers when compared with younger adults.

A new and growing area of research endeavor is the study of the relationship between certain lifestyle factors (in particular, physical activity and diet) and immune senescence. Older adults exercise less and have lower levels of cardiorespiratory fitness than do younger adults [52]. Can regular physical activity attenuate alterations in immunity in old age? Very few human studies have been conducted in this area [59,96]. The most interesting results come from cross-sectional studies of highly active elderly subjects and their sedentary peers [62,95]. Two studies have shown that mitogen-induced lymphocyte proliferation is significantly higher in elderly athletes versus sedentary controls [62,95] (Fig. [1]). In a randomized study of elderly women, however, 12 weeks of moderate cardiorespiratory exercise training did not result in any improvement in NK or T cell function relative to sedentary controls [62].

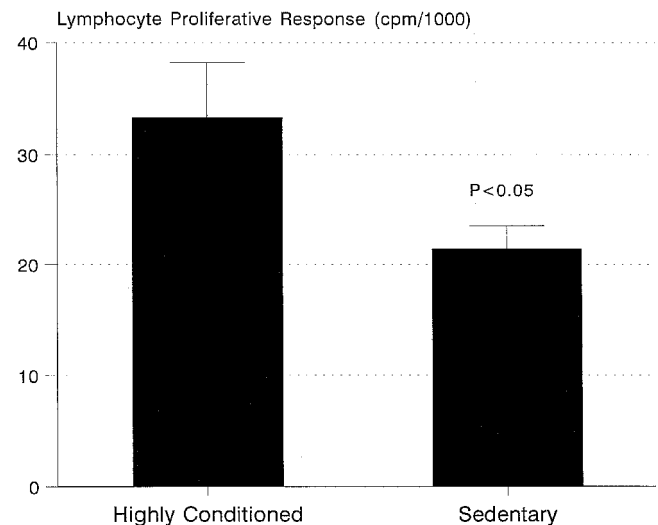


Fig. 1 PHA-induced lymphocyte proliferation was significantly greater in highly conditioned versus sedentary elderly women. Data from reference [62].

Animal studies suggest that exercise training may improve the function of some immune cells in old age, but this has not been a consistent finding (for review, see [52]). Nasrullah and Mazzeo reported that intensive exercise by aged rats during a 15-week period attenuated age-related declines in Con A-induced lymphocyte proliferation and IL-2 production [46]. Lu et al. [37] found that aging reduced and exercise training increased the capacity of resident peritoneal macrophages in mice to respond to interferon-gamma and lipopolysaccharide with increased tumor cytotoxicity.

The data in humans suggest that exercise training may need to be long-term (i.e., for multiple years) and of sufficient volume to induce changes in body weight and fitness before any change in immunity can be expected in old age [52,59]. In other words, because the aging process is so dominant in old age, long-term physical activity combined with leanness and other positive lifestyle habits may be necessary before immune function is enhanced. Few elderly individuals appear willing to make these types of changes in lifestyle, diminishing any potential public health dividend from improved immunosurveillance. Nonetheless, continued research is needed to reveal more precisely the level of physical activity needed to influence immunity in old age.

Is the Athlete an Immunocompromised Host

A common perception among elite athletes and their coaches is that prolonged and intense exertion lowers resistance to upper respiratory tract infection (URTI) [49–51,53]. Several surveys and investigations using epidemiological designs have indicated that URTI risk is elevated during periods of heavy training and in the 1–2 week period following participation in competitive endurance races [63,79–81]. Foster [20] showed that a high percentage of illnesses occurred when elite athletes exceeded individually identifiable training thresholds, mostly related to the strain of training.

Depending on the pathogen, animal experiments have shown that exhaustive relative to moderate exercise following infection often increases morbidity and mortality [51]. Davis et al. [14], for example, exposed mice to rest, 30 min of moderate exercise, or 2.5–3 h of exhaustive exercise following intranasal infection with the herpes simplex virus (HSV-1). As summarized in Fig. 2, mice exercised to fatigue had a greater overall mortality during a 21-day period than did controls or moderately exercised mice [14].

In contrast, a common belief among athletes and fitness enthusiasts is that regular exercise confers resistance against infection. Athletes have consistently indicated in surveys that when undergoing normal training they experience fewer episodes of URTI when compared to their sedentary peers [50,53]. Three randomized exercise training studies of sedentary women have demonstrated that the initiation of near-daily moderate exercise is associated with a significant reduction in URTI [62,68,70].

These epidemiological data imply that infection rates may be lower than normal in physically active individuals, but elevated when athletes overreach or engage in intense endurance events. It naturally follows that these differences in infection risk among individuals based on their position along the exer-

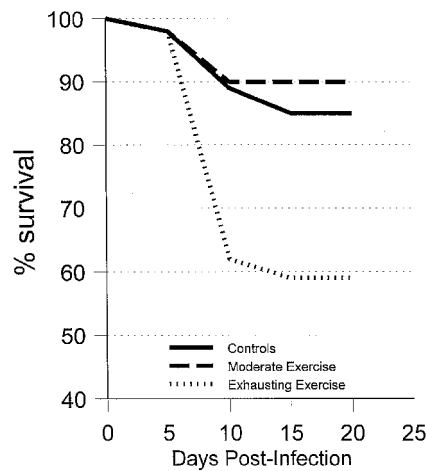


Fig. 2 Mice were infected with herpes simplex virus 1 and then exposed to rest, 30 min of moderate exercise, or 2.5–3 h of exhaustive exercise. During the next 3 weeks, mice exercised to fatigue had a greater overall mortality (41%) compared to controls (16%) and those moderately exercised (9%). Data from reference [14].

cise workload continuum should parallel variance in immune function. Two lines of investigation have developed to provide insights both supporting and challenging this assumption: 1) Do the immune systems of endurance athletes and nonathletes function differently when in a state of rest [49]? 2) Does heavy exertion lead to temporary but clinically significant changes in immunity (i.e., the “open window” theory) [77]?

Resting immune function in athletes and nonathletes

Although the URTI epidemiological data suggest that disparities should exist, attempts thus far to compare resting immune function in athletes and nonathletes have failed to provide compelling evidence that athletic endeavor is linked to clinically important changes in immunity [56,57,66,82,99,100]. Of all immune measures, only NK cell activity has emerged as a consistent indicator differentiating the immune systems of athletes and nonathletes [57,62,66,105]. As summarized in Fig. 3, NK cell activity is typically elevated in athletes, while the function of most other immune cells is normal [57,66]. However, 12–15 weeks of moderate exercise have not been associated with an elevation in NK cell activity, indicating that the exercise workload must approach athletic levels before increases can be measured [62,68,70]. Even when significant changes in the concentration 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 [49,66,77,82]. Neutrophil function, for example, has been reported to be suppressed in athletes (although this has not been a consistent finding, and may depend on the severity of training) [4,27,28,66,82]. In one report, elite swimmers undertaking intensive training had significantly lower neutrophil oxidative activity at rest than age- and sex-matched sedentary individuals, and function was further suppressed during the period of strenuous training prior to national-level competition [82]. Nonetheless, URTI rates did not differ between the swimmers and sedentary controls. In another study, URTI rates were similar in female

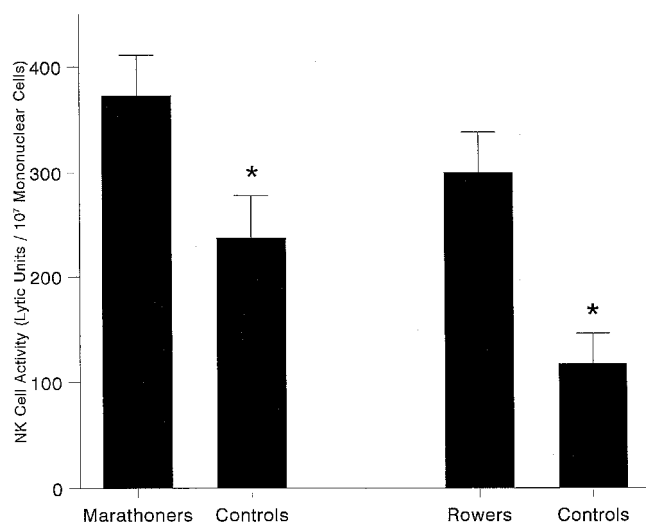


Fig. 3 Natural killer cell activity was significantly higher in elite female rowers and male marathon runners compared to nonathletic controls. Data from references [57] and [66]. * $p < 0.05$.

elite rowers and nonathletes during a 2-month winter/spring period despite higher NK cell activity (NKCA) and T cell function (whole blood assay) in the rowers [66].

Two studies indicate that salivary IgA concentration warrants further research as a marker of potential infection risk in athletes. Mackinnon et al. [38] demonstrated that elite squash and hockey athletes with low salivary IgA concentrations experienced higher rates of URTI. This was later confirmed in a study of elite swimmers by Gleeson et al. [25]. Salivary IgA levels measured in swimmers before individual training sessions showed significant correlations with infection rates, and the number of infections observed in the swimmers was predicted by the pre-season and the mean pre-training salivary IgA levels. These results need to be confirmed in larger groups of athletes followed for longer periods of time.

Immunosuppression following prolonged, intensive exercise

Several authors have theorized that the magnitude of change in immunity that occurs after each bout of prolonged exercise in athletes has more clinical significance than training-induced alterations in resting immunity [53,77,92]. During this "open window" of altered immunity (which may last between 3 and 72 h, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. Investigations are currently underway to demonstrate that athletes showing the most extreme immunosuppression following heavy exertion are those that contract an infection during the following 1–2 weeks. This link must be established before the "open window" theory can be wholly accepted in humans.

Several investigations with animal models have provided important support of the "open window" theory. Davis et al. [14], for example, have shown that in mice alveolar macrophage anti-viral resistance is suppressed 8 h following prolonged strenuous exercise to fatigue, an effect due in part to adrenal catecholamines [34].

Many components of the immune system exhibit change after heavy exertion, including the following [53,77]:

- Neutrophilia (high blood neutrophil counts) and lymphopenia (low blood lymphocyte counts), induced by high plasma catecholamines, growth hormone, and cortisol [5,13,22,29,33,53,71,97,103].
- Increase in blood granulocyte and monocyte phagocytosis and activation markers (reflecting an inflammatory response due to substances released from injured muscle cells), but a decrease in nasal neutrophil phagocytosis [3,9,18,42,74,83].
- Decrease in granulocyte oxidative burst activity [21,58,91,100,104].
- Decrease in nasal mucociliary clearance [44].
- Decrease in NK cell cytotoxic activity [53,55,61,97,110].
- Decrease in mitogen-induced lymphocyte proliferation (a measure of T cell function) [17,53,71,97].
- Decrease in the delayed-type hypersensitivity response [7].
- Increase in plasma concentrations of pro- and anti-inflammatory cytokines, e.g., tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-1 receptor antagonist (IL-1ra) [6,8,15,16,22,47,72–75,89,101,102,106,108] (Fig. 4).
- Decrease in *ex vivo* production of cytokines (interferon gamma [IFN- γ], TNF- α , IL-1, IL-2, IL-6, and IL-10) in response to mitogens and endotoxin [2,101,108].
- Decrease in nasal and salivary IgA concentration [36,39,43,64].
- Blunted major histocompatibility complex (MHC) II expression and antigen presentation in macrophages [109].

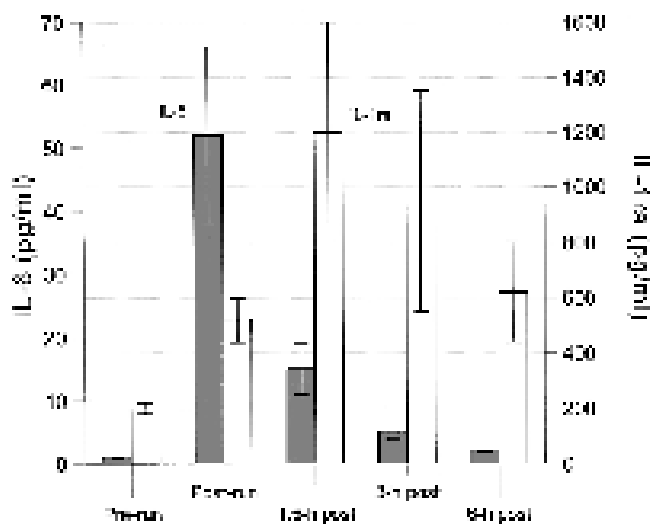


Fig. 4 Changes in IL-6 and IL-1ra for 6 h following 2.5 h of running by 10 athletes. Data from reference [67]. Shaded bars refer to IL-6, and the open bars to IL-1ra.

Taken together, these data suggest that the immune system is suppressed and stressed, albeit transiently, following prolonged endurance exercise [53,77,78]. Thus it makes sense (but still remains unproven) that URTI risk may be increased when the endurance athlete goes through repeated cycles of unusually heavy exertion, has been exposed to novel pathogens, and experienced other stressors to the immune system

including lack of sleep, severe mental stress, malnutrition, or weight loss [50,51].

Are Nutrition Supplements Effective Countermeasures to Exercise-Induced Inflammation and Immunosuppression?

Although endurance athletes may be at increased risk for URTIs during heavy training cycles, they must exercise intensively to compete successfully. An active area of investigation within exercise immunology is the effect that various drugs [1,23,35,55] or nutrient supplements may have in countering exercise-induced inflammation and immunosuppression [54,78,92,93], allowing the athlete to continue training and competing intensively without interruption from URTI.

Researchers have measured the influence of nutritional supplements, primarily zinc [98], dietary fat [107], vitamin C [60,79–81], glutamine [10–12,40,85–88,90], and carbohydrate [24,30,31,54,58,61,65,67,69] on the immune and infection response to intense and prolonged exercise [48,78,92,93].

Several double-blind placebo studies of South African ultramarathon runners have demonstrated that 3 weeks of vitamin C supplementation (about 600 mg/day) is related to fewer reports of URTI symptoms [79–81]. This has not been replicated, however, by other research teams, and the method of reporting URTI symptoms resulted in unrealistically high incidence rates. Himmelstein et al. [32] reported no alteration in URTI incidence among 44 marathon runners and 48 sedentary subjects randomly assigned to a 2-month regimen of 1000 mg/day of vitamin C or placebo. 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 h of intensive running [60].

Glutamine, a nonessential amino acid, has attracted much attention by investigators [78,87]. Glutamine is an important fuel along 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 [10,24,87]. Whether exercise-induced reductions in plasma glutamine levels are linked to impaired immunity and host protection against viruses in athletes is still unsettled, but the majority of studies have not favored such a relationship [40,87,88,94].

Research during the 1980s and early 1990s established that a reduction in blood glucose levels was 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 epinephrine levels [41,45]. Given the link between stress hormones and immune responses to prolonged and intensive exercise [53,54], it was hypothesized that carbohydrate compared to placebo ingestion should maintain plasma glucose concentrations, attenuate increases in stress hormones, and thereby diminish changes in immunity.

This hypothesis was first tested in a group of 30 experienced marathon runners [31,47,58,61]. A double-blind, placebo, randomized study was designed to investigate the effect of carbo-

hydrate fluid (6% carbohydrate beverage) ingestion on the immune response to 2.5 h of running. Drinking the carbohydrate beverage before, during (1 l/h), and after 2.5 h of running attenuated the rise in both cortisol and the neutrophil/lymphocyte ratio [58]. The immediate post-run blood glucose level was significantly higher in the carbohydrate versus placebo group and was negatively correlated with cortisol [58]. Trafficking of most leukocyte and lymphocyte subsets was lessened in accordance with the lower cortisol levels under the carbohydrate condition [31,58,61]. Carbohydrate intake also blunted the rise in IL-6 and IL-1- α , cytokines involved in the inflammatory cascade response to heavy exertion [47]. Overall, these data supported the viewpoint that carbohydrate ingestion during prolonged and intensive exercise lessens hormonal and immune responses that have been related to physiological stress and inflammation.

In a subsequent study of 10 triathletes, carbohydrate ingestion was studied for its effect on the immune response to 2.5 h of running and cycling [30,67,69]. During four sessions, subjects ran on treadmills or cycled for 2.5 h at ~75% $\dot{V}O_{2\max}$. Subjects exercised under carbohydrate (6% carbohydrate beverage) or placebo conditions (double-blinded). Carbohydrate compared to placebo ingestion (but not activity mode) was associated with higher post-exercise plasma glucose levels, lower plasma concentrations of cortisol and growth hormone, and a lessened perturbation of blood cell counts [30,67,68]. The plasma IL-6 concentration following the carbohydrate cycling trial was about one-fifth that measured after the placebo running trial [67]. IL-1- α was decreased during several hours of recovery by about 60% after carbohydrate ingestion relative to placebo [67]. For 6 h following the running and cycling bouts, an increase in blood granulocyte and monocyte phagocytosis was measured, with levels somewhat lower following the carbohydrate trials [69]. Carbohydrate ingestion also diminished the increase in granulocyte and monocyte oxidative burst activity following exercise.

Future Directions

From a public health viewpoint, the potential link between moderate exercise and altered immunosenescence is of the highest value, yet a dearth of research data exists in this area. Both animal and human studies suggest a connection between exercise and enhanced immunity among the elderly, but also indicate that a serious commitment to lifelong physical activity may be needed.

Is the athlete an immunocompromised host? For most athletes, probably not, although the answer may be “yes” during certain periods when the athlete is overreaching (e.g., after a competitive race). The immune systems of athletes and non-athletes in the resting state appear more similar than disparate. NK cell activity tends to be enhanced in athletes, but the clinical significance of this finding has yet to be established. Of greater interest to investigators has been the finding that many components of the immune system exhibit change after prolonged, heavy exertion. Most of these changes have been characterized as “stressful” or “immunosuppressive”, but other options are possible. Research is needed to establish that during this “open window” of altered immunity following exhaustive exercise, risk of subclinical and clinical infection is increased due to decreased host protection against viruses and

bacteria. Parallels have been drawn between exercise-induced and trauma-induced alterations in immunity and host protection [73, 74, 77]. Faist et al. [19] have summarized the important links between physical trauma (of sufficient magnitude to induce a large volume of tissue injury), impairment in immunologic reactivity, and increased risk of infection in patients. Many trauma-related cellular immune defects are similar to those found after prolonged and intensive exercise (e.g., decreased DTH responses, lymphopenia, decreased lymphocyte proliferative capacity and NK cell activity, a hyperactive inflammatory process) [19]. Is the trauma of a competitive marathon race, for example, of sufficient magnitude to cause the same degree of immune changes and host protection that occur following major surgery or injury?

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 with carbohydrate supplementation. 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. Overall, these data indicate that the physiological stress to the immune system is reduced when endurance athletes use carbohydrate beverages before, during, and after prolonged and intense exertion. In other words, carbohydrate beverages do appear to act as a partial countermeasure to exercise-induced inflammation and immunosuppression. The clinical significance of these carbohydrate-induced effects on the endocrine and immune systems awaits further research, however. The connection between carbohydrate ingestion and altered immunity provides an excellent opportunity and model to test whether exercise-induced changes in blood compartment immune measures are clinically important or merely transient perturbations providing nothing more than academic interest.

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