

POTENTIAL NUTRITIONAL COUNTERMEASURES TO EXERCISE-INDUCED IMMUNOSUPPRESSION

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ABSTRACT

In contrast to moderate physical activity, prolonged and intensive exertion causes numerous changes in immunity that reflect physiologic stress and suppression, and an increased risk of upper respiratory tract infection. In that multiple enzymes in immune cells require the presence of micronutrients, attempts have been made to alter changes in immunity following heavy exertion through use of nutritional supplements, primarily zinc, dietary fat, vitamin C and other antioxidants, glutamine, and carbohydrate. Except for carbohydrate supplementation, none of these nutrients has emerged as an effective countermeasure to exercise-induced immunosuppression. Data from several studies of endurance athletes suggest that carbohydrate compared to placebo ingestion is associated with an attenuated cortisol, growth hormone, and epinephrine response to heavy exertion, 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 compared to placebo ingestion suggest that physiologic stress is diminished, although clinical significance awaits further research.

Key words: immunology, infection, cytokines, carbohydrate, antioxidants, glutamine

Introduction

Exercise immunology is a relatively new area of scientific endeavor, with 80% of articles published during the past decade. Growing evidence indicates that physical activity does influence immune function and as a consequence risk of upper respiratory tract infections (URTI). This article will summarize recent investigations showing that in contrast to moderate physical activity, prolonged and intensive exertion causes numerous negative changes in immunity and an increased risk of URTI. Immune cells require glucose and glutamine for fuel, and the presence of micronutrients for enzymatic reactions. This article will review attempts by investigators to use nutritional supplements

as countermeasures to changes in immunity following heavy exertion.

Moderate physical activity

People who exercise regularly report fewer colds than their sedentary peers. Numerous surveys of fitness enthusiasts, runners, and masters athletes indicate that between 60% and 90% feel that they experience fewer colds than their sedentary peers (20, 43).

Data from three randomized studies support the viewpoint that near-daily physical activity reduces the number of days with sickness (25, 33, 34). In these studies, women in the exercise groups walked briskly 35–45 minutes, five days a week, for 12–15 weeks during the winter/spring or fall, while the con-

trol groups remained physically inactive. The results were in the same direction reported by fitness enthusiasts - walkers experienced about half the days with cold symptoms of the sedentary controls. A recent one-year epidemiological study of 547 adults demonstrated a 23% reduction in risk of URTI in those engaging in regular versus irregular moderate-to-vigorous physical activity (15). In healthy elderly subjects, URTI symptomatology during a one-year period was inversely related to energy expended during moderate physical activity (10). In Project PRIME, a randomized clinical trial that investigated interventions to increase physical activity, the odds ratio for reporting URTI symptoms was 0.50 (95% C.I., 0.28 to 0.91) among participants who engaged in a minimum of 150 minutes per week of moderate and vigorous activity compared with less active participants (44).

Other research has shown that during moderate exercise, several positive changes occur in the immune system (18, 27, 28, 29). Stress hormones, which can suppress immunity, and pro- and anti-inflammatory cytokines, indicative of intense metabolic activity, are not elevated during moderate exercise. Although the immune system returns to pre-exercise levels very quickly after the exercise session is over, each session represents a boost in immune surveillance that appears to reduce the risk of infection over the long term.

Although public health recommendations must be considered tentative, the data on the relationship between moderate exercise, enhanced immunity, and lowered risk of sickness are consistent with guidelines urging the general public to engage in near-daily brisk walking.

Is the endurance athlete at risk for respiratory infection and immune suppression?

A common perception among elite endurance athletes and coaches is that overtraining lowers resistance to URTI such as

the common cold and sore throats (20). In a 1996 survey conducted by the Gatorade Sports Science Institute, 89% of 2,700 high school and college coaches and athletic trainers checked "yes" to the question, "Do you believe overtraining can compromise the immune system and make athletes sick?" (Personal communication, 1997, Gatorade Sports Science Institute, Barrington, IL).

The results of epidemiological studies generally support the belief that URTI risk is elevated during periods of heavy training and in the 1-2 week period following participation in competitive endurance races (26). A high percentage of self-reported illnesses occur when elite athletes exceed individually identifiable training thresholds, mostly related to the strain of training (2). The majority of endurance athletes, however, do not report URTI after competitive race events. For example, only one in seven marathon runners reported an episode of URTI during the week following the March 1987, Los Angeles Marathon, compared to two in 100 who did not compete (26). URTI rates in marathon runners are even lower during the summer than winter/spring. In a study of 170 experienced marathon runners, only 3% reported an URTI during the week after a July marathon race event. (Unpublished data, author, 1993). When athletes train hard, but avoid overreaching and overtraining, URTI risk is typically unaltered. For example, during a 2.5 month period (winter/spring) in which elite female rowers trained 2-3 hours daily (rowing drills, resistance training), incidence of URTI did not vary significantly from that of nonathletic controls (30).

Together, these data indicate that there is a relationship between exercise workload and infection. Most endurance athletes should experience low-to-normal URTI risk during periods of regular training, with URTI risk rising during periods of overreaching/overtraining and competition.

Is immune function in athletes modified in parallel with infection risk? Two lines of investigation have provided insights both supporting and challenging this assumption (27):

- Do the immune systems of endurance athletes and nonathletes function differently when in a state of rest?
- Does heavy exertion lead to temporary but clinically significant changes in immunity (i.e., the "open window" theory).

Resting immune function in athletes and non-athletes

The immune system is a remarkably adaptive in its defense capabilities. It is able to generate an enormous variety of cells and molecules capable of recognizing and eliminating a limitless variety of foreign invaders (12). Attempts thus far to compare resting immune function in athletes and nonathletes have failed to provide evidence that athletic endeavor is linked to clinically important changes in immunity, despite compelling epidemiological data (21, 25, 30, 45). Of all immune measures, only NK cell activity has emerged as a somewhat consistent indicator differentiating the immune systems of athletes and nonathletes. NK cells are highly active cells that combat certain types of viruses and cancer cells. In a study comparing elite female rowers and controls, NK cell activity measured 1.6-fold higher in the rowers (30). Elevated NK cell activity has also been reported in runners and cyclists (21, 45).

Neutrophils are important components of the innate immune system, aiding in the phagocytosis of many bacterial and viral pathogens, and the release of immunomodulatory cytokines. Neutrophils are considered to be the body's most effective phagocyte, and are critical in the early control of invading infectious agents. Neutrophil function has been reported to be suppressed in athletes, but this has not been a con-

sistent finding, and may depend on the severity of training (12).

Attempts thus far to link variances in both neutrophil function and NK cell activity with risk of infection have failed. Salivary IgA concentration warrants further research as a practical and inexpensive marker of potential infection risk in athletes. The secretory immune system of the mucosal tissues of the upper respiratory tract is considered the first barrier to colonization by pathogens, with IgA the major effector of host defense (12). In a study by Gleeson et al. (5), 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 preseason and the mean pretraining salivary IgA levels. With runners, sickness rates following a competitive marathon race have been observed to be highest in those exhibiting the lowest salivary IgA levels (24). In two other studies, however, variance in salivary IgA concentration was not related to a history of URTI incidence in elite female rowers or adolescent tennis athletes (7, 17). Thus the data are inconclusive, and research is needed with larger groups of athletes followed for longer periods of time to determine the usefulness of salivary IgA concentration in predicting URTI risk in athletes.

Changes in immunity following prolonged, intensive exercise

The magnitude of change in immunity that occurs after each bout of prolonged and intensive exercise in athletes may have more clinical significance than training-induced alterations in resting immunity. During this "open window" of altered immunity (which may last between three and 72 hours, depending on the immune measure), viruses and bacteria may gain a fo-

threshold, increasing the risk of subclinical and clinical infection. Investigations are currently underway to demonstrate that athletes showing the most extreme immune suppression 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 studies with animal models have provided important support of the "open window" theory. Davis et al. (1), for example, have shown that in mice alveolar macrophage antiviral resistance is suppressed 8 h following prolonged strenuous exercise to fatigue, an effect due in part to an increase in circulating adrenal catecholamines.

Many components of the immune system exhibit change after heavy exertion, including the following (for review, see: 12, 19):

- Neutrophilia (high blood neutrophil counts) and lymphopenia (low blood lymphocyte counts), induced by high plasma catecholamines, growth hormone, and cortisol.
- 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 and blood granulocyte oxidative burst activity.
- Decrease in NK cell cytotoxic activity (an important anti-viral measure), and mitogen-induced lymphocyte proliferation (a measure of T cell function).
- Decrease in the delayed-type hypersensitivity response (DTH). DTH is a complex immunological process which involves several different cell types (including T lymphocytes) and chemical mediators, and is manifested by firm, red skin indurations.
- Increase in plasma concentrations of pro- and anti-inflammatory cytokines (e.g., tumor necrosis factor alpha (TNF- α), in-

terleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-1 receptor antagonist (IL-1ra)). Cytokines are low molecular-weight proteins and peptides which help control and mediate interactions among cells involved in immune responses. Prolonged and intensive exercise bouts induce muscle cell injury, causing a sequential release of pro- and anti-inflammatory cytokines

- Decrease in *ex vivo* production of cytokines (interferon gamma (IFN- α), TNF- α , IL-1, IL-2, IL-6, and IL-10) in response to mitogens and endotoxin. This indicates a reduced capacity of the body's immune system to produce cytokines after heavy exertion.
- Decrease in nasal and salivary IgA concentration, and nasal mucociliary clearance. This indicates an impaired ability of the upper respiratory tract to clear external pathogens.
- Blunted major histocompatibility complex (MHC) II expression and antigen presentation in macrophages. The MHC antigens are essential for reactions of immune recognition. After phagocytosis and antigen processing, small antigenic peptides are bound to MHC II and presented to T lymphocytes, an important step in adaptive immunity. Thus heavy exertion blunts macrophage expression of MHC II, negatively affecting the process of antigen presentation to T lymphocytes, and thus their ability to respond to a challenge by viruses.

These data suggest that immune function in several body compartments exhibits signs of stress or suppression for a short period following prolonged endurance exercise. Thus it makes sense 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 inc-

cluding lack of sleep, severe mental stress, malnutrition, or weight loss. A one-year retrospective study of 852 German athletes showed that risk of URTI was highest in endurance athletes who also reported significant stress and sleep deprivation (9). In other words, URTI risk is related to many factors, and when brought together during travel to important competitive events, the athlete may be unusually susceptible.

Guidelines for the athlete to reduce the risk of infection

To counter this increased risk of URTI, the athlete should consider these guidelines, each of which has a separate connection to the immune system and host protection against pathogens (12, 20):

- Keep other life stresses to a minimum (mental stress in and of itself has been linked to increased URTI risk).
- Eat a well-balanced diet to keep vitamin and mineral pools in the body at optimal levels.
- Avoid overtraining and chronic fatigue.
- Obtain adequate sleep on a regular schedule (disruption has been linked to suppressed immunity).
- Avoid rapid weight loss (has been related to adverse immune changes).
- Avoid putting the hands to the eyes and nose (a major route of viral self-innoculation).
- Before important race events, avoid sick people and large crowds when possible.
- Influenza vaccination is recommended for athletes competing during the winter months.

Rest or exercise when sick?

Athletes and fitness enthusiasts are often uncertain of whether they should exercise or rest during sickness. Human studies are lacking to provide definitive answers. Animal studies, however, generally support the finding that one or two

periods of exhaustive exercise following injection of the animal with certain types of viruses or bacteria lead to a more frequent appearance of infection and more severe symptoms (1, 6).

With athletes, it is well established that the ability to compete is reduced during sickness (3). Also, several case histories have shown that sudden and unexplained downturns in athletic performance can sometimes be traced to a recent bout of sickness. In some athletes, exercising when sick can lead to a severely debilitating state known as "post-viral fatigue syndrome" (14, 37). The symptoms can persist for several months, and include weakness, inability to train hard, easy fatiguability, frequent infections, and depression.

Concerning exercising when sick, most clinical authorities in the area of exercise immunology recommend (3, 12):

- If one has common cold symptoms (e.g., runny nose and sore throat without fever or general body aches and pains), intensive exercise training may be safely resumed a few days after the resolution of symptoms.
- Mild-to-moderate exercise (e.g., walking) when sick with the common cold does not appear to be harmful. In two studies using nasal sprays of a rhinovirus leading to common cold symptoms, subjects were able to engage in exercise during the course of the illness without any negative effects on severity of symptoms or performance capability (46, 47).
- With symptoms of fever, extreme tiredness, muscle aches, and swollen lymph glands, 2-4 weeks should probably be allowed before resumption of intensive training.

Nutritional countermeasures

Nutrition impacts the development of the immune system, both in the growing fetus and in the early months of life. Nu-

trients are also necessary for the immune response to pathogens so that cells can divide and produce antibodies and cytokines. Many enzymes in immune cells require the presence of micronutrients, and critical roles have been defined for zinc, iron, copper, selenium, vitamins A, B₆, C, and E in the maintenance of optimum immune function (35). The earliest research on nutrition and immune function focused on malnutrition. It has long been known that malnourished children have a high risk of severe and life-threatening infections. Protein-energy malnutrition adversely affects virtually all components of the immune system.

Although endurance athletes may be at increased infection risk during heavy training or competitive cycles, they must exercise intensively to contend successfully. Athletes appear less interested in reducing training workloads, and more receptive to ingesting drugs or nutrient supplements that have the potential to counter exercise-induced inflammation and immune alterations. There is some preliminary data that various immunomodulator drugs may afford athletes some protection against inflammation, negative immune changes, and infection during competitive cycles, but much more research is needed before any of these can be recommended (41).

The influence of a growing list of nutritional supplements on the immune and infection response to intense and prolonged exercise has been assessed (35). Supplements studied thus far include zinc, dietary fat, plant sterols, antioxidants (e.g., vitamins C and E, β -carotene, N-acetylcysteine, and butylated hydroxyanisole), glutamine, and carbohydrate.

Antioxidants

Can antioxidant supplements attenuate exercise-induced changes in immune function and infection risk (23, 36)? Several

double-blind placebo studies of South African ultramarathon runners have demonstrated that vitamin C (but not E or β -carotene) supplementation (about 600 mg/day for three weeks) is related to fewer reports of URTI symptoms (38, 39). This has not been replicated, however, by other research teams. Himmelstein et al. (8), for example, reported no alteration in URTI incidence among 44 marathon runners and 48 sedentary subjects randomly assigned to a two-month regimen of 1000 mg/day of vitamin C or placebo. Three of four studies have been unable to demonstrate that vitamin C or antioxidant supplements modulate immune responses following heavy exertion (11, 23, 35, 40).

Glutamine

Glutamine, a nonessential amino acid, has attracted much attention by investigators (13, 42). Glutamine is the most abundant amino acid in the body, and is synthesized by skeletal muscle and other tissues. Glutamine is an important fuel for lymphocytes and monocytes, and decreased amounts *in vitro* 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. Since skeletal muscle is the major tissue involved in glutamine production and is known to release glutamine into the blood compartment at a high rate, it has been hypothesized that muscle activity may directly influence the immune system by altering the availability of this immune cell fuel substrate.

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 (35). For example, in a crossover, placebo-controlled study of

eight males, glutamine supplementation abolished the postexercise decrease in plasma glutamine concentration but still had no influence relative to placebo on exercise-induced decreases in T and natural killer cell function (42).

One problem with the glutamine hypothesis is that plasma concentrations following exercise do not decrease below threshold levels that are detrimental to lymphocyte function as demarcated by *in vitro* experiments. In other words, even marathon-type exertion does not deplete the large body stores of glutamine enough to diminish lymphocyte function.

Carbohydrate supplements

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 (16). Given the link between stress hormones and immune responses to prolonged and intensive exercise, carbohydrate com-

pared to placebo ingestion should maintain plasma glucose concentrations, attenuate increases in stress hormones, and thereby diminish changes in immunity (as summarized in the model in Figure 3). Carbohydrate supplementation may also alter immunity following exercise by increasing the availability of energy substrate to immune cells. Glucose is the major energy substrate for immune cells.

Several studies with runners and cyclists have shown that carbohydrate beverage ingestion plays a role in attenuating changes in immunity when the athlete experiences physiologic stress and depletion of carbohydrate stores in response to high intensity ($\sim 75\text{--}80\%$ $\dot{V}O_2\text{max}$) exercise bouts lasting longer than two hours (4, 22, 31, 32). In particular, carbohydrate ingestion (about one liter per hour of a typical sports drink) compared to a placebo has been linked to significantly lower blood cortisol and epinephrine levels, a reduced change in blood immune cell counts, and lower pro- and anti-inflammatory cytokines. These data suggest that the endurance athlete ingesting carbohydrate during the race event should experience a much lo-

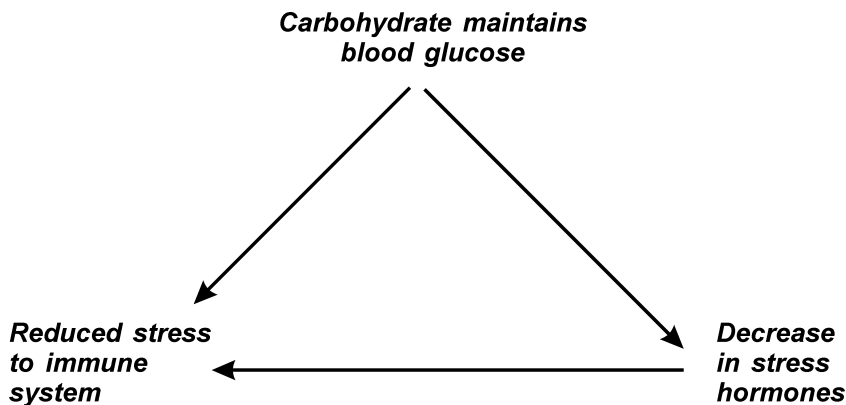


Figure 1. This model suggests that carbohydrate supplementation during prolonged and intensive exercise maintains or elevates plasma glucose concentrations, attenuating the normal rise in stress hormones, and thereby countering negative immune changes. Carbohydrate ingestion may also affect immune function by increasing the availability of glucose as a fuel substrate for immune cells.

wer perturbation in hormonal and immune measures compared to the athlete largely avoiding carbohydrate.

Conclusions and recommendations

1. By far, the most important finding that has emerged from exercise immunology studies is that positive immune changes take place during each bout of moderate physical activity. Over time, this translates to fewer days of sickness with the common cold and other upper respiratory tract infections. This is consistent with public health guidelines urging individuals to engage in near-daily physical activity of 30 minutes or greater.
2. Risk of upper respiratory tract infections can increase when athletes push beyond normal limits. The infection risk is amplified when other factors related to immune function are present, including exposure to novel pathogens during travel, lack of sleep, severe mental stress, malnutrition, or weight loss.
3. Many components of the immune system exhibit adverse change after prolonged, heavy exertion lasting longer than 90 minutes. These immune changes occur in several compartments of the immune system and body (e.g., the skin, upper respiratory tract mucosal tissue, lung, blood, and muscle). During this "open window" of impaired immunity (which may last between three and 72 hours, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection.
4. Should the athlete exercise when sick? In general, if the symptoms are from the neck up (e.g., the common cold), moderate exercise is probably acceptable and some researchers would argue even beneficial, while bedrest and a gradual progression to normal training are recommended when the illness is system-

mic (e.g., the flu). If in doubt as to the type of infectious illness, individuals should consult a physician.

5. The influence of nutritional supplements on the acute immune response to prolonged exercise has been measured in endurance athletes. Antioxidants and glutamine have received much attention, but the data thus far do not support their role in negating immune changes after heavy exertion. At this point, athletes should eat a varied and balanced diet in accordance with the Food Guide Pyramid and energy needs, and be assured that vitamin and mineral intake is adequate for both health and immune function.
6. Ingestion of a typical sports drink, about one liter per hour of exertion, has been associated with higher plasma glucose levels, an attenuated cortisol and growth hormone response, fewer perturbations in blood immune cell counts, 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 during intense exertion lasting 90 minutes or more.

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