Exercise and the Immune System - Influence of Nutrition and Ageing

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In essence, the immune system is enhanced during moderate and severe exercise, and only intense long-duration exercise is followed by impairment of the immune system. The latter includes suppressed concentration of lymphocytes, suppressed natural killer cell activity, lymphocyte proliferation and secretory IgA in saliva. During the time of immune impairment, referred to as "the open window", microbial agents, especially viruses may invade the host and infections may be established. One reason for the "overtraining effect" seen in elite athletes could be that this window of opportunism for pathogens is longer and the degree of immunosuppression more pronounced. Alterations in metabolism and metabolic factors may contribute to exercise-associated changes in immune function. Reductions in plasma-glutamine concentrations, altered plasma-glucose level, free oxygen radicals and prostaglandins (PG) released by the elevated number of neutrophils and monocytes may influence the function of lymphocytes and contribute to the impaired function of the later cells. Thus, nutritional supplementation with glutamine, carbohydrate, anti-oxidants or PG-inhibitors may, in principle, influence exercise-associated immune function. Although several intervention studies have been performed, it is premature to make recommendations regarding nutritional supplementation to avoid post-exercise impairment of the immune system.

Introduction

Exercise has significant effects on the immune system. In essence, a bout of exercise induces mobilization of immunocompetent cells to the circulation. Following strenuous exercise, but not moderate exercise, the function of the immune system is impaired for up to 72 hours (Hoffman-Goetz & Pedersen, 1994; Pedersen and Nieman, 1998; Brines et al. 1996). Epidemiological evidence exists which supports the anecdotal impression (Nieman & Henson, 1994) that regular exercise increases resistance to infections such as the common cold (Fitzgerald, 1988; Nash, 1987), whereas hard training is associated with increased respiratory tract infections (Fitzgerald, 1988).

The relationship between nutritional factors and resistance to infections has generated considerable interest over the past several decades. In industrialized countries the relationship between nutrition and immunity is of special interest in elderly subjects, since it is known that age-related immunodeficiency is aggravated in malnourished subjects. In theory, it is possible that the exercise-induced immunological changes can be modulated by nutritional factors, and that
dietary factors influence resting levels of the immune system in athletes. Furthermore, aging is associated with a suppression in the normal function of the immune system which may influence the ability to respond to physical stress. Nutritional supplementation may in theory partly revert this immune senescence. On this background a short review will be given on exercise, nutrition, aging and immune function.

Exercise and Immune Function

Acute Exercise

In relation to acute exercise, there are several consistent patterns that emerge regarding leukocyte subpopulations in the blood. The neutrophil concentration increases during exercise and continues to increase post-exercise (McCarthy & Dale, 1988). The lymphocyte concentration increases during exercise and falls below pre-exercise values following intense long-duration exercise, but is not suppressed after moderate exercise (McCarthy & Dale, 1988). The increased lymphocyte concentration is due to recruitment of all lymphocyte subpopulations to the blood. Thus, both the CD4+ T cells, CD8+ T cells, CD19+ B cells, CD16+ natural killer (NK) cells, and CD56+ NK cells increase in number during exercise and decline following intense exercise lasting at least one hour. Furthermore, following intense long-duration exercise the function of NK and B cells is suppressed. Thus, the NK cell activity (the ability of NK cells to lyse a certain number of tumor target cells) is inhibited. Furthermore, antibody production in the circulation is inhibited and the local production of secretory IgA in mucosa is inhibited (Figure 1; Pedersen, 1997; Pedersen & Nieman, 1998).

Figure 1: An acute bout of exercise induces mobilization of lymphocytes to the circulation. Following intense exercise the lymphocyte concentration decreases and the ability of the cells to proliferate, mediate cytotoxic activity and produce immunoglobulins is impaired. During this temporary post-exercise immune impairment, microorganisms may invade the body and establish as infections.
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Strenuous exercise also induces increased circulating levels of several cytokines. Initial studies described increased levels of IL-1 in plasma obtained after exercise (Cannon & Kluger, 1983; Cannon et al., 1986; Evans et al., 1986), but the possibility exists that other cytokines were measured as the latter studies were conducted prior to the availability of recombinant IL-1 proteins. As pointed out by Bagby et al. (1996), there have been a number of studies which failed to detect elevated levels of IL-1 in plasma (Northoff & Berg, 1991; Ullum et al., 1994; Sprenger et al., 1992; Cannon et al., 1991). However, IL-6 has been found to be enhanced in several studies (Northoff & Berg, 1991; Ullum et al., 1994; Sprenger et al., 1992; Bruunsgaard et al., 1997; Ostrowski et al., 1998; Rohde et al., 1997; Ostrowski et al., 1998; Ostrowski et al., 1998; Ostrowski et al., 1999) and is followed by an increase in the concentration of the IL-1 receptor antagonist (IL-1ra), a natural occurring inhibitor of IL-1 (Ostrowski et al., 1998; Ostrowski et al., 1998; Ostrowski et al., 1999). Recent data from our group described that the soluble TNF-α receptors (sTNF-αR) 1 and 2 and the chemokines IL-8 and MIP-1b are also increased in response to strenuous exercise (Ostrowski et al., unpublished data).

Bruunsgaard et al (1997) compared concentric and eccentric exercise and found an association between increased IL-6 level and muscle damage as visualized by the increase in creatine kinase. Thus, the study supports the hypothesis that the post-exercise cytokine production is related to skeletal muscle damage. Recently, we have found IL-6-mRNA in skeletal muscle biopsies obtained from runners after a marathon run (Ostrowski et al. 1998). The latter data thus indicate that IL-6 is locally produced in response to strenuous exercise or exercise-induced muscle damage. IL-1ra-mRNA was not present in the skeletal muscle, but expressed by blood mononuclear cells (BMNC) obtained after, but not before the marathon, indicating that locally produced IL-6 induces a systemic anti-inflammatory response. The cytokine cascade in response to exercise resembles that seen in response to trauma, and exercise thus may be considered a model of trauma.

**Chronic Exercise**

The immune function (resting levels) in athletes versus non-athletes has more similarities than disparities, reviewed in (Nieman, 1996). Natural immunity may be slightly increased, whereas neutrophil function has been described to be slightly suppressed. The adaptive immune system (resting state) in general seems to be largely unaffected by intensive and prolonged exercise training (Baj et al., 1994; Tvede et al., 1991; Nieman et al., 1995). The innate immune system appears to respond differentially to the chronic stress of intensive exercise, with NK cell activity tending to be enhanced while neutrophil function is suppressed (Hack et al., 1994; Nieman et al., 1993; Pedersen et al., 1989; Pyne et al., 1995).

Based on anecdotal information, a general feeling has been that while regular training promotes resistance to upper respiratory tract infections (URTI) severe exertion, especially when coupled with mental stress, places athletes at increased risk for URTI (Fitzgerald, 1991; Nieman, 1994). Based on the above mentioned epidemiological studies a relationship between exercise and URTI has been modelled in the form of a "J" curve (Figure 2). This model suggests that while the risk of URTI may decrease below that of a sedentary individual when one engages in moderate exercise training, the risk may rise above average during periods of...
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The "J" Form Curve

Risk of URTI

Above Average

Average

Below Average

Sedentary Moderate High

Amount and Intensity of Exercise

Figure 2: "J"-shaped model of relationship between varying amounts of exercise and risk of upper respiratory tract infection (URTI). This model suggests that moderate exercise may lower risk of infections while excessive amount may increase risk.

excessive high-intensity exercise (Nieman, 1994). The link between exercise-associated immune changes and sensitivity to infections may be explained by the so called "open window" of altered immunity (which may last between 3 and 72 hours, depending on the immune measure as well as the type, duration and intensity of exercise). We have previously hypothesized that viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. However, it remains to be demonstrated if athletes showing the most extreme immunosuppression following heavy exertion are those that contract an infection within the following 1-2 weeks.

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The mechanisms underlying exercise-associated immune changes are multifactorial and include neuroendocrinological factors such as adrenaline, noradrenaline, growth hormone, cortisol and beta-endorphin (Pedersen et al., 1997). Physiological factors such as increased body temperature during the exercise (Kappel et al., 1991) or oxygen desaturation (Klokker et al. 1995) may also have an impact. Altered protein metabolism, such as reduced plasma-glutamine concentrations, as a result of muscular activity has been suggested to influence lymphocyte function (Newsholme & Parry Billings, 1990), and reduced plasma-glucose has been suggested to increase stress-hormone levels and thereby alter immune function (Nieman & Pedersen, 1999). Furthermore, as a consequence of the acute catecholamine- and growth hormone-induced changes in leukocyte subsets, the relative proportion of these subsets change and activated leukocyte subpopulations may be mobilized to the blood. Free oxygen radicals and prostaglandins (PG) released by the elevated number of neutrophils and monocytes may influence the function of lymphocytes and contribute to the
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impaired function of the later cells. Thus, nutritional supplementation with glutamine, carbohydrate, anti-oxidants or PG-inhibitors may, in principle, influence exercise-associated immune function.

Glutamine

It has generally been accepted that cells of the immune system obtain their energy by metabolism of glucose. However, it has been established that glutamine is also an important fuel for lymphocytes and macrophages. Several lines of evidence suggest that glutamine is used at a very high rate by these cells, even when they are quiescent (Newsholme, 1994). It has been proposed that the glutamine pathway in lymphocytes may be under external regulation, due partly to the supply of glutamine itself (Ardawi & Newsholme, 1984). In vitro, glutamine stimulates lymphocyte proliferation, lymphokine activated killer cell activity and cytokine production (Rohde et al., 1995; Rohde et al., 1996). Skeletal muscle is the major tissue involved in glutamine production and is known to release glutamine into the blood stream at a high rate. It has been suggested that the skeletal muscle plays a vital role in maintenance of the key process of glutamine utilization in the immune cells. Consequently, the activity of skeletal muscle may directly influence the immune system. It has been hypothesized (the so called "glutamine-hypothesis") that under intense physical exercise, or in relation to surgery, trauma, burn and sepsis, the demands on muscle and other organs for glutamine are such that the lymphoid system may be forced into a glutamine debt, which temporarily affects its function. Thus, factors that directly or indirectly influence glutamine synthesis or release, could theoretically influence the function of lymphocytes and monocytes (Newsholme, 1994; Newsholme, 1990; Wallace & Keast, 1992). Following intense long-term exercise and other physical stress, the glutamine concentration in plasma declines (Parry Billings et al., 1992; Keast et al., 1995; Essen et al., 1992; Lehmann et al., 1995; Keast, 1996; Rohde et al., 1996). Furthermore, low glutamine levels have been described in athletes with the "overtraining syndrome" (Rowbottom et al., 1997; Rowbottom et al., 1996; Keast, 1996; Keast & Morton, 1992).

Clearly, optimal lymphocyte proliferation is dependent on the presence of glutamine, but there are no published data showing that glutamine supplementation restores impaired immune function post-exercise. The critical question therefore is not whether concomitant decreased plasma glutamine concentration and lymphocyte function occur following intense exercise, but whether a causal relationship exists. In two recent placebo-controlled glutamine intervention studies (Rohde et al., 1998; Rohde et al., 1998), it was found that glutamine abolished the post-exercise decline in plasma glutamine, without influencing post-exercise immunosuppression. Thus, the latter study did not support the hypothesis that the post-exercise decline in immune function is caused by a decrease in the plasma glutamine concentration.

Carbohydrate

Earlier research had established that a reduction in blood glucose levels is linked to hypotalamic-pituitary-adrenal activation, an increased release of adrenocorticotropic hormone and cortisol, increased plasma growth hormone, decreased insulin, and a variable effect on blood adrenaline levels (Nieman & Pedersen, 1999). Given the link between stress hormones and immune responses to prolonged and intensive exercise (Pedersen et al., 1997), carbohydrate
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compared with placebo ingestion should maintain plasma glucose concentrations, attenuate increases in stress hormones, and thereby diminish changes in immunity. This hypothesis has been tested in a number of studies by Nieman and colleagues (Nehlsen-Canarella et al., 1997; Nieman et al., 1997; Nieman et al., 1997) using double-blind, placebo-controlled randomized designs. Carbohydrate beverage ingestion before, during (about 1 liter/hour), and after 2.5 hours of exercise was associated with higher plasma glucose levels, an attenuated cortisol and growth hormone response, fewer perturbations in blood immune cell counts, lower granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response. Overall, the hormonal and immune responses to carbohydrate compared with placebo ingestion were diminished. Some immune variables were affected slightly by carbohydrates ingestion (eg. granulocyte and monocyte function), while others were strongly influenced (eg. plasma cytokine concentrations, and blood cell counts). The clinical significance of these carbohydrate-induced effects on the endocrine and immune systems awaits further research. At this point, the data indicate that athletes ingesting carbohydrate beverages before, during, and after prolonged and intensive exercise should experience lowered physiologic stress. Research to determine whether carbohydrate ingestion will improve host protection against viruses in endurance athletes during periods of intensified training or following competitive endurance events is warranted.

Lipids

It has been suggested that if the n-6/n-3 ratio is shifted in favour of n-6, this will result in increased production of prostaglandin PGE\(_2\) and suppress cellular immune system. During stress conditions n-3 fatty acids may counteract latent immunosuppression mediated by increasing PGE\(_2\) production which in contrast appears to be further enhanced by intake of n-6 fatty acids. The hypermetabolism n-3 fatty acids potentially acts to reduce the incidence of new infections. In animal experiments it was shown that the stress response following application of endotoxin, IL-1 or TNF was reduced when the animals were pretreated with n-3 fatty acids (fish oil). The diet rich in n-3 fatty acids caused reduced catabolism, reduced febrile reaction, decreased eicosanoid production and improved survival rate.(Johnson, 3d et al., 1993)

The possible interaction between intense acute exercise, known to suppress the immune system (Hoffman-Goetz & Pedersen, 1994), and polyunsaturated fatty acids (PUFA) was examined in inbred female C57Bl/6 mice.(Benquet et al., 1994). The animals received either a natural ingredient diet or a diet supplemented with various oils such as beef tallow, safflower, fish oil or linseed oil for an eight week period. In the group receiving 18:3 (n-3) linseed oil it was shown that linseed oil abolished post-exercise immunosuppression of the immunoglobulin M plaque forming cell response. The mechanism underlying the absence of exercise-induced immunosuppression in animals fed linseed oil may be that linseed oil diminishes the n-6/n-3 ratio and thereby diminishes the PGE\(_2\) level after intense exercise. Thus, the effect of linseed oil may be ascribed to a link between a diet rich in n-3 PUFA and abolition of prostaglandin-related immunosuppression. In support of this hypothesis, it has been shown that when the PGE\(_2\) production was inhibited by the PG-inhibitor indomethacin, exercise-induced suppression of the NK cell activity and B cell function was attenuated (Tvede et al., 1989; Pedersen et al., 1990). The possibility that n-3 fatty acids may diminish the exercise-
induced cytokine response has not been investigated and there are no published human exercise studies evaluating the role of lipids in abolishing post-exercise immunosuppression.

**Anti-Oxidants**

Anti-oxidants may in theory neutralize the reactive species which are produced by neutrophilic leukocytes during phagocytosis (Babior, 1984; Hemila, 1992). Using a double blind placebo design, Peters (Peters et al., 1993) evaluated the effect of vitamin C on the incidence of URTI during the two week period following the 90-km Comrades ultramarathon. The URTI incidence was 68% in the placebo group, whereas only 33% reported URTI when taking a 600 mg vitamin C supplementation daily for 3 weeks prior to the race. In another study Peters et al (1992) found that vitamin A supplementation had no effect on the incidence of URTI in marathoners. Only one study (Nieman et al., 1997) has evaluated the effect of vitamin C on lymphocyte function and stress hormone levels. Supplementation with vitamin C did not influence leukocyte subsets, NK cell activity, lymphocyte proliferative responses, granulocyte phagocytosis and activated burst, catecholamines and cortisol.

**Ageing and Immune Function**

Ageing is characterized by a decline in the ability of individuals to adapt to environmental stress (Makinodan & Marguerite, 1980; Miller, 1989; Miller, 1996). Ageing is associated with a functional decline in several components of the immune system. As a result, the elderly are more vulnerable, and are at increased risk of obtaining infectious diseases, tumorigenesis, and autoimmune disorder (Armstrong, 1990).

**T Cells**

One of the most striking features of immunosenescence is thymus involution. In humans, the thymus begins to involute at early stage of life, and the process is completed by mid life. Many age-related changes in the immune system can be related to the loss of thymic and T cell function. The involuted thymus has only a limited capacity to provide the circulation with “naive” T cells. There is thus a significant decrease in "naive" T cells relative to "memory" T cells. Positive and negative intrathymic T cell selection is compromised in the elderly and consequently leads to the appearance of anti-self-reactive T cells and T cells that do not express self-major histo compatibility (MHC)-restricted antigen recognition (Shinkai et al., 1996).

The number of cells that arrive in the periphery from the thymus is, however, much too low to account for peripheral turnover and essentially nothing is known about the effects of aging on the very substantial self-renewal process in the peripheral immune system. Peripheral T cells are capable, in the absence of thymic influence, of at least a 10^5-fold expansion in vivo (Miller, 1996).

The elderly have been shown to have a low total lymphocyte count. Within the T cell subsets, both CD4^+ and CD8^+ cells decrease with age, but is more pronounced regarding CD8^+ T cells showing an age-related increase of CD4^+ /CD8^+ ratio (Utsuyama et al., 1992). Moreover ageing leads to an increase in "memory" cells CD45R0^+ T cells at the expense of "naive" CD45RA^+ (i.e., virgin, previously unstimulated) T cells. This change has been documented in circulating CD4^+ and CD8^+ T cells (Shinkai et al., 1996). The age associated shift in T cell phenotype
may largely be responsible for the age-related decline in responsiveness to mitogens in vitro and new antigens in vivo (Miller, 1996). The T cell functions decline with age, as shown in vivo by tests of cutaneous delayed type hypersensitivity (DTH) and in vitro by mitogen-stimulated proliferation. The T cells show a decreased proliferation when stimulated with mitogens (Miller, 1996). The production of IL-2 and the expression of the high-affinity receptor decreases with age and, as a consequence, the T cells show a decreased ability to proliferate. The activity of cytotoxic T lymphocyte (CTL) declines with age. This can be attributed not only to the reduced number and proliferative capability of CD8+ T cells, but also to the reduced expression with age of genes coding for perforin and two CTL-associated serine esterases (Shinkai et al. 1996). Effros et al. (1994) compared T lymphocytes of centenarians and younger controls for the cell surface expression of CD28+, a costimulatory molecule that is required for optimal activation and proliferation following engagement of the T cell. They found a significant decrease in the expression of CD28+ in the elderly compared to the younger controls.

**B Cells**

The data on human blood B cell numbers are in conflict, with one group finding no evidence for any effect of age (Utsuyama et al., 1992) and a second (Paganelli et al., 1992) reporting a 4-fold decline in adult life. A third group (Hoffkes et al., 1996) showed that the CD19+CD5− B cell subset was decreased in the elderly patients. It is generally reported that B cell function is only marginally affected by the ageing process (Ben-Yehuda & Weksler, 1992; Ennist et al., 1986). As T cell function and activity are adversely affected with age, regulation of B cell function by dysfunctional T cell mechanisms likely contribute to this observation. An optimal humoral immune response requires the cooperation of both B cells and T cells. Many of the cofactors that are needed by the B cells to secrete immunoglobulins are produced by T cells and as a consequence many of the changes seen in B cells are related to the loss in T cell function (Miller, 1996; Miller, 1991). Although there is a clear loss with age in the ability to produce antibody in response to new encountered antigens, it is uncertain to what extent this decline reflects intrinsic changes in B cell function (Miller, 1996). Much of the decline in humoral immunity is associated with changes in the activities of T cells, including T cell expression of CD40L, a key factor in contact-dependent B cell activation through the cell surface CD40+ protein. The elderly have shown an increase in the serum concentrations of autoantibodies, but these are typically of low titre (Miller, 1996).

**NK Cells**

When looking at NK cell number and activity in the spleen from both mice and rats, there is a clear and consistent age-associated decline in NK cell number and activity (Nasrullah & Mazzeo, 1992; Saxena et al., 1984; Weindruch et al., 1983). However, when examining peripheral blood NK cell activity in humans, it is frequently reported that no age-associated change is found (Ferguson et al., 1995; Lighthart et al., 1986; Murasko et al., 1986) and in some cases an increase in NK cell number and activity have been observed (Xu et al., 1993; Sansoni et al., 1993; Batory et al., 1981; Krishnaraj & Blandford, 1988; Krishnaraj & Blandford, 1987). One study (Facchini et al., 1987) described that the activity of NK cells (expressed per cell basis) decreases with age.
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The Acute Phase Response in the Elderly
Ageing is associated with immune activation and changes in the balance of cytokine secretion patterns (Miller, 1996; Fagiolo et al., 1992; Hobbs et al., 1993; Bruunsgaard et al., 1999). The serum/plasma concentrations of IL-6 (Wei et al., 1992; James et al., 1997; Hager et al., 1994; Kania et al., 1995; Ershler et al., 1993; Bruunsgaard et al., 1999) and TNF-α (Bruunsgaard et al., 1999) have been reported to increase with age whereas others have found unaltered or undetectable IL-6 (Peterson et al., 1994), TNF-α (Fagiolo et al., 1992; Peterson et al., 1994; Catania et al., 1997; Mooradian et al., 1990) and IL-1 (Catania et al., 1997; Mooradian et al., 1990).

Nutrition and Ageing
Given the fact that many of the protective immune responses are impaired in old age (De Weck, 1992; Pawelec et al., 1995), that nutritional deficiencies occur commonly in the elderly (Chandra, 1989) and that nutrition is a critical determinant of immunocompetence, it has been questioned whether a causal relationship exists between nutrition, immunity and infection in old age. Supplementation with selected nutrients may improve the immune system. Thus, Meydani (1995) showed that both short- and long-term vitamin E supplementation enhanced the lymphocyte proliferative response, delayed type hypersensitivity and IL-2 production in healthy elderly subjects. However, the use of a single nutrient in large doses may lead to secondary alterations in requirements, to malabsorption of other nutrients, and in some instances, to impaired immune responses. Thus excessive intake of zinc (Chandra, 1984) or vitamins E and D (Payette et al., 1990) were associated with impairment of the cellular immune response. Watson et al (1991) showed that supplementation with varying levels of β-carotene increased the number of CD4+ cells, NK cells and IL-2 receptor expression on BMNC when the level of β-carotene supplementation was greater than 30 mg/day for 2 months. The increase in NK cells and IL-2 receptor was dose dependent and the immunomodulation coincided with an increased level of plasma β-carotene, but not plasma retinol.

Recently, Chandra (1992) tested the hypothesis that an optimum intake of all essential micronutrients in physiological amounts would result in an improvement in immune response and reduce the frequency of infection in old age. Ninety-six healthy elderly subjects were randomly assigned to receive nutrient supplementation or placebo. The subjects were followed for 12 months. It was found that the subjects in the supplementation group had higher numbers of certain T cell subsets and NK cells, enhanced proliferative response to mitogens, increased IL-2 production, higher antibody response and increased NK activity. Furthermore, the groups receiving supplementation were less likely to have illness due to infections than those in the placebo group (23 versus 48 days).

Regarding the immune system and lipid metabolism, indirect evidence exists that the natural immunity may be enhanced by n-3 fatty acids and suppressed by n-6 fatty acids. Several reports indicate that formation of PGE2 increases with ageing, and an increase in the sensitivity of the lymphocytes from elderly subjects to the inhibitory effects on proliferation by PGE2 has been shown. (Goodwin & Messner, 1979). Therefore, PGE2-induced suppression of cell-mediated immunity by administration of n-6 fatty acids may be of special relevance to the elderly subjects and in theory, diets rich in n-3 fatty acids may enhance the immune system.
system in elderly subjects.

**Exercise: Ageing and Immune Function**

Given that a number of age-related changes occur in many systems (e.g. neuroendocrine) known to alter immune function both at rest and during exercise, it would be of value to learn the extent to which both acute and chronic exercise influence immune function in the elderly (Mazzeo, 1994).

**Acute Exercise**

While few studies have been performed to date, recent evidence suggests that the ability of the immune system in older individuals to respond to the stress imposed from a single bout of exercise is maintained with age. Mazzeo et al. (1996) have investigated the effect of a single bout of exercise on immune function in young (23 ± 2 years) and elderly (69 ± 4 years) subjects. The subjects were studied before and immediately after 20 min of supine cycle exercise performed at 60% of peak capacity. The results from his study showed that in response to exercise the young subjects showed a significant decrease in PHA proliferative capacity, demonstrating that the acute bout of exercise, at that intensity and duration, was immunosuppressive. The PHA responsiveness was significantly lower for the elderly before performing the exercise test compared with the young subjects, but did not decline significantly as a result of exercise. This study indicates that immunoresponsiveness to a single bout of exercise differed across age groups. Fiatarone et al. (1989) examined the effect of age on the responsiveness of NK cells to in vivo stimulation with exercise in 8 young (30 ± 1 years) and 9 old (71 ± 1 years) subjects. The old subjects were not found to have NK cell numbers and function that were significantly different from the young subjects at baseline. In response to maximal bicycle exercise, both groups showed an increase in the NK activity. A similar result was found by Solomon (1991) who examined the effect of a maximal ergometry exercise test on NK activity and found an increase in NK activity and numbers in both the young and the old group. Crist et al. (1989) have also examined the effect of a single bout of treadmill exercise in elderly women on NK cells. One group of the elderly participated in 16 weeks of aerobic training, while the other group of elderly subjects was age-matched sedentary controls. Women participating in the training showed increases in NK activity at rest when compared with the sedentary controls. An acute bout of treadmill exercise produced an increase in NK activity in both groups; however, the increase was more significant in the trained group compared with controls.

**Chronic Exercise**

A limited number of studies has addressed the effect of endurance training adaptations on immune function in older individuals. Nieman et al. (1993) examined the effect of 12 weeks of walking (5 d/week at 60% heart rate reserve) and found no effect on basal NK activity and T cell function in previously sedentary elderly women (73 ± 1 years). T cell function and NK activity were significantly greater in a group of highly conditioned female endurance competitors (73 ± 2 years) when compared with age-matched sedentary controls, but remained below the level for the young, sedentary women. These data show a difference in immune function between moderately trained and highly conditioned women. The mechanisms responsible for this difference are uncertain, but may be related to differences in the training intensity, duration,
and frequency. Alternatively, the age at which the training is initiated could be an important factor because the highly conditioned women had begun exercising at a younger age (Mazzeo, 1996).

Shinkai et al. (1996) have examined the effect of exercise on immunosenescence in men. A cross-sectional survey examined whether habitual endurance exercisers retained a higher level of T cell function than sedentary persons in old age. Compared with the young subjects, both groups of elderly had lower circulating CD3⁺ and CD8⁺ cell counts, higher CD4⁺/CD8⁺ ratio and higher percentages of activated CD3⁺ and “memory” CD4⁺ and CD8⁺ cells. Moreover, a comparison between the active and sedentary elderly groups showed no differences in circulating counts of immunocompetent cells. However, the active elderly subjects demonstrated significantly greater proliferative responses to phytohemagglutinin and to pokeweed mitogen. These results indicate that endurance training in later life is associated with a lesser age-related decline in certain aspects of circulating T cell function.

Rail et al. (Rail et al. 1996) did not find any changes in BMNC subsets, production of IL-1β, TNF-α, IL6, IL2 or PGE₂ production, lymphocyte proliferation or delayed type hypersensitivity response after 12 weeks of high intensity training progressive resistance training in 8 healthy young (22-30 yr) and 8 healthy elderly (65-80 yr) subjects. Rincon et al. (Rincon et al., 1996) investigated the effect of an exercise intervention program of 60 min, 3 times a week for three months in 6 frail 70 years' males at risk for falling, but not suffering from serious medical problems compared with 7 controls having no intervention. Cytotoxic activity of NK cells significantly decreased during the course of the study suggesting that exercise had an adverse effect on NK activity in the very frail elderly. Another type of exercise was performed by Xusheng et al. (1989). They investigated the effect of practicing Taichiquan (style 88) exercise, a traditional Chinese keep-fit exercise. 30 (15 female 60 ± 1 and 15 male 64 ± 1 years) elderly participated in the Taichiquan exercise and 30 age-matched subjects served as controls. At rest, the total number of T lymphocytes and the number of active T lymphocytes were increased significantly in the exercise group when compared with controls. Immediately after a bout of Taichiquan exercise, a marked increase of active T lymphocytes occurred. Xusheng et al. (1990) also determined the percentage and counts of zymosan-complement complex rosette forming (B) cells and found at rest that the percentage in the Taichiquan exercise group was significantly lower than that of the age-matched controls. There was no significant difference observed between exercise group and control group for the number of ZC rosettes at rest. Immediately following a set of Taichiquan exercise the percentage and the counts were significantly increased.

Animal Studies

While results from animal studies can be more extensive, there are very few studies available. Ferrández and De la Fuente (1996) measured antibody-dependent cellular cytotoxicity (ADCC) and NK cell activity in leucocytes from 20 young (12 weeks) and 20 old (60 weeks) BALB/c mice which had performed moderate swimming until exhaustion (Facchini et al., 1987). Acute exercise produced a significant stimulation of ADCC capacity only in aged animals whereas there was no difference in NK cell activity with regard to both young and old animals. In the same study 20 old and 20 young mice performed 90 minutes
daily moderate swimming for 20 days resulting in higher ADCC in both age groups. There was no difference in cytotoxic activities at baseline between the groups. Thus, ageing did not seem to induce a decrease in cytotoxic activities during acute or chronic exercise. In a study by Barnes et al. (1991), old Fischer-344 rats were given endurance training for a 10-week period. Old rats had a poorer antibody response than young animals; however, exercise training did not influence the antibody production to specific antigen. Pahlavani et al. (1987) investigated the role of exercise training on immunosenescence in male Fischer-344 rats. Rats of four different age groups were examined (1, 6, 12 and 18 months of age, initially) after a 6-month training program. An age-related decline was found in both unstimulated, mitogen-stimulated proliferation and IL-2 synthesis. It was concluded that exercise training prevented neither the age-related decline in lymphocyte proliferation nor the IL-2 production. Furthermore, training had an adverse effect on mitogen-induced proliferation and for IL-2 production but only in the younger animals.

In another study Nasrulla and Mazzeo (1992) measured mitogen-stimulated lymphocyte proliferation, IL-2 production and NK cell cytotoxicity in splenocytes from 1-, 17- and 27-month old Fischer-344 male rats. Mitogen-induced proliferation and IL-2 production were found to decrease significantly with age in both trained and untrained animals. Training significantly reduced proliferation and IL-2 production in younger animals. This is in accordance with the findings by Lin et al. (1993). However, the proliferative response and the IL-2 production were found to increase in response to training in the old animals compared with the age-matched controls. The NK cell activity declined significantly with age and training did not alter this response. The latter finding is in contrast to several other animal studies in young animals, which have shown increased resting levels of NK cell activity in response to training. (MacNefl & Hoffman-Goetz, 1993; MacNefl & Hoffman-Goetz, 1993; MacNefl & Hoffman-Goetz, 1993; Hoffman-Goetz et al., 1994; Hoffman-Goetz et al., 1992).

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In a study of the age-related response of neutrophils and muscle damage to eccentric exercise Cannon et al. (1990) examined <30 year old subjects and >55 year old subjects. The subject groups were further divided in a double-blind placebo-controlled protocol, which examined the influence of 48 days of dietary vitamin E supplementation before the exercise. All subjects were monitored for 12 days after exercise. Dietary supplementation with vitamin E tended to eliminate the differences between the two age groups, primarily by increasing the responses of the older subjects. In another study Cannon et al., (1995) attempted to test if dietary modification of fatty acids influenced neutrophil and monocyte secretion after an in vivo inflammatory stress in older human subjects. In vivo neutrophil degranulation was assessed by plasma elastase concentrations and monocyte function was assessed by IL-1β secretion in vitro. In response to eccentric exercise, older subjects (>60 yr) taking placebo had no apparent elastase response whereas those taking fish oil supplements responded with a significant increase (142%) increase in plasma elastase similar to responses of younger reference subjects.

The same group investigated the influence of damaging eccentric exercise on in vitro production and plasma concentrations of cytokines and their relationship to
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muscle breakdown. In a double-blind placebo-controlled study they examined the effect of vitamin E supplementation for 48 hours on the exercise-induced acute phase response. The volunteers were either young (25 years) or elderly (65 years) sedentary men. They performed 45 min of eccentric exercise (downhill treadmill running). Twenty-four hours after this single session of eccentric exercise, endotoxin-induced secretion of IL-1β was augmented in cells obtained from the placebo subjects, but no significant effect was observed in cells from the vitamin E-supplemented subjects (Cannon et al. 1991). The finding by Cannon et al. (1991) that IL-1β and TNFα secretion was increased the morning after exercise without any current changes in mononuclear cell numbers indicate that the monocytes are activated in relation to eccentric exercise. The effect of vitamin E on IL-1β and IL-6 could not be ascribed to changes in prostaglandin (PGE2) (Cannon et al., 1991). Oxygen radicals enhance endotoxin-induced IL-1β production. (Kasama et al., 1989). Furthermore, the concentration of these reactants increases with exercise (Davies et al., 1982). Thus, the effects of vitamin E on the secretion of IL-1β are consistent with a mechanism involving oxygen radicals. No studies have measured the influence of anti-oxidants on plasma cytokines, which may be a better reflection of the in vivo situation.

Conclusion

Immunocompetent cells are mobilized to the circulation during an acute bout of exercise. The ability of the immune system to respond to a single bout of exercise seems to be maintained in the elderly, but there is little information about the function of the cells that are mobilized in response to exercise in old versus young individuals. It is not possible to conclude whether an endurance training program alters the age-related decline in immune function. The major reason for this uncertainty is related to the scarcity of data addressing the issue of exercise and immune function in elderly. There is especially a lack of human studies. The available data suggest that although age-related decline in immune function can be retarded, the greatest effect will be seen only in very highly conditioned subjects. Several studies suggest that there is a link between nutrition and immune function. Supplementation studies indicate that age-related immunodeficiency is partly due to undernutrition or malnutrition. The immunodeficiency has been shown to be partly abolished by refeeding and by small doses of vitamins. In theory n-3 fatty acids may enhance age-related immune function and improve resistance to infections. Few studies have addressed the potential protective role of dietary supplementation in exercise-induced immunosuppression and muscle pain. Exercise-related immunosuppression in animals was attenuated by a diet rich in n-3 fatty acids. Conflicting results exist regarding the ability of anti-oxidant supplementation to decrease the incidence of post-race URTI symptoms. However, vitamin E may inhibit the acute phase response in eccentric exercise. Glutamine supplementation has not been effective in abolishing post-exercise suppression of the immune system. Carbohydrate loading diminished the hormonal and immune responses to exercise, but did not abolish post-exercise suppression. The effect of carbohydrate supplementation on the risk of obtaining post-exercise infections awaits further research. Even though it is difficult to evaluate the individual health benefits of attenuating age- and exercise-related immunodeficiency by nutritional supplementation, the total benefit to the health of the population may be substantial.
References


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