The T Cell and NK Cell Immune Response to Exercise

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Abstract:
Exercise elicits an increase in the numbers of circulating lymphocytes and lymphocyte subsets (including NK cells) which is followed by a decrease in the numbers of cells during recovery from exercise; this lymphocytopenia appears to be due to a decrease in the percentage of type I T cells and NK cells in the circulation at this time. A decrease in mitogen-stimulated T cell proliferation and T cell production of IL-2 and IFN-γ is reported immediately after acute, intensive exercise. NK cell cytolytic activity per cell (NKCA) does not appear to change much after exercise unless the bout was prolonged, intense and stressful, in which case NKCA can be depressed for several hours. Resting immune function is not very different in athletes compared with non-athletes. However, periods of intensified training in already well trained athletes can result in a depression of immunity in the resting state which may be due to the cumulative effects of repeated bouts of intense exercise with the consequent elevation of stress hormones, particularly cortisol and anti-inflammatory cytokines (e.g. IL-6, IL-10, IL-1ra) causing temporary inhibition of type I T cell cytokine production with a relative dampening of the type I (cell-mediated) response.

Key words: Exercise; Training; Lymphocytes; Cytokines; Immune Function

Introduction

Leukocytes or white blood cells consist of the granulocytes (60-70% of circulating leukocytes), monocytes (10-15%) and lymphocytes (20-25%). Various subsets of the latter, including B cells, T cells and natural killer (NK) cells can be identified by the use of fluorescent-labelled monoclonal antibodies to identify cell surface markers (known as clusters of differentiation or cluster designators, CD). These cells have diverse functions in immune defence and wound repair. In transplant patients, it is the NK cells and T cells that are mostly responsible for tissue graft rejection. Immunosuppressant drugs are required to prevent the activation of these cells following transplant surgery. However, their circulating numbers and activity are also subject to physiological regulation. Some changes occur following prolonged strenuous bouts of exercise that cause a "natural suppression" of NK and T cell activity, which potentially may be of benefit to the transplant patient in terms of reducing the risk of rejection.

The effect of a single bout of exercise on circulating numbers of leukocytes

For strenuous exercise lasting less than 1 h there is an immediate leukocytosis consisting mainly of neutrophils and lymphocytes, which begin to recover leaving a developing neutrophilia peaking between 2-3 h post-exercise [1,2]. If the exercise is more prolonged however, these events superimpose upon each other. The initial leukocytosis appears to be produced by demargination of leukocytes due to increased shear stress and catecholamines. In contrast, the neutrophilia observed at the end of prolonged exercise or hours after brief, intense exercise is produced by release of neutrophils from the bone marrow induced by elevated plasma cortisol [1].

Acute exercise elicits characteristic biphasic changes in the numbers of circulating lymphocytes. Typically, increases in numbers of circulating lymphocytes (lymphocytosis) are observed during and immediately after exercise, with numbers of cells falling below pre-exercise levels during the early stages of recovery (lymphocytopenia), before steadily returning to resting values (Fig. 1). These changes are proportional to exercise intensity and, to a somewhat lesser extent, exercise duration.

Circulating T cell numbers

In response to acute exercise, the circulating concentration of the T cell subset ($CD3^+$) of lymphocytes also exhibits a biphasic response, with marked increases in T cell number during and immediately after exercise and significant falls in number during recovery (Fig. 2); this pattern is evident for intensive exercise of both shorter and more prolonged duration. For example, a 58% increase in T cell number was observed after just 30 min of a 2 h treadmill run at 65% of maximum oxygen uptake (VO_{2max}) and numbers fell to 42% below resting values at 2 h post-exercise [3]. This response appears to be largely related to exercise intensity since moderate exercise elicits few changes in T cell number [4]. The very close similarities between the circulating T cell responses and that of the total lymphocyte population should not be a surprise as T cells constitute around 70% of the peripheral blood lymphocytes.

Changes in numbers of the T cell subsets also exhibit biphasic responses to acute exercise [3-5]. Absolute changes in $CD4^+$ T-helper (Th) cell number are larger

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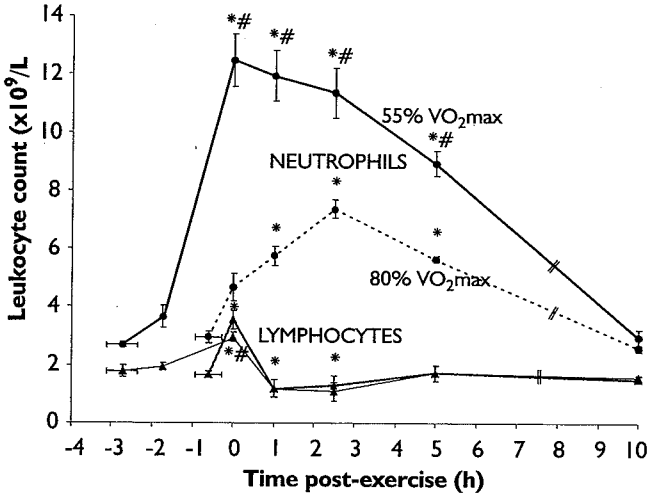

Figure 1. The effect of exercise intensity and duration on the circulating neutrophil and lymphocyte counts. Brief, high intensity exercise (37±19 min at 80% VO_{2max}) produces an initial increase in the neutrophil (o) and lymphocyte (Δ) counts, which is followed by a lymphocytopenia and developing neutrophilia. During early recovery from this bout there is a rapid remargination of leukocytes due to the falling cardiac output, shear stress and catecholamines, which is followed later in recovery by influx of neutrophils from the bone marrow and efflux of lymphocytes from the blood circulation under the influence of cortisol. In contrast, prolonged exercise (164±23 min at 55% VO_{2max}) produces a very large neutrophilia as cortisol has been elevated sufficiently long to allow new neutrophils into the circulation from the bone marrow. Mean±SEM, n=18. * indicates significant difference from pre-exercise ($p<0.05$), # indicates significant difference compared with 80% VO_{2max} trial. Data from Robson et al [2].

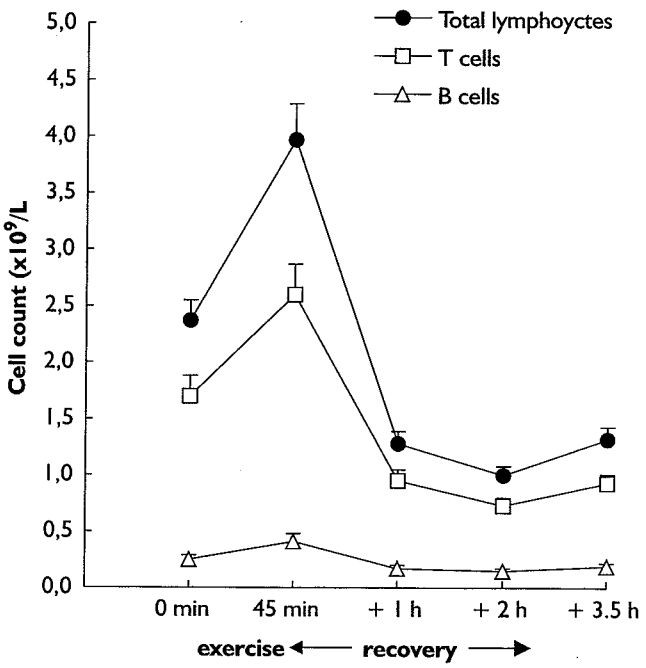

Figure 2. Changes in the circulating concentrations of total lymphocytes, T cells and B cells in response to a 45-min treadmill run at 80% VO_{2max}. Data from Nieman et al [3].

than those observed for $CD8^+$ T cytotoxic (Tc) cells, as might be expected given that $CD4^+$ cells account for up to 70% of the T cell subpopulation (Fig. 3A). However, when expressed as the percentage change from resting values, it appears that $CD8^+$ cells exhibit a greater relative increase in numbers during and immediately after exercise and more marked decline in numbers during recovery from exercise (Fig. 3B). This disproportionate change in the distribution of T cell subsets results in a change in the $CD4^+/CD8^+$ ratio, which therefore is commonly observed to decline during and immediately after exercise.

Intensive physical activity also affects the type 1/type 2 T cell balance. A 50% decrease in the percentage of $CD4^+$ and $CD8^+$ T cells producing IFN-γ upon stimulation (i.e type 1 T cells) has been reported immediately after a 2.5 h treadmill run at 75% VO_{2max} compared with resting values [6] and the percentage of type 1 T cells remained significantly lower than baseline at 2 h post-exercise. Similar findings were reported in response to exercise for the percentage of $CD4^+$ and $CD8^+$ T cells that produced IL-2 (another Th1 cytokine) following stimulation. In contrast, the percentage of $CD4^+$ and $CD8^+$ T cells that produced IL-4 following stimulation did not alter in response to exercise, even though a concomitant decline in the total number of circulating T cells was evident. These findings suggest that the decrease in T cell number following exercise is largely due to a decrease in type 1 T cells. In agreement with this, a significant decrease in the percentage of IFN-γ producing $CD4^+$ and $CD8^+$ T cells was found 2 h after a 1.5 h downhill treadmill run at 75% VO_{2max}, compared with post-exercise values [7]. Furthermore, the decrease in IFN-γ producing $CD8^+$ T cells was negatively correlated with the increase in the percentage of memory/effector ($CD45RO^+$) $CD8^+$ cells. This relationship suggests a specific decrease in the number of IFN-γ producing memory/effector $CD8^+$ T cells, although it is not clear whether these changes are due to programmed cell-death (apoptosis) or, as seems more likely, a redistribution of cells to other compartments.

Circulating Natural Killer (NK) cell numbers

Many authors have shown exercise to produce a large increase (50-500%) in the circulating natural killer (NK) cell count [4, 8, 9] (Fig. 4). The intensity and duration of the exercise appears to influence the scale of the NK mobilisation [4, 10] and the magnitude and speed of mobilisation of this lymphocyte subset is unparalleled. Infusion of catecholamines increases the number of circulating NK cells [11, 12]. Exercise-induced rises in circulating catecholamines may alter the expression of adhesion molecules on NK cells resulting in the mobilisation of NK cells into the circulation [12].

Effect of acute exercise on T and NK cell functions

T cell function

T cells play a fundamental role in the orchestration and regulation of the cell-mediated immune

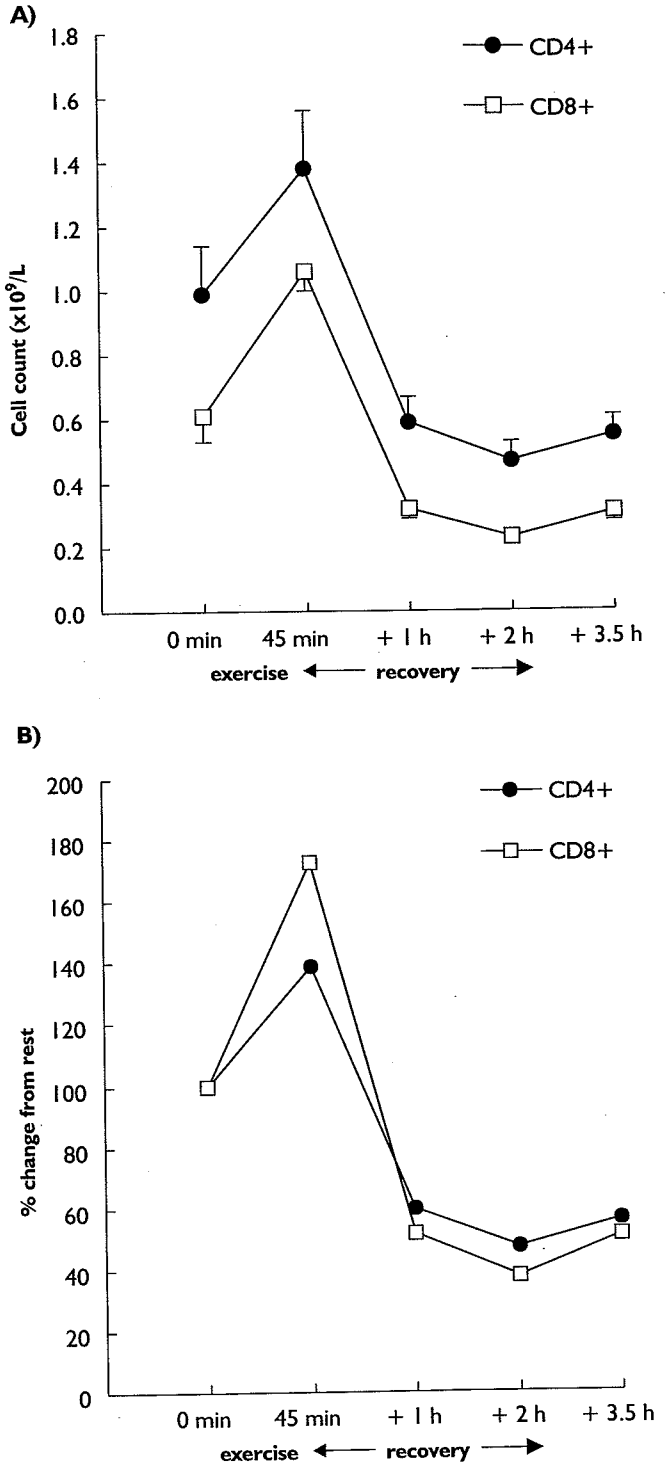

Figure 3. Changes in the absolute (A) and relative (B) circulating concentrations of $CD4^+$ and $CD8^+$ T cells in response to a 45-min treadmill run at 80% VO_{2max}. Data from Nieman et al [3].

response. One important consequence of a defect in T cell function is an increased incidence of viral infections [13]. With this in mind, it has been speculated that the apparent increased susceptibility of sportsmen and women to upper respiratory tract infections may be due to exercise-induced decreases in T cell function. One study has assessed the whole body cell-mediated response to an acute bout of prolonged strenuous exercise by injecting several antigens into the skin on the forearms of trained triathletes following a half-ironman event and found a marked impairment of *in vivo* cell-mediated immunity 48 h later compared with a group of non-exercising triathletes and a group of non-exercising moderately trained men [14].

A number of studies have assessed the effect of acute intensive exercise on T cell subset activation *in vivo* and in response to mitogen stimulation by assessing the concentration of circulating lymphocytes expressing cell surface markers of T cell activation, such as CD69 (a marker of early T cell activation), CD25 (IL-2 receptor), CD45RO (memory/effector T cells) and the HLA-DR antigen (MHC class II determinant). CD69 does not appear to be particularly responsive to exercise lasting around 1 h [15,16]. However, a study of military recruits found that following a ~2 mile training run there was a significant decrease in the percentage of $CD4^+$ cells expressing CD69 in response to mitogen-stimulation [17]. Moreover, mitogen-stimulated responses in $CD4^+$ and $CD8^+$ cells were significantly lower after exercise and during recovery in individuals with exertional heat injury [17]. In addition, immediately after an incremental treadmill run to exhaustion a marked decrease in mitogen-stimulated expression of CD69 in both $CD4^+$ and $CD8^+$ cells was observed in well-trained young men [18].

The release of cytokines by activated Th ($CD4^+$) cells largely determines whether the subsequent immune response to an antigen challenge will be cell-mediated (e.g. IL-2 and IFN-γ) or humoral (IL-4, IL-5, IL-6 and IL-13). As described previously, acute exercise affects the percentage of T cells in the circulation that produce IL-2 and IFN-γ, although this does not necessarily mean that the amount of cytokine released is reduced. However, studies that have investigated the amount of cytokine produced by stimulated lymphocytes in culture have found this to be affected by exercise. For example, prolonged exhaustive exercise was reported to decrease IFN-γ production in stimulated whole blood compared with pre-exercise values [19]. Furthermore, IL-2 production from stimulated blood mononuclear cells was markedly decreased during and after 1 h of cycling at 75% VO_{2max} compared with values at rest [20]. In contrast, IL-4 (a type 2 T cell cytokine) production by stimulated lymphocytes was unaffected by 18 min of incremental exercise consisting of 6 min at 55%, 70% and 85% VO_{2max} in active and sedentary males and females [21]. Taken together, these findings might suggest an inhibition of type 1 T cell cytokine production. However, although the predominant source of IL-2 is from Th1 cells, whole blood and mononuclear cell cultures contain T and NK cells, both of which release IFN-γ. Therefore, it is difficult to assign any changes in the production of this cytokine in stimulated cell cultures to specific alterations in T cell function. However, a recent study assessed the

effect of acute exercise specifically on intracellular cytokine production by $CD3^+CD4^+$ and $CD3^+CD8^+$ cells. It was reported that following 2.5 h of cycling exercise at 65% VO_{2max} the circulating number of phytohaemagglutinin-stimulated $CD4^+$ and $CD8^+$ lymphocytes positive for IFN-γ was decreased [22]. Furthermore, these stimulated cells produced less IL-2 and IFN-γ immediately post-exercise and at 2 h post-exercise compared with pre-exercise. In contrast, cells positive for IL-4 were virtually unaffected.

There is a general view in the literature that lymphocyte proliferation decreases during and after exercise. For example, significant decreases in mitogen-stimulated T cell proliferation have been observed following incremental treadmill test exercise to exhaustion in trained men [23] and following both 2.5 h of treadmill running and 2.5 h cycle ergometry at 75% VO_{2max} in trained male and female triathletes [24]. Furthermore, like many other measures of the immune response to exercise, the magnitude of the response appears to depend upon the duration and intensity of the exercise. For example, 45 min of treadmill running at 80% VO_{2max} was associated with a 50% fall in proliferation at 1 h post-exercise whereas only a 25% decrease in the proliferation response was observed after performing the same exercise at 50% VO_{2max} [4]. Despite this apparent consistency in the literature, there is a need for caution when it comes to the interpretation of these findings, as changes in the relative numbers of NK cells and T cells in blood samples obtained before and after exercise may affect the measured proliferation response.

One way employed by researchers to overcome the problem of disproportionate changes in numbers of lymphocyte subsets in response to exercise is to adjust the proliferation data for changes in circulating numbers of T cells. Adjusting data in this way has the apparent resulting effect that only decreases in proliferative responses following longer and more intensive exercise remain.

NK cell function

Activation of NK cells does not require recognition of an antigen-MHC II combination. NK cells may serve as a "front line of defence" before a specific response can be mounted by T and B cells. The effects of intense exercise on NK cell cytolytic activity (NKCA) appear to be biphasic, with an initial enhancement followed by a delayed suppression [11,25,26] as illustrated in Fig. 5. Many studies have shown NKCA to be higher at the end of moderate and short duration (less than 1 hour) intense exercise [27] whereas no change or a reduction of NKCA has commonly been reported following prolonged intense exercise [11,25,27]. A proposed mechanism for the delayed reduction in NK cell function is an elevated level of prostaglandins released from the relatively numerous monocytes observed 1.5-2 h after intense exercise, since this effect is abolished *in vitro* and *in vivo* by indomethacin (which inhibits prostaglandin synthesis), and is also blocked if the monocytes are removed from the culture [25]. Furthermore, adrenaline infusion to recreate plasma concentrations similar to those observed after 1 h of exercise at 75% VO_{2max}, also induced a delayed monocytosis, suppressed NK activity with a 2-h delay, which was blocked by indomethacin and removal of monocytes [11]. More recently, it has been postulated that the post-exercise fall in NKCA might be due to an exercise-induced change in the Th1/Th2 balance [28]. An important Th1 cytokine is IL-2 which appears to stimulate NK cells. IL-2 release is suppressed by corticosteroids, and reduced plasma IL-2 levels and decreased *in vitro* production of IL-2 by lymphocytes after a bout of vigorous exercise have been reported [29].

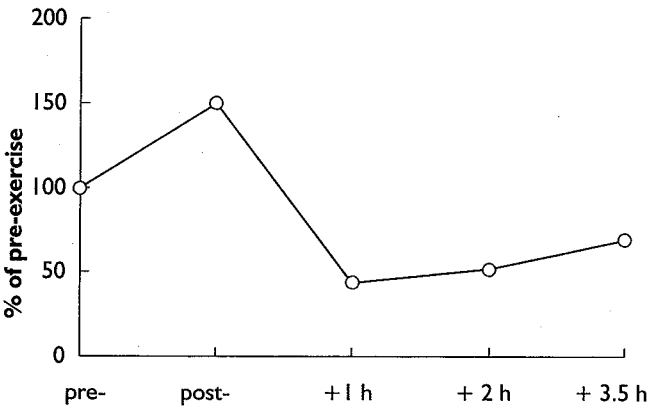

Figure 4. Changes in the circulating concentrations of natural killer cells after 2.5 h of running at 80% VO_{2max}. All post-exercise time points were statistically significant ($p<0.05$) difference from pre-exercise. Data from Nieman et al [26].

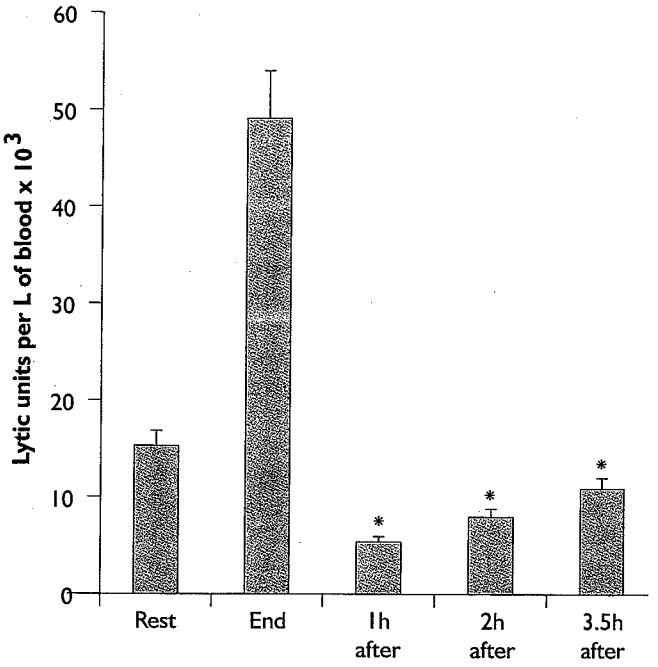

Figure 5. Changes in natural killer cell activity (expressed as lytic units per litre of blood) after 2.5 h of running at 80%VO_{2max}. *denotes a statistically significant ($p<0.05$) difference from pre-exercise. Data from Nieman et al [26].

Effects of exercise training on T cells and NK cells

Following an acute bout of exercise changes in circulating leukocyte numbers and functions normally return to pre-exercise values within 12-24 h. Cross sectional studies that have compared leukocyte numbers and functions in blood samples taken from athletes more than 24 h after their last training session with those of sedentary individuals have generally reported very few differences. Thus, in the true resting state immune function appears to be broadly similar in athletes compared with non-athletes and clinically normal levels are observed in most athletes [30].

Longitudinal studies in which previously sedentary people are subjected to weeks or months of exercise training have shown that marked changes in immune function do not occur provided that blood samples are taken at least 24 h after the last exercise bout. Furthermore, moderate exercise training in healthy young adults does not appear to have an effect on the initiation of a specific antibody response to vaccination or delayed type hypersensitivity responses as measured by the swelling that arises 48 h after injecting antigens into the skin [14]. With regular moderate intensity exercise training there is a weak suggestion of an increase in NK cell count and NKCA in trained individuals [27].

Athletes commonly intensify their training for a few days or weeks at certain stages of the season. This may induce a state of overreaching in which performance is temporarily reduced, but following a period of taper with only light training results in supercompensation and an increase in performance. Several studies in recent years have investigated the effects of short periods of intensified training on resting immune function and on immunoendocrine responses to endurance exercise. These studies indicate that several indices of immune function appear to be sensitive to the training load. Short periods of intensified training in already well-trained athletes have been shown to be associated with falls in T-lymphocyte $CD4^+/CD8^+$ ratios, a reduction in the circulating number of IFN-γ +T cells, lower mitogen-stimulated lymphocyte proliferation and NKCA [31-33]. Thus, with sustained periods of heavy training, several aspects of both innate and adaptive immunity are depressed.

Several longitudinal studies have monitored immune function in high-level athletes over the course of a competitive season. The impact of long-term training on systemic and mucosal immunity was assessed prospectively in a cohort of elite Australian swimmers over a 7-month training season in preparation for national championships [34]. The results indicated that there were no significant changes in numbers or percentages of B or T cell subsets, but there was a significant fall in NK cell numbers and percentages in the swimmers over the training season. In a study on competitive cyclists, the total number of leukocytes, T lymphocyte subsets, mitogen-induced lymphocyte proliferation and IL-2 production were measured at rest at the beginning of a training season and after six months of intensive training and a racing season, cycling approximately 500 km a week [35]. Baseline values of the tested immune parameters were within the range observed in non-trained healthy controls. At the end of the season significant decreases in absolute numbers of $CD3^+$ and $CD4^+$ cells and diminished IL-2 production were noted.

These studies suggest that athletes exposed to a long-term training periods can exhibit variations in some immune cells. The clinical significance of these variations requires more detailed investigation, though the general trend is that training of elite athletes at an intensive level over relatively long time frames suppresses systemic immunity. The cause of the depression of immunity following prolonged exercise and heavy training appears to be mostly due to the effects of elevated circulating stress hormones (particularly cortisol) and anti-inflammatory cytokines (e.g. IL-6, IL-10, IL-1ra) causing temporary inhibition of type 1 T cell cytokine production with a relative dampening of the type 1 (cell-mediated) response. When exercise is repeated frequently there may not be sufficient time for the immune system to recover fully.

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