Immunology, Nutrition, and the Athlete, Part II

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In Part I of *Immunology, Nutrition and the Athlete*, we addressed the phenomenon of exercise-induced immunosuppression and discussed how immunity is affected by endurance exercise in athletes in general. This article will focus on the known effects of diet, nutritional factors, and supplements that may be utilized to offset depressed immune function in athletes. Because the immunosuppression observed in these athletes is essentially stress-induced, many of these factors can be applied in much the same way to a healthy person with other, generalized "immune deficiencies". In fact, stress-related immunological perturbations in relation to exercise have spawned a large body of research into stress immunology and neuroimmunology.[1] Because of this, it is suggested that exercise serve as a model of transient immunosuppression that occurs following severe physical stress. This model allows for the investigation of the interactions between the endocrine, nervous and immune systems.

Immunosuppression in athletes who partake in physically demanding training or competition has multifactorial origins. Previously, we addressed some of the most well known hormonal and immunologic changes that detrimentally affect the well being of highly trained athletes. At the center of wellness, as in all populations, is proper nutrition. A diet lacking in adequate amounts of essential nutrients (and macronutrients) only serves to compound the negative influence of heavy exertion on the human body. Perhaps it is impossible to negate the compounded effects of the many factors contributing to exercise induced immunosuppression; however there are many choices available that demonstrate an ability to minimize the negative factors. Firstly, a sufficient, well balanced diet that meets energetic demands and one that also supplies adequate amounts of macronutrients (carbohydrate, protein, and fat) is the first step in preventing immunologic shortcomings. Disordered eating patterns during periods of training as well as excessive fluid replacement techniques occur at a high incidence in this group. The relatively common finding of less than optimal nutritional status in athletes definitely predisposes them to immunosuppression while specific deficiencies in macronutrients and certain micronutrients can lead to insufficient immune function as well. In addition, we will examine the efficacy of other nutrients and their use in preventing immunodeficiency in this group of people.

Glutamine

A conditionally essential amino acid, glutamine is the most abundant unbound amino acid in the body. Because certain tissues (intestine & immune) utilize larger amounts of glutamine during periods of stress, this amino acid has been studied as it applies to exercise-related immune function. Glutamine is also an effective treatment for gastrointestinal conditions, especially those involving mucosal tissue repair. Additionally, glutamine serves as an important source of fuel for lymphocytes and macrophages, and is consumed by these cells at high rates during times of rest as well.[2] Glutamine is produced primarily in skeletal muscle and is released into the blood stream at a rapid rate in times of need. Because of this, skeletal muscle and the glutamine it produces are thought to play a role in directly influencing the immune system.

Decreased levels of plasma glutamine resulting from muscular overuse are thought to affect the function of lymphocytes.[2] The “glutamine hypothesis” suggests that when the muscle is under intense physical stress, demands on it and other organs for glutamine leave the lymphoid system in a state of relative glutamine depletion. It is well known that glutamine concentration in the blood sharply declines following long-term physical stress[3], and low plasma glutamine levels are associated with overtraining.[4] Despite this evidence that glutamine plays an important role in lymphocyte function, a few studies [5,6] have demonstrated that supplementation with glutamine was able to halt the post exercise decline in glutamine *levels*, but did not significantly alter post exercise immunodeficiency. It is still unclear as to whether the amount of decrease in plasma glutamine is great enough to actually compromise immune cell function. And in some instances, speculation exists as to whether intracellular glutamine concentration is compromised as a result of decreased plasma levels following exercise. Therefore, some researchers speculate that the “glutamine hypothesis” is sufficient at explaining immunodepression as it relates to stressful conditions such as burns or other trauma, but low plasma levels following exercise do not fully explain the immunodepressed post-exercise state.[7]
Because of these findings, researchers suggest that the post exercise immune decline is not necessarily caused by lowered plasma glutamine concentrations. Empirically however, it makes sense that if a primary fuel source for an immune system component is lacking, then supplying adequate amounts may still have an effect on supporting immune function. In vitro studies should of course be interpreted with caution when applied to in vivo systems. Despite these findings, the literature is full of evidence which supports the need for exogenous glutamine supplementation in maintaining immune function in very ill patients, and the utility of this amino acid in supporting muscle protein mass. Glutamine supplementation in athletes has been shown to decrease the amount of self-reported illness in endurance athletes[8], however the exact mechanism of action is yet to be unveiled. Increasing evidence points to neutrophil function as a possible immune-specific target of glutamine supplementation.[9]

One study looked at the effect of glutamine supplementation on lymphocyte function, natural killer cell activity, T-cell proliferation, and certain hormonal indices (insulin, growth hormone, and catecholamines).[10] These investigators were able to show that glutamine supplementation prior to and following strenuous exercise attenuated decreased levels of neutrophils in comparison to the control (placebo) group. No other effects were observed. Despite these findings, the study authors concluded that glutamine has no real effect on exercise induced immune changes. Therefore, based on the clinical data regarding glutamine and immune function, we may speculate that glutamine serves as a potentially useful supplement in athletes that engage in strenuous exercise. The majority of studies suggest/utilized doses ranging from 3-6 grams per day. These doses are well below the amounts used in a variety of other immune-dysfunction related conditions and diseases. Other studies have used amounts ranging from 500 mg/kg per day in patients with radiation mucositis[11] to 40 grams per day in HIV patients.[12]

Zinc

In suggesting specific nutrients for the athlete, we operate on the assumption that certain nutrients, in varying amounts, are ingested at suboptimal levels. This assumption also supports the beliefs that athletes, in comparison to their sedentary counterparts, have a higher than normal requirement for certain nutrients, that the athlete's often strict diet may not always supply optimal amounts of these nutrients, and that minor deficiencies of these nutrients can directly alter physiologic reactions to exercise.

Zinc is the second most abundant trace element in the body, totaling nearly 2 grams.[13] During periods of increased zinc demand in the body, zinc absorption is increased and zinc already within the body is conserved.[14] Zinc is contained in over 300 enzymes that are thought to have a hand in genetic expression in the body and is a direct catalyst for over 100 enzymes.[15] Zinc is needed for growth and development, behavior and learning, proper immune function, healing of tissue damage, reproduction, taste and smell and the function of the hormones insulin and thyroid hormone.[16] A truly reliable test for zinc deficiency does not exist; current testing methods are not efficient at determining zinc status (they are neither sensitive nor specific). Zinc deficiency is best evaluated by a positive response in symptoms from supplementation. Zinc plays a large role in the function of several immune cells[17] and deficiency seems to negatively affect the function of T cells.[18]

Zinc is thought to inhibit viral replication in the common cold as well.[19] Despite this information, there is little evidence that dietary zinc influences exercise *performance* per se; however zinc may prove to be useful, as it is known that intense exercise can lead to changes in zinc metabolism in the body.[20] A study observing serum zinc levels in athletes over a nine month training season demonstrated significant decreases in serum levels after 5 months; this was not explained by changes in diet, plasma protein concentrations, hormonal indices, or infections or inflammatory conditions.[21] This study supports the notion that zinc status (as determined by serum levels) may become altered in athletes. In fact, plasma zinc levels are known to vary following various grades of exercise intensity, and high levels of endurance-type exercise affects the long range patterns of zinc metabolism (long term endurance training leads to significantly decreased resting serum zinc levels in both males and females in comparison to sedentary individuals).[22] Supplementation with zinc is one piece of the very large immunocompentence puzzle. Done appropriately, zinc supplementation (if necessary-optimal amounts of zinc can be consumed in the proper, healthy diet) may assist the athlete in maintaining optimal immune function during the training season. If supplementation does occur, this should be done with caution, as excessive amounts of zinc in the diet can result in a secondary copper deficiency.

Antioxidants

A large amount of information suggests that physical exercise generates increased amounts of reactive oxygen species, or free radicals. Although the necessary technology has not been used to directly measure free radical production resulting from exercise, most investigations in this area focus on measures of lipid peroxidation as a principle indicator of exercise-induced free radicals. Primarily, damage caused by free radicals affects DNA and RNA structure and function thereby promoting mutations and cancer, and they can inactivate enzyme complexes affecting cellular machinery. It is thought that free radicals released from cellular components in the body may adversely influence the function of lymphocytes, thereby warranting antioxidative treatment to offset possible immune perturbations. It is important to note that free radicals are continuously generated in the human body, with some having beneficial uses as a vital part of immune defense.

At present, it is not entirely conclusive that long-term antioxidant supplementation will affect these positive aspects of free radical production; in theory however antioxidants may dampen the oxidative processes in neutrophils seen during phagocytosis.[23] It is known that supplementation with the antioxidant vitamins C and E can have favorable effects on lipid peroxidation markers, and there is limited evidence that vitamin C and E have a modulating effect on immune function in those who engage in strenuous exercise. One study showed that vitamin C was able to reduce the number of upper respiratory tract (URTI) symptoms in the two-week period following an ultramarathon, when supplementation was started 3 weeks before the race.[24] Interestingly, another study was unable to show changes, or effects, on lymphocyte function and stress hormone levels with vitamin C supplementation with 1000 milligrams per day in the 8 days immediately preceding a 2.5 hour run at 75-80% VO2 max.[25] Proponents of vitamin C would more than likely argue that this amount, used in a medical perspective, is insufficient. When using vitamin C medicinally, oftentimes doses larger than 1000 milligrams are often necessary. The previous study is yet another good example of a clinical trial that defines the lower limits of orthomolecular dosing of vitamins. A study that favored a slightly higher dose of vitamin C (1500 milligrams) demonstrated a decrease in the plasma cytokine concentrations of IL-6, IL-10, IL-1RA, and IL-8 in ultramarathon runners.[26] A comparison group in this study was supplemented with only 500 milligrams of vitamin C (for a week prior to the race) and did not display similar immune function indices. As with much of the research surrounding vitamin C and immune function, it appears that in order to effectively modulate the immune system, larger doses of the vitamin are necessary.

The use of an antioxidant vitamin combination (containing 18 mg beta-carotene, 900 mg vitamin C, and 90 mg vitamin E) was studied in relation to immune cell response to prolonged exercise in a group of endurance athletes.[27] Test subjects took the supplement for 7 days preceding a 2-hour run performed at 65% VO2 max. Blood samples were taken immediately before and after the run and neutrophil oxidative burst activity, cortisol and glucose concentrations, white blood cell counts, and serum anti-oxidant vitamin concentrations were all measured. Neutrophil oxidative burst function was found to be significantly higher following the exercise; however no other parameter differences were noted. This study suggests that supplementation with certain antioxidants may benefit a particular component of immune function in endurance athletes, and therefore may be a useful strategy for this population. Clearly the absolute physiological implications of antioxidant supplementation remains to be defined; however the judicious use of antioxidants as a supplement can definitely provide insurance in those with substandard diets and/or undergoing the rigors of intense physical activity. Research in the future will undoubtedly reveal additional antioxidant effects on immunity in athletes.

Magnesium

Magnesium is known to have modulatory effects on the immune system. More specifically, magnesium is involved in the both the nonspecific and specific immune responses; magnesium plays a role in inflammation, apoptosis, and variation in number and function of leukocytes.[28] Magnesium has been the subject of several studies investigating its role in exercise performance, with the majority of them refuting its role as an ergogenic aid, outside of deficiency states.[29,30] However, when employed to assist immune function, magnesium appears to exhibit some utility. In a trial lasting two months, investigators examined the effects of magnesium in exercise-induced immune function alteration.[31] In one arm of the study, it was noted that in vitro formation of free radicals by immune cells was attenuated to a certain degree, while in a second study arm, the effect of magnesium supplementation was shown to enhance chemotaxis in granulocytes. However, placebo and study groups both demonstrated the same degree of lymphopenia following exhaustive exercise. Seemingly insignificant, this study shows a positive, specific effect of another nutrient in enhancing immune function in athletes. Although this investigation did not show a role of magnesium in preventing exercise-induced immunosuppression, it does demonstrate a supportive role of magnesium in immune function.

Iron

Iron deficiency anemia is thought to be more prevalent in athletes, especially in younger female athletes, than in the general sedentary population.[32] In those that have iron deficiency anemia, not only is performance decreased but immune function is compromised as well. Poor dietary choices, increased rate of red cell iron and whole body iron turnover are increased in athletes, while increased sweating and urination are slight, additional avenues of iron loss in athletes. Younger female athletes may consider using low-dose iron supplementation, under the guidance of a physician, to ensure anemia prevention and proper immune function.

Vegetarian versus Carnivore

An interesting study examined the difference in immune function in groups of vegetarian and carnivorous diets.[33] The study design placed subjects on different diets for 6-week periods, with a 4-week interval in which they could consume their regular diet, then put each group on the opposite respective diet. One of the diets (carnivorous) was comprised of 69% animal protein while the other was a lacto-ovo vegetarian diet comprised of 82% vegetable proteins. Each diet was balanced with ratios of 57% energy derived from carbohydrate, 14% from protein, and 39% fat. Investigators looked at lymphocyte subpopulation and function at the conclusion of each diet following a bout of exercise. Fiber and fatty acid content were twice as high in the vegetarian diet as the meat diet. No differences were found in leukocyte subpopulation number or function following the two diet periods. An interesting follow up to this study would entail longer periods of time on each respective diet, or choosing athletes that have trained and consistently eaten such diets for a period of months to years, rather than a few weeks.

Eleutherococcus senticosus and Panax ginseng

Much research regarding the effects on adaptogenic botanicals exists on athletic performance, echoing other studies that demonstrate the effectiveness of these botanicals on regular physiology. Investigators have examined the role of two ginsengs (Eleutherococcus senticosus (Siberian ginseng) and Panax ginseng (Korean ginseng) and their effect on endurance athlete's immune function.[34] Study subjects received 8 milliliters per day (equivalent to 2 grams dried root) of one or the other botanicals or placebo for 6 weeks. The hormones cortisol, testosterone, and the testosterone to cortisol ratio were measured, along with numbers of circulating T cells, T-helper (CD4) and T-suppressor (CD8) cells, natural killer cells, and B lymphocytes, as well as the CD4 to CD8 ratio. No changes in any of the above were noted in the Panax ginseng supplemented group from pre to post testing/measurement. However, the Siberian ginseng group demonstrated a decrease in the testosterone to cortisol ratio by 28.7%, (cortisol increased while testosterone levels decreased) meaning that Siberian ginseng increased hormonal indices of stress. Investigators commented that these results, while contrary to what they had expected, are consistent with animal studies which have suggested a threshold of stress below which Siberian ginseng seems to increase the stress response and above which it seems to decrease the stress response. Adaptogenic herbs have fascinating effects on physiology, and much research is needed to clarify their use in circumstances of physical stress.

Conclusion

The mechanisms by which physical stress modulates immune function are complex, involving numerous factors, both immunologic and neuroendocrine. Despite many individual factors having been identified, clear-cut mechanisms are elusive. Multiple endocrine and metabolic factors are involved in the phenomenon of exercise-induced immune dysfunction. This of course leaves the clinician with many possible leads in supporting the patient who undergoes physical stresses, both voluntary and involuntary. Based on the research reviewed in this brief article, it seems unlikely that any one nutrient or botanical will have a relevant effect on immune function; however, the information contained herein provides more pieces to the puzzle, several of which when applied appropriately may provide an effect that can further decrease the probability of contracting illness in times of physical stress.

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