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Nutritional strategies to counter stress to the immune system in athletes, with special reference to football

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Abstract
Although epidemiological data indicate that athletes are at increased risk of upper respiratory tract infection during periods of heavy training and the 1–2 week period following endurance race events, there is very limited information on the responses to football training and match-play. For several hours after heavy exertion, components of both the innate (e.g. natural killer cell activity and neutrophil oxidative burst activity) and adaptive (e.g. T and B cell function) immune system exhibit suppressed function. Although such responses to football training and competition do not appear to be as pronounced, variations in immune cell numbers and function are reported in professional footballers over the course of a season. Attempts have been made through nutritional means (e.g. glutamine, vitamins C and E, and carbohydrate supplementation) to attenuate immune changes following intensive exercise and thus lower the risk of upper respiratory tract infection. Carbohydrate supplementation during heavy exercise has emerged as a partial countermeasure and attenuates increases in blood neutrophil counts, stress hormones, and inflammatory cytokines, but has little effect on decrements in salivary IgA output or natural killer cell function. Animal research indicates that other nutritional components such as beta-glucan, quercetin, and curcumin warrant human investigations to determine if they are effective countermeasures to exercise-induced immune dysfunction.

Keywords: *Exercise, lymphocytes, neutrophils, cytokines, antioxidants, carbohydrate*

Introduction

Mounting evidence indicates that physical activity influences immune function and risk of certain types of infection, such as upper respiratory tract infections (URTI). In contrast to moderate physical activity, prolonged and intensive exertion causes numerous negative changes in immunity and an increased risk of URTI. Footballers, as elite athletes, must train intensively to compete at the highest levels and therefore may also be at increased risk of URTI and suppressed immune function. There is a growing interest in potential nutritional countermeasures to exercise-induced immune dysfunction. This article is a current review of these nutritional countermeasures. To date, only a few studies have observed susceptibility for URTI and immunological changes in professional footballers (with fewer still examining nutritional countermeasures); most studies in this area have been conducted on endurance athletes. However, wherever possible data will be highlighted from footballers collected over a season or in response to a match, or from studies employing football-specific protocols. Where this is not possible, any extrapolation of findings from endurance athletes to football play should be made with caution, since the physiological demands of football training and play are not necessarily the same as those of endurance training and competition. This highlights the need for further football-specific research in this area.

Exercise, immunity, and URTI risk

Although the relationship between exercise and URTI and other types of infections has been explored since early in the twentieth century (Baetjer, 1932), the number of well-designed epidemiological and exercise training experimental trials on humans is still small, limiting our understanding of this important topic (Nieman, 1997a, 2003).

There is a common belief among fitness enthusiasts that regular exercise confers resistance against URTI. A survey of 750 masters athletes (ranging in age from

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40 to 81 years) showed that 76% perceived themselves as less vulnerable to viral illnesses than their sedentary peers (Shephard, Kavanagh, Mertens, Qureshi, & Clark, 1995). Three epidemiological studies (Kostka, Berthouze, Lacour, & Bonnefoy, 2000; Matthews *et al.*, 2002; Strasner, Barlow, Kampert, & Dunn, 2001) and three randomized experimental trials (Nieman *et al.*, 1990b, 1993, 1998a) have provided important data in support of the value of frequent and moderate physical activity in reducing URTI risk. Other studies indicate that during moderate exercise or vigorous exercise that incorporate rest intervals, several positive changes occur in the immune system (Nehlsen-Cannarella *et al.*, 1991; Nieman, 2000; Nieman & Nehlsen-Cannarella, 1994; Nieman, Henson, Austin, & Brown, 2005b).

In contrast to the benefits of moderate physical activity, a common perception among elite athletes and their coaches is that heavy exertion and overtraining lead to immune dysfunction and an elevated risk of URTI. A growing number of epidemiological investigations support this belief and will be reviewed in the next section. Data from animal studies have been difficult to apply to the human condition, but in general have supported the finding that one or two periods of exhaustive exercise following inoculation leads to a more frequent appearance of infection and a higher fatality rate (but results differ depending on the pathogen, with some more affected by exercise than others) (Davis *et al.*, 1997; Pedersen & Bruunsgaard, 1995).

Heavy exertion and URTI: Epidemiological evidence

The relationship between exercise and URTI may be modelled in the form of a ''J'' curve (Nieman, 1997a). This model suggests that although the risk of URTI may decrease below that of a sedentary individual when one engages in moderate exercise training, risk may rise above average during periods of excessive amounts of high-intensity exercise.

The ''J'' curve model also suggests that immunosurveillance mirrors the relationship between infection risk and exercise workload. In other words, it makes sense that if regular moderate exercise lowers infection risk, it should be accompanied by enhanced immunosurveillance. On the other hand, when an athlete engages in unusually heavy exercise workloads (e.g. overtraining, a competitive endurance race event, or even heavy match schedules), infection risk should be related to diminished immunosurveillance.

Much more research using larger pools of participants and improved research designs is necessary before this model can be wholly accepted or rejected. The epidemiological studies used self-reported URTI data (primarily retrospective, with two studies using one-year daily logs). Few have attempted to verify symptomatology using viral identification or verification by physicians. There is some concern that the symptoms reported by endurance athletes following competitive race events may reflect those associated with an inflammatory response rather than URTI (Castell *et al.*, 1997; Drenth *et al.*, 1995; Nehlsen-Cannarella *et al.*, 1997).

With these limitations in mind, several epidemiological reports suggest that athletes who engage in marathon-type events and/or very heavy training are at increased risk of URTI. Nieman, Johanssen, Lee, Cermal and Arabatzis (1990a) reported that 12.9% of marathon runners reported URTI during the week following the Los Angeles Marathon compared with 2.2% of control marathon runners (odds ratio = 5.9). Forty percent of the runners reported at least one URTI episode during the 2 month winter period before the marathon race. Controlling for various confounding factors, it was determined that runners training more than 96 km $\cdot$ week^{-1} doubled their odds for sickness compared with those training less than 32 km $\cdot$ week^{-1}. Similar results have been reported by Heath *et al.* (1991), Linde (1987), Nieman *et al.* (2002a, 2003b, in press), and Peters and colleagues (Peters, 1990; Peters & Bateman, 1983; Peters, Goetzsche, Grobbelaar, & Noakes, 1993; Peters, Goetzsche, Joseph, & Noakes, 1996; Peters-Futre, 1997). Risk of URTI following a race event may depend on the distance, with an increased incidence conspicuous only following a marathon or ultramarathon (Nieman, Johanssen, & Lee, 1989). With this is mind, the question arises of how relevant these findings are to football training and match-play. Unfortunately, research to assess this is limited. Nevertheless, one small study of 15 top league professional Belgian footballers over a season showed a higher incidence of URTI compared with untrained controls (Bury, Marechal, Mahieu, & Pirnay, 1998). Over a year (July to July), 22 episodes of URTI were diagnosed by a respiratory physician in the footballers, with only 9 episodes diagnosed in the control group. The majority of the infections in players were diagnosed during the winter months, which is in line with usual seasonal variations in URTI rates. Interestingly, this period also coincided with the main part of the competitive season, when it may be speculated that physiological demands on players were increased (although no training or match data were reported by the authors).

Together, these epidemiological studies imply that heavy acute or chronic exercise is associated with an increased risk of URTI. Thus it makes sense that URTI risk may be increased when an 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. 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 (Konig, Grathwohl, Weinstock, Northoff, & Berg, 2000). 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. This could be of equal relevance to professional footballers, particularly during periods of fixture congestion with domestic, regional, and international competitions taking place. Furthermore, other factors also play an important role in a player's susceptibility for URTI. Being in close proximity with other players who may have or be incubating a cold-causing virus through shared accommodation, changing facilities, and the practice of sharing drinking bottles during training and matches will increase exposure to the viruses that cause URTI.

Most 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 (Nieman *et al.*, 1990a). When athletes train hard, but avoid overreaching and overtraining, URTI risk is typically unaltered. For example, during a 2½ month period (winter/spring) in which elite female rowers trained $2-3\ \mathrm{h}\cdot\mathrm{day}^{-1}$ (rowing drills, resistance training), the incidence of URTI did not vary significantly from that of non-athletic controls (Nieman *et al.*, 2000a).

Exercise-induced changes in immune function

Together, these data imply that there is a relationship between exercise and infection, and that heavy exertion may suppress various components of immunity. Research data on the resting immunity of athletes and non-athletes, however, are limited and present a confusing picture at present (Nieman, 1997b). For example, the few studies available suggest that the innate immune system responds differentially to the chronic stress of intensive exercise, with natural killer cell activity tending to be enhanced while neutrophil function is suppressed (Nieman *et al.*, 1995b, 1999; Pyne, Baker, Fricker, McDonald, & Nelson, 1995; Smith & Pyne, 1997). The adaptive immune system (resting state) in general seems to be largely unaffected by athletic endeavour.

Each acute bout of cardiorespiratory endurance exercise leads to transient but significant changes in immunity and host defence (Gabriel & Kindermann, 1997; Hoffman-Goetz and Pedersen, 1994; Nieman *et al.*, 1997b, 2002a, 2003a, 2004; Pedersen & Brunsgaard, 1995; Petersen & Pedersen, 2005). Natural killer cell activity, various measures of T and B cell function, upper airway neutrophil function, and salivary IgA concentration have all been reported to be suppressed for at least several hours during recovery from prolonged, intense endurance exercise (Bruunsgaard *et al.*, 1997; Gabriel & Kindermann, 1997; Mackinnon & Hooper, 1994; Müns 1993; Nieman *et al.*, 1995a, 1995c, 2001, 2003b; Shinkai *et al.*, 1993).

Compared with endurance events, only a few papers have examined immunological changes in professional footballers. Bury *et al.* (1998) found no effect of a competitive season on total numbers of leukocytes, but did observe an increase in numbers of circulating neutrophils and a decrease in the numbers of total lymphocytes (accounted for by an decrease in CD^+ T lymphocytes and resulting in a decrease in the CD4/CD8 ratio) over the course of the season. Furthermore, significant falls in both neutrophil chemotaxis and phagocytosis and in PHA-stimulated T lymphocyte proliferation were reported. However, there was little change in NK cell number or cytotoxity during the season. Rebelo *et al.* (1998) also observed increases in neutrophil numbers and a fall in the CD4/CD8 ratio in 13 professional Portuguese players at the end of a competitive season compared with pre-season values. More recently, Gleeson (2004) monitored immune changes of 18 members of the first team squad of an English Premier League team that was involved in the European Champions League in addition to domestic competition. In this study, no changes in neutrophils, lymphocytes, or CD4/CD8 ratio were found yet a decrease in NK cell numbers was observed, in contrast to the findings of Bury *et al.* (1998) and Rebelo *et al.* (1998). Furthermore, during the season, the numbers of $CD45RO^+$ T lymphocytes (a mixture of memory cells, important in long-term recognition of antigens and in generating the adaptive response to recall antigens, and short-term activated T cells) fell significantly, with very low levels recorded by the end of the season. The numbers of $CD45RA^+$ T lymphocytes (naïve cells that have not yet encountered antigen) increased. The fall in $CD45RO^+$ cells and NK cells can be viewed as potentially disadvantageous to the body's defence against viral pathogens, such as URTI (Gleeson, 2004). Interestingly, salivary IgA concentration and MHCII expression on monocytes were also lowest at the time when form (wins/losses ratio and league position) was at its lowest. Finally, Malm, Ekblom and Ekblom (2004a) found that a 5 day football training camp for Swedish elite junior footballers resulted in decreases in T and B

lymphocytes, but no change in total leukocytes and NK cells compared with values before the camp.

A few studies have investigated the acute effects of football play following matches (Malm, Ekblom, & Ekblom 2004b) or in response to field or laboratory-based tests designed to simulate the activity patterns and physiological demands of football (Bishop, Blannin, Robson, Walsh, & Gleeson, 1999; Bishop, Gleeson, Nicholas, & Ali, 2002; Bishop *et al*., 2005). In these studies, increases in numbers of circulating neutrophils, lymphocytes and lymphocyte subsets, leukocyte adhesion molecules, and plasma levels of IL-6 have been observed after exercise, in addition to decreases in neutrophil function. However, the magnitude of these alterations is not as great as that observed following endurance-type events, even when exercise was performed following an overnight fast (Bishop *et al*., 1999, 2002, 2005). Two of these studies have looked at the effect of match or simulated play on consecutive days on immunological measures: Bishop *et al*. (2005) found that lymphocyte proliferation responses following exposure to influenza were unaffected by the exercise on the first day but were significantly lower before exercise on the second day compared with the same time on day 1. On both days, exercise was performed at the same time of day. Malm *et al*. (2004b) reported reduced expression of lymphocyte adhesion and signalling molecules 6 h after the second of two games played 20 h apart. Unfortunately, this study did not take any measurements after the first game or immediately before the second game, making it difficult to assess the extent of any ''carry-over'' from the first game. Furthermore, the games were held at different times of day and thus it could be argued that diurnal changes may have had some influence on the results.

It is suggested that alterations in immune measures observed following intensive exercise create an ''open window'' of decreased host protection, during which viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection (Figure 1). Although this is an attractive hypothesis, no one has yet demonstrated conclusively that athletes showing the most extreme immunosuppression are those that contract an infection (Lee, Meehan, Robinson, Mabry, & Smith, 1992; Mackinnon, Ginn, & Seymour, 1993). In one study, salivary IgA secretion rate decreased by nearly half in a group of 155 ultramarathon runners following a 160 km race (Nieman *et al*., 2005c). Nearly one in four runners reported an URTI episode during the 2 weeks following the race, and the decrease in sIgA secretion rate was significantly greater in these runners (54%) than in those not reporting URTI (31%). It is doubtful, however, that sIgA output alone can be used to predict URTI at the individual athlete level. In this study, the overall predictive value for URTI was 55%, indicating that sIgA output was more useful at the group than the individual level, and that other factors need to be discovered and combined with sIgA before URTI risk can be predicted for individual athletes.

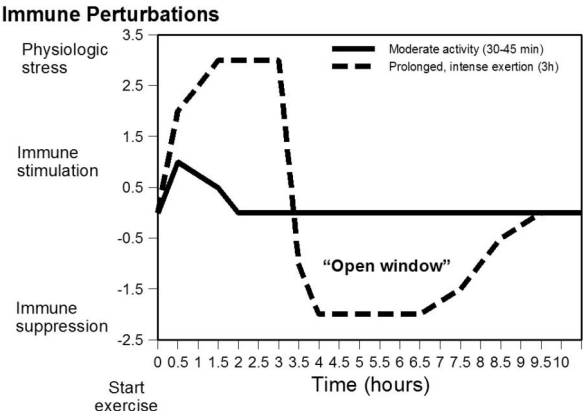

Figure 1. The ''open window theory''. Moderate exercise causes mild immune changes; in contrast, prolonged, intensive exercise (90 min or longer) leads to a downturn in immunosurveillance that increases the likelihood for opportunistic upper respiratory tract infections.

Nutritional countermeasure strategies

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

Nutritional immunology is a rapidly growing area of scientific scrutiny, and four key principles have emerged:

1. Almost all nutrients in the diet play a crucial role in maintaining an ''optimal'' immune response (Calder & Kew, 2002). A varied, healthy diet provides all the nutrients needed for good immune function in most healthy adults, and vitamin/mineral supplements do not ''boost'' immunity above normal levels.
2. Deficient intakes of energy and nutrients can have negative consequences on immune status and susceptibility to pathogens. Protein-energy-malnutrition (PEM) causes a downturn in most aspects of immune function and strongly increases the risk of various types of infection (Keusch, 2003).

3. Some nutrients (i.e. glutamine, arginine, fatty acids, vitamin E) provide additional benefits to immunocompromised persons (i.e. the frail elderly) or patients who suffer from various infections, and is now called ''immunonutrition'' (Calder, 2004; Grimble, 2005).
4. Advanced supplements may prove useful in countering immune suppression for healthy adults during unusual mental and physical stress (Hamer, Wolvers, & Albers, 2004). For example, dietary beta-glucans shift inflammatory profiles to a Th1 type and thus enhance resistance against bacterial and parasitic infections, n-3 fatty acids from fish oils (eicosapentaenoic acid and docosahexaenoic acid) dampen inflammatory responses, and Gingko biloba lowers NFκB and activator protein 1 activation, possibly due to its high content of polyphenols (Plat & Mensink, 2005).

The influence of nutritional supplements on the immune and infection response to intense and prolonged exercise is an active area of research by multiple investigators (Gleeson, Nieman, & Pedersen, 2004). Supplements studied thus far in humans include zinc, dietary fat, plant sterols, antioxidants (e.g. vitamins C and E, beta-carotene, *N*-acetylcysteine, and butylated hydroxyanisole), glutamine, and carbohydrate. Except for carbohydrate beverages, none of these supplements has emerged as an effective countermeasure to exercise-induced immune suppression (Gleeson *et al.*, 2004; Nieman, 2001; Nieman & Pedersen, 2000). Antioxidants and glutamine have received much attention, but the data thus far do not support their role in negating immune changes after heavy exertion.

Carbohydrate supplements

Research during the 1980s and early 1990s established that a reduction in blood glucose was linked to hypothalamic-pituitary-adrenal activation, an increased release of adrenocorticotrophic hormone and cortisol, increased plasma growth hormone, and increased plasma epinephrine concentrations (Murray, Paul, Seifert, & Eddy, 1991). Stress hormones have an intimate link with some aspects of immune function.

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$75–80% $\dot{V}O_{2max}$) exercise bouts lasting more than 90 min (Nehlsen-Cannarella *et al.*, 1997; Nieman *et al.*, 1997a, 1997c, 1998b, 2001, 2003a). In particular, carbohydrate ingestion (about one litre per hour of a typical sports drink) compared to a placebo has been linked to reduced change in blood immune cell counts, and lower pro- and anti-inflammatory cytokines. However, carbohydrate ingestion during intense and prolonged exercise is largely ineffective in countering post-exercise decrements in natural killer and salivary IgA output.

The average intensity of a football match is in the region of 70% $\dot{V}O_{2max}$ and laboratory-based protocols that closely simulate the activity patterns and physiological demands of football match-play have shown that carbohydrate ingestion compared to placebo can negate some of the immune responses associated with placebo ingestion (Bishop *et al.*, 2005). In response to a validated football-specific intermittent running protocol performed at the same time of day on consecutive days, carbohydrate ingestion was associated with lower post-exercise $CD3^+$ counts on both days. Furthermore, before exercise on the second day T lymphocyte proliferative responses to influenza were 80% higher with carbohydrate ingestion than placebo. Interestingly, these responses occurred despite no significant fall in plasma glucose concentration immediately after exercise with placebo ingestion and no effect of carbohydrate ingestion on cortisol responses to the exercise. This perhaps suggests that the role of cortisol is not as crucial as was originally thought. One note of caution to consider when extrapolating these findings to a true training session or match is that the exercise was performed following an overnight fast and so the magnitude of the alterations observed may be greater than might be seen had a pre-match meal been consumed.

These effects appear to be dependent on the average intensity of the exercise. Protocols in which the average intensity has been lower than that typically observed in competitive matches have found smaller changes in immune measures and little effect of carbohydrate ingestion on these (Bishop *et al.*, 1999). With this in mind, it is likely that immune responses to match-play could depend on an individual's playing position.

Overall, these data indicate that physiological stress to some aspects of the immune system is reduced when athletes use carbohydrate during intense exertion lasting 90 min or more. Does this mean that athletes using carbohydrate beverages during competitive events will lower their risk of sickness afterwards? One study in endurance athletes suggests this is so, but more research is needed (Nieman *et al.*, 2002a).

Antioxidants

Heavy exertion increases the generation of free radicals and reactive oxygen species (ROS) through several

pathways, including oxidative phosphorylation, an increase in catecholamines, prostanoid metabolism, xanthine oxidase, and NAD(P)H oxidase (Urso & Clarkson, 2003). Neutrophils and macrophages migrate to the site of contraction-induced muscle damage, infiltrate the muscle tissue, activate the release of cytokines, and produce additional ROS. Most ROS are neutralized by a sophisticated antioxidant defence system consisting of a variety of enzymes and non-enzymatic antioxidants including vitamin A, E, and C, glutathione, ubiquinone, and flavonoids. Intensive and sustained exercise, however, can create an imbalance between ROS and antioxidants, leading to oxidative stress that not only causes lipid peroxidation and protein oxidation, but may also impact immune function. A recent study of professional Polish footballers reported the presence of elevated levels of specific antibodies against oxidized low-density lipoproteins in 7 of the 11 players studied (Klapcińska *et al.*, 2005). This reflects enhanced oxidative stress, suggested by the authors to be induced by these players' regular participation in intensive physical training. Interestingly, this oxidative stress was evident despite their apparently normal blood antioxidant status.

Can taking additional antioxidant supplements attenuate exercise-induced changes in immune function and infection risk? Unfortunately, no studies in footballers have attempted to answer this question. However, several double-blind placebo studies of South African ultramarathon runners did demonstrate that vitamin C (but not E or beta-carotene) supplementation (about 600 mg $\cdot$ day^{-1} for 3 weeks) was related to fewer reports of URTI symptoms (Peters 1990; Peters & Bateman, 1983; Peters *et al.*, 1993, 1996; Peters-Futre, 1997). This has not been replicated, however, by other research teams. Himmelstein, Robergs, Koehler, Lewis and Qualls (1998), for example, reported no alteration in URTI incidence among 44 marathon runners and 48 sedentary individuals randomly assigned to a 2 month regimen of 1000 mg $\cdot$ day^{-1} of vitamin C or placebo. Most randomized, placebo-controlled studies have been unable to demonstrate that vitamin C supplements modulate immune responses following heavy exertion (Nieman *et al.*, 1997b, 2002b; Nieman, Peters, Henson, Nevines, & Thompson, 2000b).

Vitamin E functions primarily as a non-specific, chain-breaking antioxidant that prevents the propagation of lipid peroxidation. The vitamin is a peroxyl radical scavenger and protects polyunsaturated fatty acids within membrane phospholipids and in plasma lipoproteins. The effect of vitamin E supplementation on the inflammatory and immune response to intensive and prolonged exercise is largely unstudied and equivocal. Cannon *et al.* (1991) found that vitamin E supplementation of 800 IU $\cdot$ day^{-1} for 48 days attenuated endotoxin-induced IL-6 secretion from mononuclear cells for 12 days after running downhill on an inclined treadmill. Singh *et al.* (1999) showed no effect of vitamin E supplementation (4 days, 800 IU $\cdot$ day^{-1}) on the increase in plasma IL-6 following a 98 min treadmill run at 65–70% $\dot{V}O_{2max}$ to exhaustion. Petersen *et al.* (2002) reported no influence of vitamin E and C supplementation (500 mg and 400 mg, respectively, for 14 days before and 7 days after) on the plasma cytokine response to a 5% downhill 90 min treadmill run at 75% $\dot{V}O_{2max}$.

Two months of vitamin E supplementation at a dose of 800 IU/ $\cdot$ day^{-1} α-tocopherol did not affect increases in plasma cytokines, perturbations in other measures of immunity, or oxidative stress in triathletes competing in the Kona Triathlon World Championship race event (Nieman *et al.*, 2004). On the contrary, athletes in the vitamin E group experienced greater lipid peroxidation and increases in plasma levels of several cytokines than members of the placebo group following the triathlon. Despite these indications that vitamin E exerted pro-oxidant and pro-inflammatory effects, race performance did not differ between athletes in the vitamin E and placebo groups. In general, vitamin E supplementation to counter immune suppression and oxidative stress in endurance athletes cannot be recommended.

Glutamine

Glutamine, a non-essential amino acid, has attracted much attention by investigators (Mackinnon & Hooper, 1996; Rohde *et al.*, 1995; Rohde, MacLean, & Pedersen, 1998). 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 has 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. A reduction in URTI incidence rates has been reported following marathon race events in runners consuming beverages containing glutamine (Castell, Poortmans, & Newsholme, 1996; Castell *et al.*, 1997).

Whether exercise-induced reductions in plasma glutamine are linked to impaired immunity and host protection against viruses in athletes is still unclear, but the majority of studies have not favoured such a relationship (Nieman & Pedersen, 2000). For example, in a crossover, placebo-controlled study of eight males, glutamine supplementation abolished

the post-exercise decrease in plasma glutamine concentration but still had no influence relative to placebo on exercise-induced decreases in T and natural killer cell function (Rohde *et al.*, 1998).

One problem with the glutamine hypothesis is that plasma concentrations following exercise do not decrease below threshold values 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.

Nutritional components requiring further study in athletes

There are many nutritional components that have the potential to serve as countermeasures to immune dysfunction in athletes. Data from cellular and animal studies indicate that quercetin, beta-glucan, and curcumin warrant further testing in human athletes, and many other advanced supplements will be added to this list over the next decade.

Polyphenolic compounds are abundant throughout the plant kingdom and are found in a wide variety of human foods. The effects of dietary polyphenols are of great current interest due to their antioxidative, anti-inflammatory, and possible anti-carcinogenic activities (Gee & Johnson, 2001). The flavonoids, which are the best defined group of polyphenols in the human diet, comprise a large and complex group, all of which contain a three-ring structure with two aromatic centres and a central oxygenated heterocycle. Flavonoids provide much of the flavour and colour to fruits and vegetables. More than 5000 different flavonoids have been described (Ross & Kasum, 2002). There are six major subclasses of flavonoids, including flavonols, the subclass that includes quercetin. Epidemiological studies have shown flavonoid intake (mostly quercetin) to be inversely associated with mortality from cardiac heart disease. Quercetin is a potent antioxidant *in vitro*, and protection against the oxidative damage to LDL implicated in atherogenesis has been suggested as a possible mechanism (Wiseman, 1999). There is consistent evidence that quercetin may reduce the risk of lung cancer, and this may be due to its effects on cell cycle control and apoptosis (Neuhouser, 2004). Humans can absorb significant amounts of quercetin (particularly in the glucoside form) and it would appear to be sufficiently bioavailable to act as an antioxidant *in vivo* (Wiseman, 1999).

Quercetin regulates the expression of some genes including transcription factor nuclear factor-kappaB (NFκB) (Moskaug, Carlsen, Myhrstad, & Blomhoff, 2004). In one study, quercetin inhibited NFκB activation and diminished the induction of both pro-inflammatory cytokine transcription for IL-1beta, TNF-alpha, monocytes chemoattractant protein-1, and macrophage inflammatory protein-1 (Rangan, Wang, Tay, & Harris, 1999). In another study, rats fed 100 mg quercetin per kilogram of body mass daily for 7 weeks had significantly enhanced natural killer cell activity (NKCA) compared with controls (Exon, Magnuson, South, & Hendrix, 1998). Quercetin as a potent antioxidant may reduce free radical damage to tissues during exercise, and thus reduce NFκB activation of gene expression for IL-1beta and TNF-alpha. Thus there is some biologic plausibility that quercetin could influence immune function changes, inflammation, and oxidative stress in exercising humans, and studies have been initiated to determine if quercetin is an effective countermeasure.

Beta-glucan, a polysaccharide derived from the cell wall of yeast, fungi, algae, and oats, has well-documented immunostimulant properties. Beta-glucan can enhance the activities of both innate and specific immune function and has been shown to enhance the resistance to various viral, bacterial, protozoan, and fungal diseases, as well as to promote anti-tumour activity. A series of studies have shown that oral feedings of oat beta-glucan can offset exercise-induced immune suppression and decrease susceptibility to URTI and tumour metastasis in a mouse model of exhaustive exercise and short-term heavy training (Davis *et al.*, 2004; Murphy *et al.*, 2004). In one study, oat beta-glucan blocked the increase in morbidity and mortality after intranasal inoculation of herpes simplex virus type 1 (HSV-1) combined with treadmill running to fatigue for three consecutive days (Davis *et al.*, 2004). This protective effect was linked to an increase in macrophage antiviral resistance to HSV-1 but not NK cytotoxicity. Studies have been initiated to determine if this effect also occurs in human athletes.

Curcumin is the major curcuminoid in the Indian spice turmeric, and has potent anti-inflammatory activity. Ingestion of curcumin for 3 days prior to muscle-damaging downhill running attenuated muscle damage and hastened recovery of endurance performance in mice (J. M. Davis, personal communication). Curcumin may serve as a more effective anti-inflammatory than ibuprofen during and following heavy exertion, but research in human athletes is needed. Use of ibuprofen during ultra-marathon race events has been linked to elevated plasma cytokine and endotoxaemia (Nieman *et al.*, 2005a).

Conclusions

The risk of upper respiratory tract infection 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.

Many components of the immune system exhibit adverse change after prolonged, heavy exertion lasting more than 90 min. 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 3 and 72 h, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. Of the various nutritional countermeasures that have been evaluated thus far, ingestion of carbohydrate beverages during intense and prolonged exercise has emerged as the most effective. However, carbohydrate supplementation during exercise decreases exercise-induced increases in plasma cytokines and stress hormones, but is largely ineffective against other immune components including natural killer cell function and salivary IgA. Ongoing research will determine the value of other nutritional components in countering immune dysfunction in heavily exercising athletes.

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