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Effect of Dietary Intake on Immune Function in Athletes

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Abstract

Athletes are exposed to acute and chronic stress that may lead to suppression of the immune system and increased oxidative species generation. In addition, the tendency to consume fewer calories than expended and to avoid fats may further compromise the immune system and antioxidant mechanisms. The exercise stress is proportional to the intensity and duration of the exercise, relative to the maximal capacity of the athlete. Muscle glycogen depletion compromises exercise performance and it also increases the stress. Glycogen stores can be protected by increased fat oxidation (glycogen sparing). The diets of athletes should be balanced so that total caloric intake equals expenditure, and so that the carbohydrates and fats utilised in exercise are replenished. Many athletes do not meet these criteria and have compromised glycogen or fat stores, have deficits in essential fats, and do not take in sufficient micronutrients to support exercise performance, immune competence and antioxidant defence. Either overtraining or under nutrition may lead to an increased risk of infections. Exercise stress leads to a proportional increase in stress hormone levels and concomitant changes in several aspects of immunity, including the following: high cortisol; neutrophilia;

lymphopenia; decreases in granulocyte oxidative burst, nasal mucociliary clearance, natural killer cell activity, lymphocyte proliferation, the delayed-type sensitivity response, the production of cytokines in response to mitogens, and nasal and salivary immunoglobulin A levels; blunted major histocompatibility complex II expression in macrophages; and increases in blood granulocyte and monocyte phagocytosis, and pro- and anti-inflammatory cytokines. In addition to providing fuel for exercise, glycolysis, glutaminlysis, fat oxidation and protein degradation participate in metabolism and synthesis of the immune components. Compromising, or overusing, any of these components may lead to immunosuppression. In some cases, supplementation with micronutrients may facilitate the immune system and compensate for deficits in essential nutrients. *In summary*, athletes should eat adequate calories and nutrients to balance expenditure of all nutrients. Dietary insufficiencies should be compensated for by supplementation with nutrients, with care not to over compensate. By following these rules, and regulating training to avoid overtraining, the immune system can be maintained to minimise the risk of upper respiratory tract infections.

Immune responses to stress, and the stresses themselves, are undoubtedly multifactorial. Some of the factors that influence the immune system have been suggested to be: innate immune competency that is genetically predisposed, precipitating physiological, psychological and environmental stresses, and the hormonal responses associated with these stresses. It has been reported that athletes are more susceptible to infections than sedentary individuals, in spite of the observation that their basal immune system is not compromised.[1-4] There is convincing evidence that nutrition plays an important role, particularly during exercise stress, in immune function. Athletes are distinguished from sedentary individuals by their higher level of energy expenditure, which may require utilisation of specific nutrients. The intensity and duration of the exercise alters the metabolic pathways that are used. It has recently been suggested that there is no consistent relationship between nutritional interventions, exercise immunology, and alterations in the risk of upper respiratory tract infection (URTI), but this has yet to be established.[3]

Dietary intake of nutrients has the potential to affect, directly and indirectly, virtually all aspects of the immune system, as most nutrients are involved in the synthesis and regulation of immune factors. Carbohydrate availability is well recognised for its role in immune competency and its effects on the physiological stress of exercise.[2] The role of lipids on the immune responses to exercise has been under appreciated. The overemphasis on carbohydrates and avoidance of fats compromises an athlete's ability to take in even minimal levels of some micronutrients and fats.

The purpose of this review is to present the factors that affect the susceptibility of athletes to infections, including the type of exercise, effects of exercise training and, particularly, the role of dietary intake of nutrients. We will emphasise the roles of total caloric intake and the intake of dietary lipids, as the role of carbohydrate has been well described previously.[5-7]

1. Exercise and Substrate Use

Acute exercise is a 'stressor', as it results in increased metabolism, excess heat production, and widespread physiological and hormonal adjustments that are differentially influenced by both its intensity and duration relative to the athlete's maximal capacity.[8] If exercise is carried out routinely (chronic exercise), the body adapts (training effect) and the stress imposed is either minimised or reduced. Overtraining, when combined with current attitudes about dietary intake, is often associated with consumption of less total calories than expended and intake

of fewer fats than needed.[9] Nutritional imbalances, caused by reduced dietary intake or exaggerated caloric expenditure, result in depletion of intramuscular energy stores of glycogen and fats. The combination of these over-stresses, and reduced energy stores, may result in increased stress caused by exercise. This stress may compromise the immune system during exercise training and performance and lead to an increase in infection rate. The intensity of exercise determines the rates of use of the various metabolic pathways, while the duration determines the amounts of the various stored fuels used. The recruitment of fast-twitch muscle fibres during higher intensity exercise requires anaerobic-glycolytic energy, which leads to lactic acid production and lower pH; and the stresses imposed on the system are significantly elevated.

The relative contribution of carbohydrates and fats to energy expenditure during exercise depends on various factors such as intensity and duration of the exercise, the athlete's genetic predisposition, the diet, and training status. As exercise intensity increases, the rate of carbohydrate utilisation increases, while fat oxidation increases and then plateaus, in slow-twitch fibres. During higher workrate exercises, where fast-twitch fibres are used, anaerobic glycolysis dominates and the exercise time is limited by lactic acid build-up or decreased pH. During prolonged exercise (more than 2 hours), exercise intensity is limited and fat is a major source of fuel, and may exceed 90% of the total requirement in extreme circumstances.[10]

Fats and carbohydrates taken-up and oxidised from the blood can provide 20 to 30% of the total oxidation from maximal to low aerobic exercise, respectively.[11,12] The remaining 70 to 80% of fats and carbohydrates oxidised come from intramuscular fat and glycogen stores. Glycogen is stored as a droplet in the cytosol and is available to both slow- and fast-twitch fibres. Intramuscular fat is stored as triglyceride, but more importantly in droplets, which are in contact with the mitochondria.[13] These fat stores provide most of the fat oxidised during exercise and they become depleted during endurance exercise at all levels of oxygen uptake ($\dot{V}O_2$).[14,15] Trained participants have a higher level of fat oxidation than sedentary individuals, and genetically gifted athletes have even higher levels of fat oxidation, at all levels of exercise.[11] Recent studies have established the potential role of fat oxidation in glycogen sparing,[8] and, in fact, have shown that increasing fat intake can increase exercise endurance and maximal aerobic power in some athletes.[16-18]

Stress hormones are known to have potent immunomodulatory effects. The stresses imposed by exercise may have an impact on immune function, as circulating levels of stress hormones [adrenaline (epinephrine), noradrenaline (norepinephrine) and cortisol] in the blood are increased. In addition, the ability to repair muscle damage, caused directly by mechanical factors or secondarily to oxidative stress, may be influenced by the individual's immune status. Immune function may be related to the balance between the amount and type of fat in the diet and the utilisation of fat as a fuel during exercise.

Endurance training may result in adaptations such as increases in the number of mitochondria, the amount of oxidative enzymes, mitochondrial contents, triglyceride oxidation, free fatty acids (FFA) uptake, alterations in the mobilisation of FFA from adipose tissue, increased stores of intramuscular fats and glycogen, and increased removal of lactic acid by oxidative metabolism in slow-twitch muscle fibres.[10,11]

2. Dietary Intake

2.1 Macronutrient Intake

A diet comprised of 12% protein (1.2 to 1.4 g/kg/day), 60 to 70% carbohydrate (8 to 10 g/kg/day) and 18 to 28% fat (0.8 to 1.0 g/kg/day) is often recommended for athletes.[1] Studies in both male and female runners have reported that their caloric intakes are only 65 to 75% of their estimated caloric expenditure,[19-21] and that many runners are on diets low in fat.[9,20,22,23] Increasing the fat intake of runners from 15 to 42% increased total caloric intake by 17 to 26% and brought the runners near energy balance.[24] To insure muscle stores, the in-

take of carbohydrates must equal the carbohydrates oxidised during exercise training and performance. Currently, diets of 8 to 10 g/kg body mass are recommended, which could account for 60 to 70% of the total calories.[1] An examination of a series of studies on high- and low-fat diets[16,17,24] leads to the conclusion that a carbohydrate intake of at least 35% of the total calories, on a diet balanced in calories, maintains muscle glycogen stores sufficiently to support endurance exercise. Low dietary fat intake has been related to hormone irregularities, such as reduced prolactin levels and amenorrhoea.[25] Reduced fat and total caloric intake compromises maximal aerobic power and exercise endurance.[16,24] This observation could be corrected, in part, by increasing total caloric intake; however, dietary fat intake has to be increased to maximise endurance performance.[16,17,24] Protein intake (0.8 g/kg/day) in the diets of most athletes is sufficient to meet the demands.[24] For many sports, 12% of total calories from protein is recommended. Although protein is generally not considered a primary source of energy for re-synthesis of ATP, it may play an important role.[26] Ingestion of branch-chain amino acids before, during or after exercise does not improve performance.[26]

2.2 Micronutrient Intake

The increase in $\dot{V}O_2$ during exercise may lead to an increase in oxygen free-radical formation, and thus to an increased need for antioxidants. The recommended daily amount (RDA) of vitamin A is 1 mg/day. High levels of vitamin A intake (>5 to 10 mg/day) may cause toxic effects and even liver damage.[1,27] Vitamin B12 (cyanocobalamin) is found only in animal foods. Thus, athletes who are vegetarian or avoid meat may be deficient in vitamin B12. Athletes on low-fat, vegetarian or low-energy-balance diets are often deficient in zinc, iron, selenium and copper. Iron intake is lower on a low-fat diet, particularly in women. Calcium intake is below the RDA on low-fat diets.[19,20] Zinc status is increased on high-fat diets; however, runners are still below the RDA for zinc.[19,20] It is well documented that many female athletes consume too few total and fat calories.[24,28] It is also clear that these imbalances result in depleted muscle glycogen and, importantly, fat stores. In addition, significant defects in micronutrients, iron and zinc, may be present. Of particular concern is the female athlete triad (disordered eating, amenorrhoea and osteoporosis). A 20-week programme of a daily sport nutrition supplement, with increased protein and micronutrient intake and maintained serum concentrations of vitamin B12, folic acid, zinc and iron, and 1 day of rest per week, restored menstruation.[29]

3. Immune Function Related to Exercise

Exercise, both high-intensity and prolonged, is a stress to the body that is determined by relative intensity (exercise intensity/maximal capacity). It brings about a proportional increase in stress hormone levels and concomitant changes in immunity, including the following: high cortisol; neutrophilia; lymphopenia; decreases in granulocyte oxidative burst, nasal mucociliary clearance, natural killer (NK) cell activity, lymphocyte proliferation, the delayed-type sensitivity response, and the production of cytokines in response to mitogens; increases in nasal and salivary immunoglobulin (Ig) A levels; blunted major histocompatibility complex II expression in macrophages; and increases in blood granulocyte and monocyte phagocytosis, and pro- and anti-inflammatory cytokines.[1,4,30-32] The acute effects of exercise on lymphocytes are mediated by adrenaline and noradrenaline, whereas neutrophils are mediated by cortisol.[33] Cortisol is known to influence the redistribution of lymphocyte subsets from the blood to peripheral tissues.

3.1 Exercise Responses

Exercise-related immunological changes include signs of inflammation, such as the release of inflammatory mediators, activation of various white blood cells and complement, and induction of acute-phase proteins. Nevertheless, signs of immunosuppression, such as decreased T- and B-cell function, or impaired cytotoxic or phagocytic activity, can also be observed. Both single bouts of exhausting physical activity and chronic exercise (overtrain-

ing) may impair immune responses and increase an athlete's vulnerability to acute and chronic inflammation and reduced post-exercise tissue repair.[33,34]

The immune responses to the stresses of exercise involve coordination of many cell types, soluble factors, and messenger molecules in the blood and throughout the body. Although exercise-induced effects on the immune system may be transient, such temporary changes could increase the vulnerability to infection and, if exercise is chronic and/or severe, may place athletes at high risk. A recent study has shown that even moderate-intensity endurance exercise has a great impact on the innate immune system.[2]

Researchers have implied that regular and moderate exercise improves the ability of the immune system to protect the host from infection.[30,32,35] Training is associated with up-regulation of the antioxidant defence system.[36] Resting levels of NK cells (natural immunity) are enhanced as a result of training.[33] Leucocyte number is clinically normal and remains unchanged with training.[32] Moderate exercise training has little effect on cell function and does not affect serum or mucosal Ig and antibody levels.[32] Although glutamine concentration is decreased during exercise, there is little evidence that this is affected by training.[32]

Overtraining results from long-term overstress and is a complex syndrome that is a combination of signs and symptoms, including the following: deterioration of performance, muscle/joint pain, mental fatigue, depression, loss of bodyweight, loss of appetite, negative nitrogen balance, increased basal metabolism, and elevated resting and delayed transient changes in heart rate.[2,35,37] Stress responses of the neuroendocrine, hypothalamic, adrenal and gonadal systems are altered.[2] These autonomic changes result in changes in catecholamine, glucocorticoid and testosterone levels.[35] It has been proposed that subacute, exercise-induced musculoskeletal trauma will result in the release of local inflammatory factors and cytokines.[35] With repeated exercise, inflammatory responses become chronic and circulating monocytes become activated and produce pro-inflammatory cytokines. Systemic inflammation then leads to signs and symptoms of overtraining.[35] Overtraining is undoubtedly multifactorial, but the systemic immune response to exercise is a central component that has to be evaluated.

3.2 Lymphoid Cell Subsets/Function

Both high- and moderate-intensity exercise are associated with shifts in circulating proportions of NK cells, which influence the interpretation of data about NK cytolytic activity (NKCA).[38] Long-term running may induce some change in lymphocyte subpopulations.[39] Chronic submaximal exercise increases mobilisation of neutrophils, decreases mobilisation of lymphocytes, and decreases the absolute and relative numbers of neutrophils at rest.[40] Dietary lipid intervention may modulate lymphoid cell subsets, and thereby alter proliferative responses, cytokine production and so on, in pathological conditions such as autoimmune diseases and anorexia.

While the number of lymphocytes in the blood may be elevated by physical exercise, lymphocyte function may be impaired. *In vitro* impairment of responses to mitogens has been associated with a variety of immune deficiencies *in vivo*, such as changes in CD4/CD8 ratios, decreases in the production of interleukin (IL)-2, increases in prostaglandin E2 (PGE2) levels, increases in macrophage function, and so on. Such reduced responses to mitogens may be sufficient to allow micro-organisms and viruses time to evade early immunological recognition and establish ongoing infection in runners. Generally, moderate-intensity exercise may decrease the proliferative response by 35 to 50%.[41]

3.3 Cytokines/Other Soluble Factors/Neuroendocrine System

Cytokines are important in initiating and regulating the immune response and in influencing almost all immune functions. Cytokines, which various immunocompetent cells produce in response to appropriate stimuli, mediate many immune functions and orchestrate the immune system. The excessive or insufficient production of cytokines may contribute to infectious, immunological and inflammatory diseases. A balance between pro- and anti-

inflammatory cytokines is essential for maintaining a sound immune system. Exercise can alter the release of numerous cytokines and modulate their receptor systems. Such changes may trigger inflammatory and acute-phase responses. Increases in IL-1, IL-6 and tumour necrosis factor (TNF)-α have been found in supernatants from lipopolysaccharide-stimulated peripheral blood mononuclear (PBMN) cells isolated from untrained persons 2 hours after bicycle exercise. Plasma IL-6 and TNF-α levels increase following long-distance running. Plasma IL-6 levels negatively correlate with plasma lactate levels at rest. As IL-6 has growth-promoting potential, high lactate production, by inhibiting the production of IL-6, may contribute to the decreased muscle function observed in patients with mitochondrial myopathy.[42] IL-6 is produced locally in skeletal muscle in response to exercise. It induces hepatic glucose output and lipolysis, suggesting an important link between contracting skeletal muscle and exercise-associated metabolic changes.[43] There is evidence suggesting that systemic elevation of cytokines occurs in the serum after strenuous exercise. The activation of serum-soluble immunoactive markers, such as soluble IL-2 receptors (sIL-2R), soluble intercellular adhesion molecule-1 (sICAM-1), soluble TNF-receptor (sTNF-R) and neopterin, may be influenced by exercise.[44] The enhanced metabolism occurring during exercise may produce unknown intermediate products that are responsible for initiating leucocyte activation and cytokine release. Dietary lipids have an effect on cytokine balance. Fish oil, containing anti-inflammatory omega-3 fatty acids, is known to lower the production of IL-1, IL-6 and TNF-α by macrophages. Cytokine inhibitors and anti-inflammatory cytokines may restrict the magnitude and duration of the inflammatory response to exercise.[45] Intense exercise can cause suppression of mucosal immune parameters.[46] Low levels of salivary IgM and IgA, in particular the IgA1 subclass, have been linked to an increased risk of respiratory illness.[47] The mechanisms underlying mucosal immune suppression are not clear, but may reflect alterations in T-cell cytokine control mechanisms.[47]

The immune system is closely linked to the neuroendocrine system. Exercise is known to activate the pituitary-adrenocortical axis to increase cortisol levels. Neuroendocrine factors released in situations of stress, such as intense exercise, are suggested to be partly responsible for exercise-induced changes in the immune system. Most immunosuppressive responses induced by intense exercise correlate with increases in circulating cortisol.[48,49] It has been established that the leucocytosis induced by exercise is mediated by catecholamines and glucocorticoids,[50] and the specific immune response of lymphocytes is also mediated by adrenaline, glucocorticoids, β-endorphin, and other stress hormones.[51] Muscular exercise increases the concentrations of a number of stress hormones in the blood, including adrenaline, noradrenaline, growth hormone, β-endorphins, and cortisol, whereas the concentration of insulin decreases slightly.[52] Adrenaline and noradrenaline may be responsible for the immediate effects of exercise on lymphocyte subpopulations and cytotoxic activities. Cortisol may be responsible for maintaining lymphopenia and neutrocytosis after exercise of long duration.[53]

4. Dietary Intake, Exercise and Immune Function

4.1 Dietary Carbohydrate

Glucose and glutamine are critical fuels for the cells of the immune system. High-carbohydrate diets are designed to keep the liver and muscle stores of glycogen high to ensure glucose/glycogen availability during exercise. The use of glucose as a substrate is significantly reduced when lymphocytes proliferate;[1,54] however, glycolysis and glutaminlysis remain high. The high turnovers of glucose and glutamine are proposed to regulate the rates of synthesis of purine and pyrimidine nucleotides during the lymphocyte cycle.[1,21]

Reduction in blood glucose levels has been linked to hypothalamic-pituitary-adrenal (HPA) activation, increased release of adrenocorticotropic hormone (ACTH) and cortisol, increased levels of plasma growth hormone, decreased levels of insulin, and

variable adrenaline levels.[55,56] Maintaining plasma glucose concentrations can attenuate increases in stress hormones and diminish changes in immunity. Carbohydrate ingestion during prolonged and intensive exercise lessens hormonal and immune responses that have been related to physiological stress and inflammation.[57] Carbohydrate intake also blunted the rise in IL-6 and IL-1 receptor antagonist (IL-1ra) involved in the inflammatory cascade response to heavy exertion.[57] Consumption of carbohydrates (but not glutamine or other amino acids) during exercise attenuates rises in stress hormones, such as cortisol, and seems to limit the degree of exercise-induced immune suppression, at least for non-fatiguing bouts of exercise.[58] Carbohydrate ingestion during high-intensity exercise (>75% $\dot{V}O_{2max}$ for >2 hours) that produces significant stress is associated with increased plasma glucose levels, attenuated cortisol and growth hormone responses, fewer perturbations in blood immune cell counts, reduced granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response.[4] Mononuclear phagocytes use glucose at a significantly greater rate than glutamine, and the presence of carbohydrate availability can influence the level of plasma glucose.[1] Concanavalin A–stimulated proliferation of lymphocytes and macrophages is sustained in short-term exercise, but may be markedly reduced in prolonged exercise.[4,59] This may be one possible mechanism that increases the risk of infections in endurance or overtrained athletes.

Cortisol release from the adrenal gland is stimulated by activation of the HPA axis release of ACTH. The cortisol release is proportional to the stress of exercise, and glucose availability is a critical factor in cortisol release before, during and after (recovery) exercise. Cortisol suppresses serum IgA, IgG and IgM production, the lymphocyte proliferative response to mitogens, and NKCA.[1] Ingestion of drinks containing glucose has been shown to increase blood glucose, improve endurance running performance and, importantly, to lower plasma cortisol levels and circulating leucocyte subsets. Carbohydrate ingestion attenuates the inflammatory response to acute exercise through reduced levels of IL-6, total anti-inflammatory IL-1ra and cortisol.[1,60,61]

Muscle-cell injury often occurs during exercise, as evident from the rise in plasma creatine kinase activity. The muscle damage causes an increase in post-exercise cytokine release. Several studies have suggested that the effects of carbohydrates on IL-6 production are primarily associated with muscle glycogen availability, rather than with a reduced inflammatory response. As the release of IL-1ra follows that of IL-6, reduced plasma levels of IL-1ra observed with carbohydrate ingestion may therefore be a function of a reduced inflammatory response.[5] It has been suggested that carbohydrate lowers muscle-derived IL-6, thus altering cytokine release. Carbohydrate release has no effect on NKCA, phagocytosis of monocytes and granulocytes, and oxidative burst activity.[1,61] The effects of a high-carbohydrate diet, with minimal required protein, does not alter lymphocyte number or function.[1,9]

4.2 Dietary Fat

Dietary fat intake is considered a disadvantage by many athletes, as illustrated by the recommendation that the diet contain only 20% of total calories as fat.[1] The important roles that fats play in building membranes, and as a fuel for exercise, require us to evaluate the perception that dietary fat intake should be kept very low. Recent studies have shown that low-fat diets compromise endurance performance.[16,17,24] The mechanisms by which lipids may modulate immune function may involve several factors and mediators.[62,63] Fats are used as fuel by lymphocytes; however, when stressed by mitogens, lymphocytes appear to increase their metabolism with glucose use.[1,21] The regulation of fuel selection by lymphocytes is not clear, as some fats inhibit glucose/glutamine use while others do not.[1] Both the quantity and type of dietary lipids are known to have modulatory effects on the cellular immune system at the biochemical and molecular levels, including the production and expression of cytokines.[64,65] Dietary omega-6 lipids generally increase the levels of pro-inflammatory

cytokines and inflammatory PGs, while omega-3 lipids may decrease the levels of such cytokines and inflammatory PGs.[66-68] In rats, a diet rich in omega-3 polyunsaturated fatty acids (PUFAs) significantly reduced glutamine decarboxylation, and this reduction in glutamine decarboxylation may lead to suppression of lymphatic proliferative responses.[1,39]

Scientists now recognise that many metabolic processes respond directly or indirectly to pro-inflammatory cytokines. Such cytokine-mediated 'reprogramming' of metabolism ensures an adequate supply of nutrients for proliferation of lymphocyte and macrophage populations, for antibody production, and for hepatic synthesis of acute-phase proteins. Pro-inflammatory cytokines have been linked to altered nutrient uptake and utilisation. Anabolic processes are interrupted, and companion catabolic activities are amplified. Changing dietary fat consumption may alter the immune system and hormone levels, as lipids are components of biomembranes, serve as precursors for certain steroid hormones and PGs, have a role in regulating eicosanoid synthesis, and interact directly with cellular activation processes.

Dietary lipids, which are known to influence the fatty acid composition of biological membranes, are incorporated into membrane lipid components, which mostly are phospholipids. Fatty acids must be considered important determinants of the behaviour, including enzyme and receptor function, of membranes.[1,25] A change in the fatty acid composition of phospholipids may affect signal transduction and, consequently, eicosanoid and/or cytokine production.[1,25] Dietary omega-6 lipids (linoleic and linolenic acids present in vegetable oils such as corn oil and soybean oil) generally increase the levels of pro-inflammatory cytokines and inflammatory PGs, while long-chain omega-3 lipids [eicosapentanoic acid (EPA) and docosahexanoic acid present in oil from marine sources such as fish oil] may decrease the levels of such cytokines and inflammatory PGs.[63,67] Thus, both the quality and quantity of dietary fat may modulate exercise-induced alterations to the immune system.[64,67]

It is clear that cytokines affect whole-body nutrition and metabolism, and are responsible for many of the clinically observed nutritional effects of injury, infection, cancer, fever, hyper-metabolism, anorexia, protein catabolism, cachexia, and altered fat, glucose and trace-mineral metabolism.[69] These metabolic and nutritional effects of cytokines are influenced by the nutritional status of the host, which is generally altered during the course of the critical illness. In future, specialised diets and selective cytokine-blockers are likely to be important components of the overall care of catabolic patients.

Human studies reported to date have consistently demonstrated a decrease in the production of pro-inflammatory cytokines when moderate to high levels of marine-derived omega-3 PUFAs are taken orally.[68,70] *In vitro* production of IL-1β and TNF-α in stimulated PBMN cells was reported to decrease after 6 weeks of omega-3 PUFA fish oil supplementation in male volunteers.[64] *In vitro* addition of EPA to human PBMN cells was also reported to inhibit the production of IL-2 and the expression of IL-2 receptor.[71,72]

Exercise causes some injuries in muscles and joints that may increase levels of PGE2.[35] Both the quantity and type of dietary fat are known to influence the level of PGE2. It is known that high-fat diets tend to increase the level of plasma PGE2. It is evident from animal studies that diets high in omega-6 PUFAs generally increase plasma PGE2 levels and PGE2 production by lipopolysaccharide-stimulated macrophages.[73] This indicates that dietary fat may help reduce the stress caused by exercise and, therefore, has less or no adverse effects on well-trained athletes who engage in exercise. Biomembranes serve barrier functions and serve as a store for precursors of rapidly generated, structurally diverse intracellular and extracellular lipid-derived mediators. Cytokines exert a dramatic multilevel impact in regulating enzymes involved in generating lipid-derived mediators central to cytokine action.

Increased endurance capacity in response to increased dietary fat has been observed in both animal[74] and human studies.[70] The effects of three levels of dietary fat (low, medium and high; 4 weeks

on each diet) on the immune status of runners has been reported.[75] The dietary fat in these studies was distributed between saturated (40%), monounsaturated (37%) and polyunsaturated (23%). The effects of these diets on PBMN cell number, lymphoid cell subsets, the proliferative response to lectins, and on the *in vitro* production of pro- and anti-inflammatory cytokines by PBMN cells (before and after a short bout of exhaustive exercise) were determined. Increased dietary fat levels significantly increased levels of the anti-inflammatory cytokine IL-2 after exercise. The proliferative response to pokeweed mitogen by PBMN cells also decreased with increases in dietary fat and exercise.

It may be possible to reduce the chronic stress on the immune system associated with overtraining through appropriately selecting the amount of dietary fat and matching total caloric intake to caloric expenditure. It may be possible to overcome the inflammatory effects of exercise by providing dietary lipids that have a tendency to lower the inflammatory effect through modulating pro- and anti-inflammatory cytokines and free-radical generation. A high-fat diet decreased plasma IL-6 levels in women after endurance running. Both exercise and the high-fat diet increased IL-2 levels and lowered IL-6 levels, suggesting that the level of specific pro-inflammatory cytokines may be modulated through increased dietary fat intake, thus off-setting the pro-inflammatory effects of exercise. It appears that increasing dietary fat can increase endurance run-time without adverse effects on plasma levels of cortisol, PGE2, and interferon-γ.[76]

Evidence has accumulated in the past decade that strenuous aerobic exercise is associated with oxidative stress and tissue damage caused by the generation of oxygen free radicals. Depletion of each of the antioxidant systems increases the vulnerability of various tissues and cellular components to reactive oxygen species. Thus, it is conceivable that dietary supplementation with specific antioxidants could be beneficial.[77] During severe oxidative stress such as strenuous exercise, the enzymatic and non-enzymatic antioxidant systems of skeletal muscle are unable to cope with free-radical formation. This results in an increase in lipid peroxidation. However, exercise and training appear to augment the antioxidant defence system of the body.[78] Whether this augmented defence system can keep up with the increase in lipid peroxidation with exercise is not known. Exercise training has little effect on hepatic or myocardial enzyme systems, but can cause adaptive responses in skeletal muscle antioxidant enzymes, particularly glutathione peroxidase.

In endurance runners, plasma lipid peroxides were increased after an endurance run, in both men and women. Plasma lipid peroxide concentrations were lower on a high-fat diet compared with lower-fat diets. When data were analysed to determine the effects of fat intake on endurance running in women, plasma lipid peroxide levels after exercise were lower on the high- rather than lower-fat diets.[76]

4.3 Dietary Protein

An impairment of host defence mechanisms has been observed with moderate and severe protein imbalance (i.e. when intake differs markedly from consumption).[1,79] Diets very low in protein (<20%) or very high in protein (>60%) were shown to impair phagocytic activity and IL-2 production in an animal model.[1] A protein imbalance is particularly harmful to the T-cell system.[1,18,80]

Glutamine supplementation in a randomised, placebo-controlled study of marathon runners did not influence exercise-induced immunological changes.[81] Decreases in plasma glutamine levels have been observed in response to various stressors including prolonged exercise.[82,83] Whether the exercise-induced decrease in glutamine is linked to impaired immunity is not clear, but most studies have not favoured this concept.[82-84] The utility of plasma glutamine levels as a marker (because glutamine requirements increase during stress) for overtraining has recently been highlighted, but the best way to determine glutamine levels has not been worked out[85] because several additional factors such as injury, infection and nutritional status need to be considered.

Glutamine is used at a high rate by lymphocytes and macrophages. It is oxidised as a fuel and for the synthesis of DNA and RNA.[33,85] Exercise may have a negative effect on glutamine balance, leading to depleted reserves in skeletal muscle.[1,85,86] Skeletal muscle plays an important role in providing glutamine for proper functioning of the immune system.[85] Plasma glutamine levels are depleted in proportion to the intensity and duration of exercise[85,86] and remain depressed post-exercise. Overtrained athletes, who may be fatigued and have negative energy balances, have a significant reduction in basal and postexercise glutamine levels.[85,87] Normal daily protein intake or protein supplementation (20 g/kg/day) for 3 weeks in negative-energy-balance athletes ensures adequate levels of glutamine and other proteins.[85,87,88] Ultramarathon runners had a decreased incidence of infections after a race when they took glutamine 5g in 300ml of water immediately and 2 hours after the event.[50] While low protein intake can be harmful, high protein intake can cause a 25% decrease in plasma glutamine due to increased renal uptake.

4.4 Micronutrients

Low total caloric, low-fat, low red meat diets may not provide essential micronutrients, including vitamins. Vitamin B12 and folic acid are essential for the normal production of both red and white blood cells. A deficiency in vitamin B12 or folic acid may lead to an impaired lymphocyte proliferative response to mitogens and a reduction in phagocytic and bacterial capacity for neutrophils.[63] Vitamin C (ascorbic acid) increases the proliferative responses of T-lymphocytes and attenuates the suppressive effect of glucocorticoids on immune function.[63] In one study, supplementation with ascorbic acid 500mg, tocopherol (vitamin E) 270mg and β-carotene 18mg significantly reduced the post-marathon infection rate from 40 to 15% of the runners.[44] Ascorbic acid supplementation (600 to 1000 mg/day for 3 weeks) reduced the symptoms of URTI in runners in response to 2.5 hours of running.[4] Tocopherol (200 mg/kg of food for 50 days) stimulated the helper activity of T-lymphocytes, stimulated mononuclear cell production of IL-1β (535 mg/day for 48 days), and depressed mitogen-induced lymphocyte proliferation and the antibacterial activity of peripheral blood leucocytes (300 mg/day for 3 weeks).[1,70,74] These effects may be optimised when tocopherol is taken with ascorbic acid.

Although supplementation with several antioxidants should theoretically provide greater protection of tissues against exercise-induced oxidative stress, the data in humans are contradictory. Supplementing with a combination of α-tocopherol 400IU and ascorbic acid 200mg per day for 4.5 weeks before participating in a standard marathon did not alter lipid peroxidation, but decreased creatine kinase levels 24 hours post-marathon.[89] Supplementation with tocopherol 294mg, ascorbic acid 1000mg and ubiquinone 60mg per day did not have any additional benefits.[90] Currently available information appears to support the enhanced intake of vitamin B, ascorbic acid, tocopherol and carotenoid- and flavonoid-rich foods to raise daily intakes to above RDAs for sedentary individuals. Supplementation with a single antioxidant nutrient is not recommended because of hazards caused by excessive fat-soluble vitamins, or peroxidation and pro-inflammatory responses caused by excess ascorbic acid. Evidence to support high dosages of antioxidant vitamins preventing exercise-related immunosuppression is lacking.

Very high-carbohydrate and vegetarian diets may be low in protein, and poor sources of micronutrients such as zinc, iron, selenium and copper, thus compromising the athlete's immune status. There are several metalloenzymes that are zinc-dependent, including those involved intranscription and the synthesis of proteins.[30] Low zinc intake may compromise the immune system, as dietary zinc has an important role in thymic function, T-lymphocyte development, lymphocyte proliferation, T-cell dependent B-cell functions and, thus, in resistance to infections. In zinc-deficient athletes, supplementation (zinc 25mg and copper 1.5mg twice per day for 6 days) resulted in generation of lower levels of superoxide free radicals by activated neutrophils,

and exaggerated suppression of T-lymphocyte proliferation in response to phytohaemagglutinin or concanavalin-A.[1,30] Mega-doses of zinc (150mg twice per day for 6 weeks) have detrimental effects on the immune system, including a reduced T-lymphocyte proliferative response to mitogens, and impaired polymorphonuclear cell phagocytic and chemotactic activity. Thus, mega-doses of zinc are not recommended.

Immune function is particularly sensitive to the availability of iron. Iron deficiency depresses lymphocyte proliferative responses to the following: mitogen stimulation; delayed cutaneous hypersensitivity; macrophage IL-1 production; reduced production of interferon; and NKCA.[1,64] On the other hand, high doses of iron may be detrimental to the immune system; for example, free iron helps bacterial growth.

Selenium is an antioxidant and cofactor of glutathione peroxidase/reductase and, thus, selenium deficiency could affect all aspects of the immune system.[1] Copper deficiency is associated with impaired antibody formation, inflammatory responses, phagocytic killing power, and NKCA and lymphocyte-stimulation responses.[1]

5. Conclusions/Clinical Implications

There is a perception that athletes are susceptible to infectious illness, increased oxidative stress and delayed muscle repair, implying impaired immune function, although such susceptibility is not universally found and may be caused by overtraining and/or under-nutrition. It has been shown that low-calorie diets and low-fat diets may compromise intramuscular energy stores and do not provide enough essential micronutrients; such changes may compromise the immune system. Acute and chronic exercise may alter immune cell numbers and function for 24 to 48 hours. Monitoring the athlete's training quality, as well as his/her perceptions of fatigue, stress, the presence of infections, quality of sleep, and muscle soreness, may be used to evaluate risks to the immune system.

As intensive training can be very demanding, all athletes need sufficient total calories to meet their energy demands. The source of these calories (fat, carbohydrate and protein) should meet the individual's caloric expenditure during training and performance. Failure to accomplish this results in depletion of intramuscular stores of glycogen and fats and reduces performance. It is clear that diets with <20% carbohydrate or <20% fat are insufficient to maintain intramuscular stores of glycogen and fats, respectively. The optimum blend of carbohydrates and fats for different athletes is controversial and remains to be investigated.

Glucose has a direct and indirect effect on the immune system. Specifically, low levels of glucose result in increased levels of inflammatory cytokines and plasma cortisol. Carbohydrate ingestion before, during and after exercise has been the only nutritional intervention used thus far to evaluate moderate exercise-induced immune suppression.[32] one consequence of a high-carbohydrate diet is that critical micronutrients such as zinc, iron, selenium and copper are not sustained and, thus, negatively affect immune function.

High oxidative metabolism may increase the production of oxygen free radicals. Supplementation with antioxidant vitamins, trace-element cofactors of antioxidant enzymes, ascorbic acid, tocopherol and β-carotene, may be beneficial.[1,37] Although no clear guidelines for β-carotene supplementation have been approved, 30 mg/day is considered adequate.[1] As a precaution, vitamin B12 supplementation is recommended for athletes on negative-energy-balance diets, particularly vegetarians. An intake of ascorbic acid 1g per day for 3 weeks before competition has been recommended.[1] Larger doses of ascorbic acid are associated with negative effects (diarrhoea, joint pain, and kidney stones). High doses of tocopherol over a long period (550 mg/day for 50 days) may provide some protection against the negative effects of exercise. The diets of athletes often contain mega-doses of vitamins (10 to 1000 times RDA); however, this is not useful and, in fact, may be harmful. Athletes are recommended to consume zinc-rich foods, but athletes on low caloric intake, fat-free diets, or who are vegetarians, are recommended to take a supple-

ment of zinc 10 to 20mg/day.[1] Athletes are recommended to have iron intakes of 17.5 mg/day (men) or 23 mg/day (women). This recommendation can easily be met through an energy balanced diet that includes fats and meats. In vegetarians, or athletes on low-energy-balance diets, supplementation is recommended. Both selenium and copper should be available in sufficient amounts to meet the daily requirements of energy-balanced diets containing sufficient fats and meats. In under-nourished athletes, supplementation should be performed carefully because of the potential negative consequences.

A low-fat diet comprised of too few calories is immunosuppressive in runners. It may be possible to overcome some of the adverse immunosuppressive effects of exercise on the immune system of runners through carefully selecting both the quantity and type of dietary fat. Consuming increasing levels of dietary fat (up to 42% of total caloric intake) does not elevate fasting levels of triglycerides, total cholesterol, or high-density lipoprotein cholesterol in the plasma of runners, suggesting that higher fat consumption can be recommended for athletes without increasing the risk of cardiovascular disease. The intensity and duration of exercise will affect both carbohydrate and fat oxidation and, thus, determine the amount of carbohydrate, and the amounts and types of fat that should be ingested to meet the exercise demands and maintain immunocompetence. Fat intake may be particularly important in female athletes where low-caloric/low-fat-intake diets are associated with amenorrhoea and diminished exercise performance.

As indomethacin has been shown to counter post-surgical, PG-mediated immunosuppression, it has been suggested that athletes take it.[1] As ingestion of omega-3 PUFAs has an effect similar to indomethacin, experiments are needed to determine the best course for athletes. It should be cautioned that, because excessive dosages of omega-3 PUFAs have immunosuppressive effects, dose-response curves have to be worked out before recommending a policy.

A significantly negative protein balance suppresses virtually all components of the immune system. This may be a factor in athletes who are overtrained or who have low total and/or protein caloric intakes, thus leading to a negative nitrogen balance. If athletes are calorically balanced, and the percentage of calories from protein is constant, the increased caloric intake will increase protein intake in proportion to protein catabolism. Athletes who are overtrained, fatigued or who have a documented low protein intake, may benefit from supplementation with protein for a 2- to 3-week period, after which they should return to a normal protein intake, as high levels of protein are as bad for the immune system as a low protein intake.

The upper limit of fat intake and lower limits of carbohydrate intake are still not known. Based on available data, even athletes in heavy training have sufficient protein intake as long as it is 12 to 15% of total calories; thus, supplementation is not recommended, irrespective of age or gender.[26] Carbohydrate and fat intakes of 35% of total calories, on diets balanced in caloric intake and expenditure, are sufficient to maintain both muscle glycogen and fat stores. Thus, one could suggest a 'baseline diet' of 12% protein, 35% carbohydrate and 35% fat. The remaining 18% of the total calories could be distributed among carbohydrates, fats and proteins with the ratio being determined by the type of sport activity. For example, distance runners may take more fat, high-intensity intermittent athletes more carbohydrate, and weightlifters more protein (up to 15%). The treatment of overtraining has been suggested to include: reducing the intensity/duration of training, eliminating monotonous training, altering loading and regeneration phases, getting regular sleep, and obtaining an adequate quantity and quality of nutrition.[2]

Athletes should consume a diet comprised of varying amounts of total calories, carbohydrates, fats and proteins that are consumed during their training and competition. Compromising any of these elements results in reduced performance and a suppression of the immune system, leading to an increased risk of infection. It is of great concern that many athletes are on low total calorie and low-fat diets that result in not only depleted intramuscular

fat stores and essential fatty acids, but also deficiencies in many micronutrients. The unavailability of fat to oxidise and spare glycogen and build the immune system, leads to reduced exercise performance and increased stress and risk of infection. Although the exact balance of a diet is unproven, a baseline diet that comprises of 15% protein, 35% carbohydrates and 35% fats, and of a caloric intake that is balanced to caloric expenditure, is recommended. The remaining 15% consumed should be made up of the specific substrate(s) expended.

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