

Can Nutrition Limit Exercise-Induced Immunodepression?

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Prolonged exercise and heavy training are associated with depressed immune cell function. To maintain immune function, athletes should eat a well-balanced diet sufficient to meet their energy, carbohydrate, protein, and micronutrient requirements. Consuming carbohydrate during prolonged strenuous exercise attenuates rises in stress hormones and appears to limit the degree of exercise-induced immune depression. Recent evidence suggests that antioxidant vitamin supplementation may also reduce exercise stress and impairment of leukocyte functions. Further research is needed to evaluate the effects of other antioxidants and dietary immunostimulants such as probiotics and echinacea on exercise-induced immune impairment.

Key words: exercise, immunity, leukocytes, macronutrients, micronutrients, training

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IMMUNE FUNCTION AND THE NUTRITION OF ELITE ATHLETES

The immune system protects against, recognizes, attacks, and destroys elements that are foreign to the body. The immune system can be divided into two broad functions: innate (natural and non-specific) and acquired (adaptive and specific) immunity, which work synergistically. Any attempt of an infectious agent to enter the body immediately activates the innate system. This so-called “first line of defense” comprises three general mechanisms with the common goal of restricting microorganism entry into the body: 1) physical/structural barriers (e.g., skin, epithelial linings, mucosal secretions); 2)

chemical barriers (e.g., pH of bodily fluids and soluble factors such as lysozymes and complement proteins); and 3) phagocytic cells (e.g., neutrophils and monocytes/macrophages) and cytotoxic cells (natural killer cells). Failure of the innate system and the resulting infection activates the acquired system, which aids recovery from infection. Monocytes or macrophages ingest, process, and present foreign material (antigens) to lymphocytes. This is followed by clonal proliferation of T- and B-lymphocytes that possess receptors that recognize the antigen, engendering specificity and “memory” that enable the immune system to mount an augmented cell-mediated and humoral (antibody) response when the host is re-infected by the same pathogen. Critical to the activation and regulation of immune function is the production of cytokines, including interferons (IFNs), interleukins (ILs), and colony-stimulating factors (CSFs). A fundamental characteristic of the immune system is that it involves multiple functionally different cell types, which permits a large variety of defense mechanisms. Assessing immune function status therefore requires a thorough methodological approach targeting a large spectrum of immune system parameters. However, there are currently no instruments available to predict the cumulative effects of several small changes in immune cell functions determined in vitro on host resistance to infection.¹

A heavy schedule of training and competition can lead to immune impairment in athletes, and this is associated with an increased susceptibility to infections, particularly upper respiratory tract infections (URTI).^{2,3} This exercise-induced immune dysfunction seems to be mostly due to the immunosuppressive actions of stress hormones such as adrenaline and cortisol. Since many of the immunological changes to acute exercise appear to arise in response to stress hormones, factors such as exercise intensity and duration and subject fitness, which influence stress hormone secretion, will affect the immune response. Both circulating leukocyte numbers and functions are affected by catecholamines,⁴ which are elevated by acute exercise in an intensity-dependent manner. Subject fitness has a bearing on the relative intensity of a bout, and will therefore alter the immunological outcome to an acute exercise bout.⁵ Furthermore,

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exercise-induced elevations in cortisol affect the leukocyte count and function, and the secretion of this hormone is affected by the intensity and duration of exercise.⁶

Mild to moderate exercise (<50% $\text{VO}_{2\text{max}}$) seems to reduce cortisol concentrations due to an enhanced elimination and a suppressed secretion, whereas more intense exercise (>60% $\text{VO}_{2\text{max}}$) increases cortisol.⁶ However, if the bout is sufficiently prolonged, even relatively moderate intensities can elicit increases in cortisol, because it is released to increase gluconeogenesis and maintain blood glucose concentrations.⁷ Exercise intensity and duration both contribute to the metabolic stress of the bout and thus influence fuel depletion. Since recent evidence suggests that skeletal muscle can release IL-6 when fuel provision becomes challenged,⁸ and this cytokine is known to have immunological actions,⁹ factors such as intensity, duration, and subject fitness, all of which can influence metabolic demand, will affect the immunological outcome.

Acute exercise appears to modify T-cell function and, as for many other aspects of immune function, such effects are proportional to exercise intensity and duration. There is evidence that prolonged acute exercise is associated with a decrease in T-cell IL-2 and IFN- γ production immediately after exercise, and a decline in the number of circulating T cells that secrete IFN- γ .¹⁰ There are numerous reports in the literature of decreased mitogen-stimulated T-cell proliferation following acute exercise,^{11,12} but interpretation of these findings may be confounded by the presence of natural killer (NK) cells and B cells in the cell cultures. Furthermore, *in vitro* stimulation with mitogen does not necessarily reflect the more subtle responses of cells following a specific antigen encounter within the body. Moreover, exercise may alter T-cell function *in vitro* through an increase in the rate of apoptosis in cell culture rather than a decrease in T-cell proliferation.¹³

The effect of exercise on humoral immune function has been assessed through measurements of serum and mucosal immunoglobulin concentration *in vivo* and lymphocyte immunoglobulin synthesis following *in vitro* mitogen stimulation. Serum immunoglobulin concentration remains either unchanged or slightly increased in response to brief or prolonged exercise.¹⁴ Mucosal immunoglobulin production has been chiefly assessed by measurement of immunoglobulin-A (IgA) in saliva, with intensive exercise frequently associated with a decline in the s-IgA concentration and/or secretion rate.¹⁵

In general, post-exercise immune function depression is most pronounced when the exercise is continuous, prolonged (>1.5 hours), of moderate to high intensity (55%–75% $\text{VO}_{2\text{max}}$), and performed without food intake. Periods of intensified (overreaching) training lasting one

week or more result in chronically depressed immune function.¹⁶ Although elite athletes are not clinically immunodeficient, it is possible that the combined effects of small changes in several immune parameters may compromise resistance to common minor illnesses such as URTI. Protracted immune depression linked with prolonged training may determine susceptibility to infection, particularly at times of major competitions.¹⁵ Hundreds of studies have now been conducted that confirm both acute and chronic effects of exercise on the immune system, yet there are still very few studies that have been able to show a link between exercise-induced immune depression and increased incidence of illness in athletes. This is an important issue that needs to be addressed in future studies, but this will be a difficult task. Even among the general population, we do not know the impact of small changes in specific immune parameters on risk of infection.¹ Most clinical studies have only been concerned with the risk of life-threatening illness in immunodeficient patients, not with the risks of contracting common infections such as colds and flu.

Nutritional deficiencies can also impair immune function, and there is a vast body of evidence that many infections are increased in prevalence or severity by specific nutritional deficiencies.¹⁷ However, it is also true that excessive intakes of individual micronutrients (e.g., n-3 polyunsaturated fatty acids, iron, zinc, and vitamins A and E) can impair immune function and some (particularly excess iron) can increase the risk of infection.¹⁷ As most athletes are aware, even medically harmless infections can result in decrements in athletic performance. This review will consider the various components of the diet that can potentially influence the degree of exercise-induced immunodepression.

Undoubtedly, a key to maintaining an effective immune system is to avoid deficiencies of the nutrients that play an essential role in immune cell triggering, interaction, differentiation, or functional expression. Malnutrition decreases immune defenses against invading pathogens and makes the individual more susceptible to infection.^{17,18} Infections with certain pathogens can also affect nutritional status by causing appetite suppression, malabsorption, increased nutrient requirements, and increased losses of endogenous nutrients.¹⁸

MACRONUTRIENTS

Protein and Energy

It is well accepted that an inadequate intake of protein impairs host immunity, with particularly detrimental effects on the T-cell system, resulting in increased incidence of opportunistic infections.^{17,18} It is not surprising that protein deficiency impairs immunity,

because immune defenses are dependent on rapid cell replication and the production of proteins with important biological activities such as immunoglobulins, acute phase proteins, and cytokines. In humans, protein-energy malnutrition has been found to depress the number of mature, fully differentiated T-lymphocytes and the *in vitro* proliferative response to mitogens, although the latter is reversible with nutritional repletion.¹⁹ Additionally, in protein-energy malnutrition, the T-lymphocyte CD4⁺/CD8⁺ (helper/suppressor cell) ratio is markedly decreased and phagocytic cell function, cytokine production, and complement formation are all impaired.

Essentially all forms of immunity have been shown to be affected by protein-energy malnutrition in humans, depending on the severity of the protein deficiency relative to energy intake. While it is unlikely that athletes would ever reach a state of such extreme malnutrition unless dieting very severely, some impairment of host defense mechanisms is observed even in moderate protein deficiency.¹⁹ Among the athletic population, individuals at most risk from protein deficiency are those undertaking a program of food restriction in order to lose weight, vegetarians, and athletes consuming unbalanced diets (e.g., with an excessive amount of carbohydrate at the expense of protein). Often, deficiencies in protein and energy will be accompanied by deficiencies in micronutrients. Energy-restricted diets are common in sports in which leanness or low body mass is thought to confer a performance or aesthetic advantage (e.g., gymnastics, figure skating, endurance running) or is required to meet certain body weight categories (e.g., boxing, martial arts, weight lifting, rowing). Indeed, this has led to the identification of a new subclinical eating disorder called “anorexia athletica,” which has been associated with an increased susceptibility to infection.²⁰ Even short-term dieting can influence immune function in athletes. For example, it has been shown that a loss of 2 kg of body mass over a 2-week period adversely affects macrophage phagocytic function.²¹

Fat

Relatively little is known about the potential contribution of dietary fatty acids to the regulation of exercise-induced modification of immune function. Two groups of polyunsaturated fatty acids (PUFAs) are essential to the body: the omega-6 (n-6) series, derived from linoleic acid, and the omega-3 (n-3) series, derived from linolenic acid. These fatty acids cannot be synthesized in the body and therefore must be derived from the diet. There are reports that diets rich in n-3 PUFAs improve the conditions of patients suffering from diseases characterized by an overactive immune system, such as rheumatoid arthritis, so it is thought that they have anti-inflam-

matory effects.¹⁸ It has been suggested that high intakes of n-6 PUFAs (such as arachidonic acid) relative to intakes of fatty acids of the n-3 group may exert an undesirable influence on inflammation and immune function during and after exercise,²² though direct evidence of this is currently lacking. However, a recent study showed that n-3 PUFA supplementation did not influence the exercise-induced elevation of pro- or anti-inflammatory cytokines.²³ More research is needed on the effects of altering essential fatty acid intake on immune function after exercise and during periods of heavy training.

Carbohydrates

Since many aspects of exercise-induced immune function impairment seem to be caused by elevated levels of stress hormones, nutritional strategies that effectively reduce the stress hormone response to exercise would be expected to limit the degree of exercise-induced immune dysfunction.²⁴ There is considerable experimental evidence that supports a beneficial effect of carbohydrate feeding during exercise,^{25,26} although it is not clear if the magnitude of such an effect is sufficient to affect infection risk.

Consumption of carbohydrate during exercise attenuates (i.e., reduces the magnitude of) rises in plasma catecholamines, growth hormone, adrenocorticotrophic hormone, cortisol (Figure 1), and cytokines.²⁵ Carbohydrate intake during exercise also attenuates the trafficking of most leukocyte and lymphocyte subsets, including

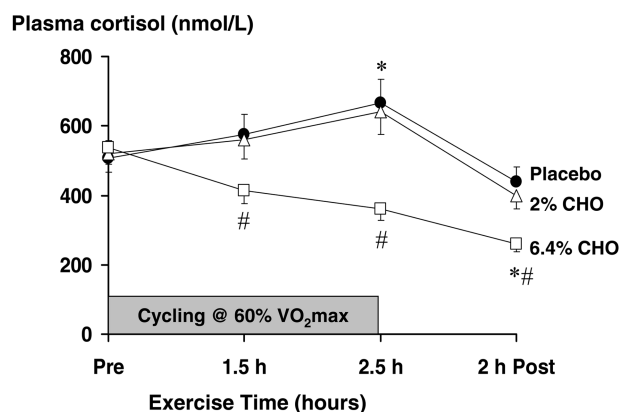


Figure 1. Consumption of 30 to 60 g carbohydrate per hour as a 6.4% w/v beverage during 2.5 h strenuous cycling exercise attenuates rises in plasma cortisol observed on the placebo trial. * = significantly different from pre-exercise ($P < 0.05$); # = significantly lower than placebo ($P < 0.05$). Note that ingesting a small amount of carbohydrate as a 2% w/v beverage has no significant effect on the plasma cortisol response to exercise. The volume of drinks consumed was 500 mL immediately pre-exercise and 200 mL every 20 min during exercise. Data from Lancaster et al.¹⁵

the rise in the neutrophil to lymphocyte ratio,²⁵ prevents the exercise-induced decrease in neutrophil function,²⁷ and reduces the extent of the diminution of mitogen-stimulated T-lymphocyte proliferation²⁸ following prolonged exercise (Figure 2). Very recently, it was shown that consuming 30 to 60 g of carbohydrate per hour during 2.5 h of strenuous cycling prevented both the decrease in the number and percentage of IFN- γ -positive T lymphocytes and the suppression of IFN- γ production from stimulated T lymphocytes (Figure 3) observed in the placebo control trial.¹⁰ IFN- γ production is critical to antiviral defense and it has been suggested that the suppression of IFN- γ production may be an important mechanism leading to an increased risk of infection after prolonged exercise bouts.²⁹

In a randomized, counterbalanced, crossover study, carbohydrate beverage ingestion during a 3-h treadmill run at 70% $\text{VO}_{2\text{max}}$ attenuated plasma levels of interleukin (IL)-6, and IL-10, and muscle gene expression for IL-6 and IL-8 compared with placebo beverage ingestion.³⁰ The 3-h treadmill run in both the carbohydrate and placebo trials induced gene expression within the muscle for two primary pro-inflammatory cytokines IL-1 β and tumor necrosis factor-alpha (TNF α). IL-6 and IL-8, which are often considered to be components of the secondary inflammatory cascade, were also expressed, but to a smaller degree, in the carbohydrate trial. Anti-inflammatory indicators, including plasma IL-1-receptor antagonist, IL-10, and cortisol, were also decreased with carbohydrate feeding. These data suggest that carbohydrate ingestion attenuates the secondary but not the

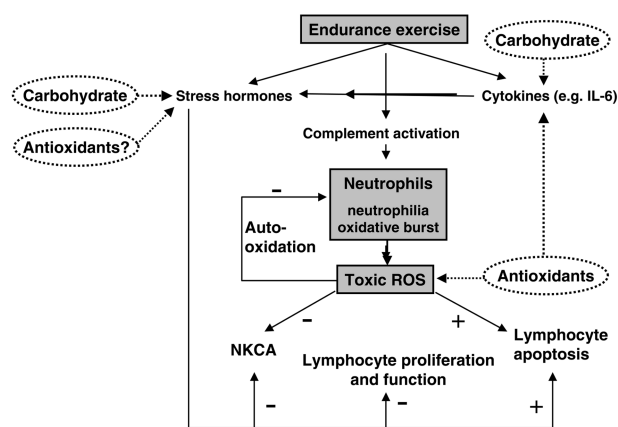


Figure 2. Mode of action of carbohydrate and antioxidant supplements in limiting exercise-induced immune function depression. Carbohydrate ingestion during prolonged exercise maintains plasma glucose availability and limits rises in circulating interleukin-6 (IL-6), cortisol, and adrenaline. Antioxidant supplementation for several weeks also attenuates rises in circulating IL-6 and cortisol during exercise, elevates the plasma antioxidant capacity and scavenges reactive oxygen species (ROS) generated by active muscle and activated neutrophils.

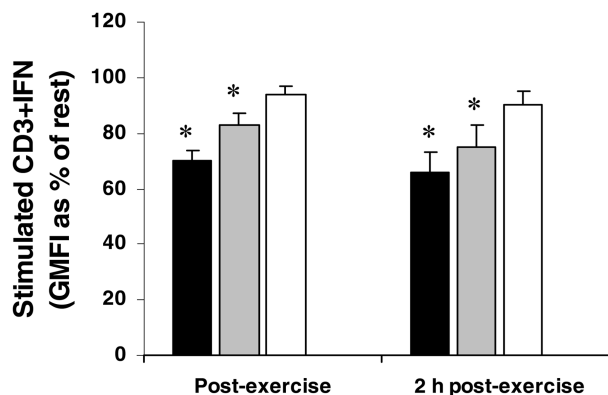


Figure 3. Consumption of 30 to 60 g carbohydrate per hour as a 6.4% w/v beverage during 2.5 h strenuous cycling exercise prevents the suppression of interferon (IFN)- γ production from stimulated T lymphocytes observed on the placebo control trial. * = Significantly lower than pre-exercise ($P < 0.05$). Note that ingesting a small amount of carbohydrate as a 2% w/v beverage is not as effective. The volume of drinks consumed was 500 mL immediately pre-exercise and 200 mL every 20 min during exercise. Black bars = placebo; gray bars = 2% carbohydrate; white bars = 6.4% carbohydrate. Data from Lancaster et al.¹⁵

primary pro-inflammatory cascade, decreasing the need for immune responses related to anti-inflammation.³⁰

When carbohydrate is ingested during prolonged exercise, the release of IL-6 from working muscles can be totally inhibited,³¹ and the exercise-induced expression of a number of metabolic genes are blunted compared with exercise in the fasted state.³² Infusion of IL-6 in humans stimulates cortisol secretion (with plasma cortisol levels reaching values similar to those observed during exercise and with a similar time course) and induces lipolysis and elicits a strong anti-inflammatory response.³³ Thus, although carbohydrate ingestion during exercise attenuates the IL-6 response and so reduces the magnitude of the cortisol-induced lymphocytopenia, it will at the same time inhibit lipolysis, reduce the anti-inflammatory cytokine response to exercise, and attenuate the expression of a number of metabolic genes in the exercised muscle. In other words, it is possible that carbohydrate ingestion during exercise sessions could limit metabolic adaptation of skeletal muscle to training. However, it can also be argued that carbohydrate intake during training allows the athlete to work harder and longer, and as yet there is no evidence that physiological and performance adaptations are impaired by carbohydrate intake during training sessions. Indeed, recent studies indicate that appropriate carbohydrate intake is necessary for improvements in endurance performance following periods of intensified training that temporarily induce overreaching.^{34,35}

While carbohydrate feeding during exercise appears to be effective in minimizing some of the immune perturbations associated with prolonged continuous

strenuous exercise, it seems less effective for less-demanding exercise of an intermittent nature, such as football³⁶ or rowing³⁷ training. It is also apparent that carbohydrate feeding is not as effective in reducing immune cell trafficking and functional depression when continuous prolonged exercise is performed to the point of fatigue.³⁸ Pre-exercise carbohydrate feeding does not seem to be very effective in limiting exercise-induced leukocytosis or depression of neutrophil function.³⁹ Further, evidence that the beneficial effect of feeding carbohydrate on immune responses to exercise actually translates into a reduced incidence of URTI following prolonged exercise such as marathon races is currently lacking. Although a trend for a beneficial effect of carbohydrate ingestion on post-race URTI was reported in a study of 98 marathon runners,⁴⁰ this did not achieve statistical significance and larger-scale studies are needed to investigate this possibility.

The size of the glycogen stores in muscle and liver at the onset of exercise also influence the hormonal and immune response to exercise. The amount of glycogen stored in the body is rather limited (usually less than 500 g) and is affected by recent physical activity and the amount of dietary carbohydrate intake. When individuals perform prolonged exercise following several days on very-low-carbohydrate diets (typically <10% of dietary energy intake from carbohydrate), the magnitude of the stress hormone (e.g., adrenaline and cortisol) and cytokine (e.g. IL-6, IL-1ra, and IL-10) response is markedly higher than when individuals are on normal or high-carbohydrate diets.^{41,42}

It has been speculated that athletes deficient in carbohydrate are placing themselves at risk for the known immunosuppressive effects of cortisol, including the suppression of antibody production, lymphocyte proliferation, and NK cell cytotoxic activity. In the study by Mitchell et al.,⁴² it was observed that exercising (1 h at 75% $\text{VO}_{2\text{max}}$) in a glycogen-depleted state (induced by prior exercise and 2 days on a low-carbohydrate diet) resulted in a greater decrease in circulating lymphocyte numbers at 2 hours post-exercise compared with the same exercise performed after 2 days on a high-carbohydrate diet. In this study, the manipulation of carbohydrate status did not affect the decrease in mitogen-stimulated lymphocyte proliferation that occurred after exercise. However, a more recent study by Bishop et al.⁴³ showed that lymphocyte proliferation responses to mitogen and influenza were lower 24 h following a 90-minute intermittent high-intensity exercise bout when subjects consumed a placebo beverage compared with a carbohydrate beverage before, during, and following the exercise bout (Figure 4). Interestingly, these differences were independent of changes in the plasma cortisol

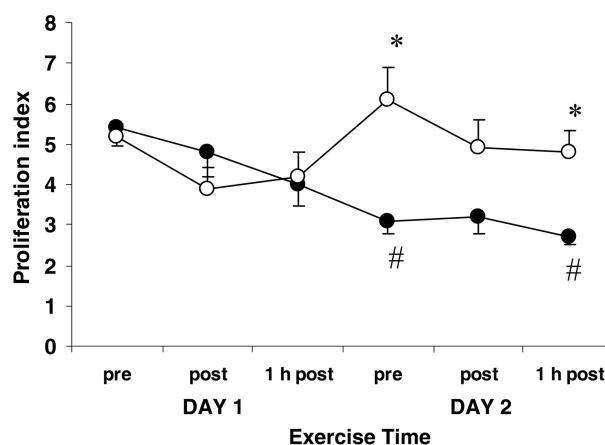


Figure 4. Mitogen (phytohemagglutinin)-stimulated T-lymphocyte proliferative response (increase relative to unstimulated cells) before and after two bouts of high-intensity intermittent exercise performed on consecutive days with either carbohydrate (6.4% w/v; white circles) or placebo (black circles) beverage ingestion before, during, and after exercise bout. * = Significantly higher than placebo ($P < 0.05$); # = significantly lower than pre-exercise on day 1 (placebo only; $P < 0.05$). Data from Bishop et al.³⁰

concentration, implying that these carbohydrate effects were mediated via a different mechanism.

Fluid Intake during Exercise

The consumption of beverages during exercise not only helps to prevent dehydration (which is associated with an increased stress hormone response), but also helps to maintain saliva flow rate during exercise. Saliva contains several proteins with antimicrobial properties including IgA, lysozyme and α -amylase. Saliva secretion usually decreases during exercise. Regular fluid intake during exercise is reported to prevent this effect, and a recent study has confirmed that regular consumption of lemon-flavored, carbohydrate-containing drinks helps to maintain saliva flow rate, and hence saliva IgA secretion rate, during prolonged exercise compared with a restricted fluid intake regimen.⁴⁴

MICRONUTRIENTS

Minerals

Several minerals are known to exert modulatory effects on immune function, including zinc, iron, magnesium, manganese, selenium, and copper, yet with the exception of zinc and iron, isolated deficiencies are rare. Field studies consistently associate iron deficiency with increased morbidity from infectious disease.^{17,18} Furthermore, exercise has a pronounced effect on both zinc and iron metabolism.⁴⁵ Requirements for these minerals

are certainly higher in athletes compared with sedentary people because of increased losses in sweat and urine. However, excess intakes of some minerals (particularly iron and zinc) can impair immune function and, at least for iron, have been shown to increase susceptibility to infection.^{17,18,45} Therefore, supplements should be taken only as required and regular monitoring of iron status (serum ferritin and blood hemoglobin) and zinc status (erythrocyte or leukocyte zinc content) is probably a good idea.

The efficacy of zinc supplementation as a treatment for the common cold has been investigated in at least 11 studies that have been published since 1984. The findings have been equivocal and recent reviews of this topic have concluded that further research is necessary before the use of zinc supplements to treat the common cold can be recommended.^{46,47} Although there is only limited evidence that taking zinc supplements reduces the incidence of URTI,⁴⁸ in the studies that have reported a beneficial effect of zinc in treating the common cold (i.e., reduction of symptom duration and/or severity) it has been emphasized that zinc must be taken within 24 h of the onset of symptoms to be of any benefit. Potential problems with zinc supplements include nausea, bad taste reactions, lowering of HDL-cholesterol, depression of some immune cell functions (e.g. neutrophil oxidative burst), and interference with the absorption of copper.⁴⁵

Vitamins

Several vitamins are essential for normal immune function. Deficiencies of the fat-soluble vitamins A and E and the water-soluble vitamins folic acid, B₆, B₁₂, and C impair immune function and decrease the body's resistance to infection.^{17,18} Correcting existing deficiencies with specific vitamin supplements can be effective in restoring immune function to normal levels, and moderately increasing the intake of some vitamins (notably vitamins A and E) above the levels normally recommended may enhance immune function, particularly in the very young and the elderly.¹⁷ Consuming megadoses of individual vitamins, which appears to be a common practice in athletes, can actually impair immune function and have other toxic effects.¹⁸

In a recent exercise study, supplementation of athletes with 600 mg/d of vitamin E for 2 months prior to an iron man triathlon event resulted in elevated oxidative stress and inflammatory cytokine responses during the triathlon compared with placebo.⁴⁹ In a study on elderly people (N = 652), a daily 200 mg vitamin E supplement increased the severity of infections, including total illness duration, duration of fever, and restriction of physical activity.⁵⁰ However, in that study, health assessment was by self-evaluation, which could be a limiting factor,

particularly in an elderly population whose cognitive function was not described.

In a recent large, placebo-controlled trial (N = 617 elderly nursing home residents) by Meydani et al.,⁵¹ which used weekly documentation by nurses and physicians to assess health status, fewer participants receiving daily supplementation with 200 IU vitamin E acquired one or more URTIs, and the vitamin E group had a lower incidence of colds than the placebo group. Recently, vitamin E supplementation (600 mg/d) in patients with ischemic heart disease has been demonstrated to have either no effect on all-cause mortality⁵² or to increase the number of patients who died compared with placebo.⁵³ In contrast in a large cohort of women (N = 22,000), there was a 24% reduction in risk for cardiovascular death in those who took a supplement of 600 IU/d vitamin E every other day for 10 years, and no effect on overall mortality.⁵⁴ Meydani et al.⁵⁵ concluded that 200 mg of vitamin E daily represents the optimal level for the immune response. Intakes in excess of 300 mg/d of vitamin E in the human diet have been associated with decreases in phagocytic cell function.^{56,57} Megadoses of vitamin A may impair the inflammatory response and complement formation, and may have other pathological effects, including an increased risk of fetal abnormalities when consumed by pregnant women.⁵

Vitamins with antioxidant properties including vitamins A, C, and E and β -carotene (provitamin A) may be required in increased quantities in athletes to inactivate the products of exercise-induced reactive oxygen species generation.⁵⁸ However, there are no convincing data demonstrating an effect of nutritional antioxidants on exercise performance. Increased oxygen free-radical formation that accompanies the dramatic rise in oxidative metabolism during exercise could potentially inhibit immune responses^{18,59} and contribute to exercise-induced lymphocytopenia by activating apoptosis (an internal program that allows cells to "commit suicide").⁶⁰ Reactive oxygen species inhibit locomotor and bactericidal activity of neutrophils, inhibit NK cell cytotoxic activity, reduce the proliferation of T- and B-lymphocytes and promote lymphocyte apoptosis (Figure 2).⁶⁰ Sustained endurance training appears to be associated with an adaptive up-regulation of the antioxidant defense system,⁶¹ though this may be insufficient to protect athletes who train extensively.⁵⁸

Vitamin C (ascorbic acid) is found in high concentrations in leukocytes and has been implicated in a variety of anti-infective functions, including the promotion of T-lymphocyte proliferation, the prevention of corticosteroid-induced suppression of neutrophil activity, and the inhibition of virus replication.⁶² It is also a major water-soluble antioxidant that is effective as a scavenger of reactive oxygen species in both intracellular and

extracellular fluids. Vitamin C is also required for the regeneration of the reduced form of the lipid-soluble antioxidant vitamin E.

In a study by Peters et al.⁶³ using a double-blind, placebo design, it was determined that daily supplementation of 600 mg (15 times the Reference Nutrient Intake) of vitamin C for 3 weeks prior to a 90-km ultramarathon reduced the incidence of symptoms of URTI (68% compared with 33% in age- and sex-matched control runners) in the 2-week post-race period. In a follow-up study, Peters et al.⁶⁴ randomly divided participants in a 90-km ultramarathon (N = 178), and their matched controls (N = 162) into four treatment groups receiving either 500 mg vitamin C alone, 500 mg vitamin C plus 400 IU vitamin E (1 IU is equivalent to 0.67 mg), 300 mg vitamin C plus 300 IU vitamin E plus 18 mg β -carotene, or placebo. As runners were requested to continue with their usual habits in terms of dietary intake and the use of nutritional supplements, total vitamin C intake of the 4 groups was 1004, 893, 665, and 585 mg daily, respectively. The study confirmed previous findings of a lower incidence of symptoms of URTI in those runners with the highest mean daily intake of vitamin C, and also indicated that the combination of water-soluble and fat-soluble antioxidants was not more successful in attenuating the post-exercise infection risk than vitamin C alone (Figure 5). This study certainly provides some support for the notion that megadoses of vitamin C reduce URTI risk in endurance athletes, though a limitation is that infection symptoms were self-reported and

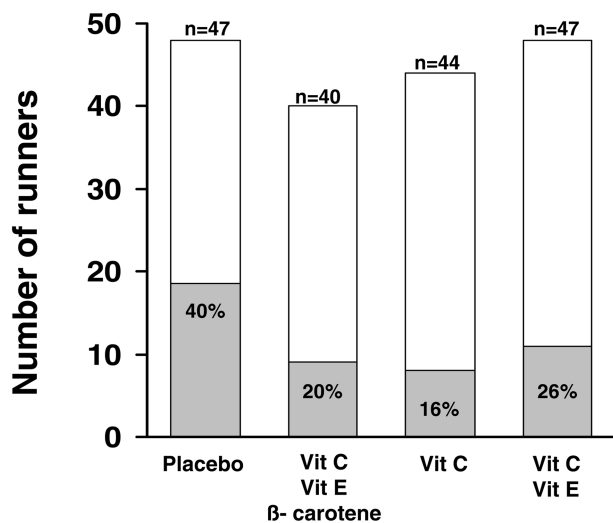


Figure 5. The incidence of upper respiratory tract infection (URTI) in the week following the 1993 Comrades Marathon (90-km) in South Africa. Different groups of runners received different combinations of antioxidant supplements or placebo for 3 weeks prior to the ultramarathon. The incidence of URTI in a control group of 45 non-runners receiving placebo was 20%. White areas = asymptomatic; gray areas = symptomatic. Data from Peters et al.⁴⁶

not clinically confirmed in these studies. Similar studies have not been able to replicate these findings. For example, Himmelstein et al.⁶⁵ reported no difference in URTI incidence among 44 marathon runners and 48 sedentary subjects randomly assigned to a 2-month regimen of 1000 mg/d vitamin C or placebo. Furthermore, a subsequent double-blind, placebo-controlled study found no effect of vitamin C supplementation (1000 mg/d for 8 days) on the immune response to 2.5 h running,⁶⁶ though a larger dose of vitamin C supplementation (1500 mg/d for 7 days prior to the race and on race day) did reduce the cortisol and cytokine response to a 90-km ultramarathon race.⁶⁷ However, in the latter study, no difference in URTI incidence was found between subjects on vitamin C and placebo treatments. Again, URTI was self-evaluated and a confounding factor in this study was that subjects consumed carbohydrates during the race ad libitum, and this was retrospectively estimated.

In a more recent randomized, double-blind, placebo-controlled study, 1500 mg/d vitamin C for 7 days before an ultramarathon race with consumption of vitamin C in a carbohydrate beverage during the race (subjects in the placebo group consumed the same carbohydrate beverage without added vitamin C) did not affect oxidative stress, cytokine or immune function measures during and after the race.⁶⁸ In contrast, it has recently been reported that 4 weeks combined supplementation with vitamin C (500 mg/d) and vitamin E (400 IU/d) prior to a 3-h knee extension exercise protocol reduced muscle IL-6 release and reduced the systemic rise in both circulating IL-6 and cortisol (Figure 6).⁶⁹ Furthermore, administration of the antioxidant N-acetyl-L-cysteine (a precursor of glutathione) to mice prevented the exercise-induced reduction in intracellular glutathione concentration and markedly reduced post-exercise apoptosis in intestinal lymphocytes.⁶⁰ Thus, although there are some inconsistencies in the literature regarding antioxidant supplementation and immune responses to exercise, there is some basis for believing that such supplementation could have beneficial effects in alleviating exercise-induced immunodepression.

DIETARY IMMUNOSTIMULANTS

Glutamine

Glutamine is the most abundant free amino acid in human muscle and plasma and is utilized at very high rates by leukocytes to provide energy and optimal conditions for nucleotide biosynthesis. Indeed, glutamine availability is considered important to lymphocytes and other rapidly dividing cells including the gut mucosa and bone marrow stem cells. Prolonged exercise is associated with a fall in the plasma concentration of glutamine, and

Plasma cortisol (nmol/L)

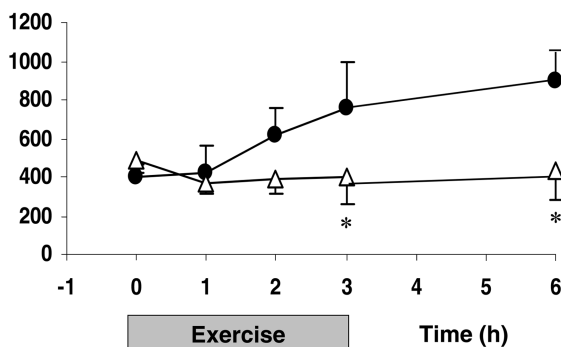


Figure 6. The effect of 4 weeks of antioxidant supplementation (500 mg/d vitamin C and 400 IU/d vitamin E) compared with placebo on plasma cortisol responses to 3 h of dynamic knee extensor exercise. Black circles = placebo; white triangles = antioxidant supplementation. Data from Fischer et al.⁵¹

it has been hypothesized that such a decrease could impair immune function.^{70,71}

It has been suggested that exogenous provision of glutamine supplements may be beneficial by maintaining the plasma glutamine concentration and hence preventing the impairment of immune function following prolonged exercise. Castell et al.⁷² have provided the only prophylactic evidence that an oral glutamine supplement (5 g in 330 mL water) consumed immediately after and 2 h after a marathon reduces the incidence of URTI (in the 7 days following the race). However, it is unlikely that this amount of glutamine supplementation could actually have prevented the post-exercise decrease in the plasma glutamine concentration. Provision of glutamine has been shown to have a beneficial effect on gut function, morbidity and mortality, and on some aspects of immune cell function in clinical studies of diseased or traumatized patients. However, several recent studies that have investigated the effect of large amounts of glutamine supplementation during and after exercise on the exercise-induced decrease in lymphokine-activated killer cell activity, neutrophil function, and mitogen-stimulated lymphocyte proliferation have failed to find any beneficial effect.^{73,74}

Branched-Chain Amino Acids

Very recently, Bassit et al.⁷⁵ reported that supplementation of branched-chain amino acids (6 g/d for 15 days) prior to a triathlon or 30-km run in experienced male triathletes and marathoners, respectively, prevented the approximately 40% decline in mitogen-stimulated lymphocyte proliferation observed in the placebo control group after exercise. Branched-chain amino ingestion was associated with increased lymphocyte IL-2 and IFN- γ production. The post-exercise decrease in plasma

glutamine concentration was prevented by the branched-chain amino acid ingestion, but it is not clear if this was the mechanism of action or if there was a direct effect of the branched amino acids themselves. More research is needed to resolve these conflicting findings of branched-chain amino acids and glutamine supplementation on immune responses to exercise.

β -Carotene

β -carotene (pro-vitamin A) acts both as an antioxidant and an immunostimulant, increasing the number of T-helper cells in healthy humans and stimulating NK cell activity when added in vitro to human lymphatic cultures.^{76,77} Furthermore, elderly men who had been taking β -carotene supplements (50 mg on alternate days) for 10 to 12 years were reported to have significantly higher NK cell activity than elderly men on placebo.⁷⁸ However, supplementing runners with β -carotene or vitamin A was found to have an insignificant effect on the incidence of URTI following a 90-km ultramarathon.^{64,79}

Echinacea

Several herbal preparations are reputed to have immunostimulatory effects, and the consumption of products containing *Echinacea purpurea* is widespread among athletes. However, few controlled studies have examined the effects of dietary immunostimulants on exercise-induced changes in immune function. In one recent, double-blind, placebo-controlled study, the effect of a daily oral pretreatment for 28 days with pressed juice of *E. purpurea* was investigated in 42 triathletes before and after a sprint triathlon.⁸⁰ Another subgroup of athletes were treated with a magnesium supplement. The most important finding was that during the 28-day pretreatment period, none of the athletes in the echinacea group fell ill, compared with three subjects in the magnesium group and four subjects in the placebo group.

Numerous experiments have demonstrated that echinacea extracts do indeed demonstrate significant immunomodulatory activities. Among the many pharmacological properties reported, macrophage activation has been demonstrated most convincingly.^{81,82} Phagocytotic indices and macrophage-derived cytokine concentrations have been shown to be responsive to echinacea in a variety of assays, and activation of polymorphonuclear leukocytes and NK cells has also been demonstrated.⁸³ Changes in the numbers and activities of T- and B-lymphocytes have been reported, but are less certain. Despite this cellular evidence of immunostimulation, pathways leading to enhanced resistance to infectious disease have not been described adequately. Several dozen human experiments, including a number of blind,

randomized trials, have reported health benefits. The most robust data come from trials testing echinacea extracts in the treatment for acute URTI. Although suggestive of modest benefit, these trials are limited both in size and in methodological quality. In a recent randomized, double-blind, placebo-controlled trial, administering unrefined echinacea at the onset of symptoms of URTI in 148 college students did not provide any detectable benefit or harm compared with placebo.⁸⁴

Therefore, while there is a great deal of moderately good-quality scientific data regarding the *in vitro* effects of echinacea on selected immune cell functions, its effectiveness in treating illness or in enhancing human health is still debated, and it is not yet known if echinacea is effective in modifying exercise-induced immunodepression.

Probiotics

Probiotics are food supplements that contain “friendly” gut bacteria. There is now a reasonable body of evidence showing that regular consumption of probiotics can modify the population of the gut microflora and influence immune function.^{85,86} Some studies have shown that probiotic intake can improve rates of recovery from rotavirus diarrhea, increase resistance to enteric pathogens, and promote anti-tumor activity; there is even some evidence that probiotics may be effective in alleviating some allergic and respiratory disorders in young children.⁸⁷ However, to date, there are no published studies of the effectiveness of probiotic use in athletes.

Alcohol and Caffeine

Although there are some established health benefits of regular light to moderate alcohol consumption, including reduced risk of myocardial infarction, ischemic stroke, diabetes, and osteoporosis,⁸⁸ it is well established that excessive intake of alcohol has negative effects on immune function.⁸⁹ For other obvious reasons, alcohol should not form a significant part of an athlete’s diet. Although red wine contains flavonoids, polyphenol compounds with potent antioxidant properties, these can also be obtained from the juice of black grapes. Polyphenols are also found in abundance in berries, green tea, dark chocolate, and other foods.

Caffeine is the most commonly consumed drug in the world, and athletes frequently use it as an ergogenic aid.⁹⁰ It improves performance and endurance during prolonged exhaustive exercise.^{90,91} At present, there is little information of the effects of caffeine ingestion on immune function at rest or during exercise. The addition of pharmacological doses of caffeine to cell culture media is associated with a dose-dependent suppression

of *in vitro* mitogen-stimulated lymphocyte proliferative responses and cytokine production in humans.⁹² In rats, the *in vivo* administration of 6 mg/kg/d of caffeine caused the NK cell cytotoxicity and the pokeweed mitogen-stimulated B-cell proliferative response to be significantly decreased,⁹³ though in the same study, the administration of three times this dose of caffeine was associated with a significant increase in phytohemagglutinin-stimulated T-cell proliferation. *In vitro*, a broad range of caffeine concentrations (1–1000 mg/L) exhibited dose-dependent inhibition of both B- and T-cell proliferative responses.⁹³ Recent exercise studies have demonstrated that caffeine compared with placebo ingestion 1 h before a bout of intensive endurance exercise was associated with greater perturbations in the numbers of circulating lymphocytes, CD4⁺, and CD8⁺ cells, and an increased percentage of CD4⁺ and CD8⁺ cells expressing the early activation marker CD69 *in vivo* both before and after exercise.⁹⁴ Furthermore, the post-exercise decrease in neutrophil oxidative burst activity was attenuated by caffeine ingestion.⁹⁵ It is thought that these effects may be largely mediated through caffeine’s action as an adenosine receptor antagonist and as an inhibitor of cyclic AMP-specific phosphodiesterase activity.^{92,94}

CONCLUSIONS

Dietary deficiencies of energy, protein, and specific micronutrients are associated with depressed immune function and increased susceptibility to infection. An adequate intake of iron, zinc, and vitamins A, E, B₆, and B₁₂ is particularly important for the maintenance of immune function. Athletes need to avoid micronutrient deficiencies. To maintain immune function, athletes should eat a well-balanced diet sufficient to meet their energy requirements. This should ensure an adequate intake of protein and micronutrients. For athletes on energy-restricted diets, vitamin supplements are desirable.

An athlete exercising in a carbohydrate-depleted state experiences larger increases in circulating stress hormones and a greater perturbation of several immune function indices. Thus, sufficient carbohydrate intake to restore glycogen stores on a daily basis is desirable. Consumption of carbohydrate (30–60 g/h) in drinks during prolonged exercise is recommended, as this practice appears to attenuate some of the immunodepressive effects of prolonged exercise. However, the clinical significance of this has yet to be determined.

Routine consumption of megadoses of vitamins and minerals is not advised. Excess intakes of some micronutrients (e.g. iron, zinc, vitamin A) can impair immune function. Convincing evidence that so-called “immune-

boosting” supplements such as glutamine, echinacea, and probiotics prevent exercise-induced immune impairment is currently lacking. Current evidence regarding the efficacy of such supplements in preventing or treating common infections is limited (particularly in athletes), and there is insufficient evidence to recommend these supplements at this time.

It is still debatable whether antioxidant supplements are required or desirable for athletes. There is conflicting evidence of the effects of high-dose vitamin C in reducing post-exercise incidence of URTI, and this practice has not yet been shown to prevent exercise-induced immune impairment. Elevations of vitamin E intake up to about 200 mg/d seem to be effective in reducing URTI incidence in the general population, and several recent studies indicate that several weeks of antioxidant vitamin (C and E) supplementation can attenuate stress hormone and cytokine responses to prolonged exercise.

Thus, the answer to the question posed in the title of this paper is that appropriate nutrition can go some way in limiting exercise-induced immunodepression, but this remains a fertile area for future research.

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