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Exercise and the Immune System – Focusing on the Effect of Exercise on Neutrophil Functions

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1. Introduction

A relationship between intense exercise, leukocytosis and susceptibility to illness was already reported at the beginning of the past century (1-3). Today there is a consensus among researchers and clinicians that exercise have effects on various aspects of the immune function (4). The complexity of the underlying mechanisms and the clinical implications and directions need continuous evaluation. Investigators face challenges associated with immune measures and the interpretation of their changes. They should bear in mind that there is inter-individual variability of the exercise capacity, recovery, stress tolerance and immunocompetence. Short exposure to exercise could promote beneficial and apropriate physiological response of the immune system, while heavy exertion could be detrimental to health. In recent years, the development of advanced laboratory techniques contributed to enrich our knowledge and deepened the understanding of the mechanisms underlying the immune system in sports medicine. The development of fluorescent antibodies techniques allow identifying cell sub-types and receptors. Molecular technology and new cytokine methods of identification have permitted the detection of humoral factors present in the body at low concentrations, for short periods of time and to study the effect of exercise on gene expression profiles (5,6).
Studies on recreational and elite athletes should be systematic and well controlled in order to formulate evidence-based guidelines to preserve a balanced immune function.

2. The immune system

The immune response can be divided into innate, natural-non-adaptive immunity and acquired-adaptive immunity. Innate immunity is the first response to physical or chemical foreign agents and it occurs naturally and immediately, providing the first line of defense in early stages of the infection. The innate immunity is comprised of phagocyte cells, natural killer cells, soluble factors as the complement and acute phase proteins, as well as the mucosal immune responses. The acquired immunity occurs after an adaptive, specific response to a pathogen and involves the antigen-antibody response. It includes B and T lymphocytes and the immunoglobulines (7).

In the innate immunity phagocytes can recognize and act immediately against the foreign agent without prior exposure, while the adaptive immunity is characterized by a specific response to the infectious agent, becoming fully activated after a lag period. The innate mucosal defenses are the first line of defense against pathogens present at the mucosal surfaces. The 'Common Mucosal Immune System' is a network of organized structures that protect the oral cavity, the respiratory, thegastrointestinal and the urogenital systems. The major effector function of this system is the secretory IgA (8,9).

The adaptive immunity involves the action of specialized immune cells, as are the lymphocytes, which generate antibodies against specific microorganisms, killing them directly or activating other cells through the secretion of cytokines. This adaptive response generates memory which is the basis of the preventive immunization. Both systems of immunity, the innate and the acquired, work synergistically and are essential for an optimal function of the immune response. Phagocytes play an important role in the initiation of the adaptive response by presenting antigens and secreting cytokines that stimulate cells of the adaptive system.

Neutrophils (55-65% of blood leukocytes) and monocytes (5-10%) play an important role in innate immunity and provide a major defense system against microorganisms. They act as the first line of defense against infectious agents and are involve in the muscle tissue inflammatory response to exercise-induced injury (10). The multi-step phagocytic process is activated in response to invasion of foreign microorganisms and includes the rolling and adherence of neutrophils to the blood vessel endothelium, the diapedesis and chemotaxis towards the invading organism, the ingestion, degranulation and the oxidative burst, ending with killing of the pathogen (11). Experienced and well equipped laboratories in this specific field, have established the normal range values, based on a large number of subjects examined, in health and disease. Today it is possible to assess the different steps of the phagocytic process and to detect dysfunctions at each level (11-13).

3. Exercise and the immune response – Clinical implications

The potential influence of exercise on the immune system could be beneficial, detrimental or neutral. The immune response depends on the type of the particular exercise, its intensity, volume and duration. While mild or moderate exercise was shown to be beneficial, acute intense or prolonged exercise elicits depression of several aspects of the immune response. The fitness level of the performers could also exert influence in their immunological response. It seems that there is a combination of physiological and psychological factors, known to exert their influences on the immune system. Appropriate interpretation of the immune response is vital for determining the clinical directions and the integral training program for each athlete.

The physical activity could affect one or all three arms of the immune system, the humoral, the phagocytic and the cellular arm. Eventually, dysfunction of one or more arms of the immune system could lead to the outburst of an infection. In general, the etiology of infections is usually of bacterial origin when the humoral or phagocytic arm is affected, while viral–parasitic infections are usually originated when the cellular arm is involved. Excessive, prolonged training and major competitions have been long considered factors affecting the susceptibility to infections in athletes (14-16), however, in shorter and less

competitive events infections are less common (7). Frequent illness has been associated with the overtraining syndrome in athletes (17-19). During heavy exertion could be an immune suppression that creates an 'open window' of decreased host protection. Bacteria or viruses may gain a foothold, increasing the risk of subclinical and clinical infections (17, 20). In team sports or in other sports where participants are in close physical contact before, during or after the sporting event, both the infected individual and the fellow sportsmen may become infected. Some infections may appear in clusters in the sports setting, such as gastroenteritis, herpes simplex, meningitis, viral hepatitis, skin infections, tonsillo-pharyngitis (21,22). A large number of viruses and bacteria can give rise of myocarditis that can be aggravated by physical exertion (15).

There is consistent data suggesting that male endurance athletes may develop after 1 to 2-wk period increased rates of Upper Respiratory Tract Infection (URTI), following marathon or ultramarathon race events (16,23,24). URTI appears to be the most common minor viral infection in athletes. The current consensus is that the cause of URTI in athletes is uncertain (4). There is today disagreement whether 'sore throats', frequently reported by athletes, are caused by infections or are a reflexion of other inflammatory stimuli mimicking URTI (25,26). Cytokines play an important role in modulating the immune function, inducing changes that increase the risk of infection or the appearance of inflammatory symptoms (27). The physician diagnosis of URTI is based on clinical symptoms and signs, rather than by determining the infectious etiology. In few studies the pathogen was identified as the usual respiratory pathogens associated with URTI in the general population **(4).** The salivary IgA concentrations and secretion rates have been shown to be significantly decreased in athletes with prolong high intensity exercise (28,29). We could hypothesize that their immunity is reduced with an increase tendency to develop URTI. Other markers of infection as antimicrobial proteins in saliva (α-amylase, lactoferrin, and lysozyme) have been identified (26,30). Further, viral infections as URTI may lead to a debilitating state and an unexplained deterioration in athletic performance. Viral infections could run a protracted course of easy fatigability, myalgia and lethargy for weeks or even months (31). Additionally, it seems that athletes are more susceptible to develop Infectious Mononucleosis (32).

Infections of non-viral origin, as bacterial pneumonia, mycoplasma and Chlamydia myocarditis, sinusitis, etc., although uncommonly reported in athletes, could also develop following intense exercise (2,15,33). Athletes could aggravate the course of the disease during incubation periods of infections (34,35).

Neutrophils comprise the majority of circulating leukocytes and represent the early body's response in the battle against bacterial and fungal infections. Multi-factorial elements could be involved in the neutrophil behavior and in the immune responses to exercise, as neuro-endocrine mediators (36), corticosteroid release, interleukin production (37) and oxy-reduction processes associated with free radical production (38). Most studies show that of all subsets of circulating leukocytes, mainly neutrophils and lymphocytes, increase dramatically during exercise (39,40). The magnitude is related to the exercise intensity and duration, being more persistent with intense, prolonged exercise (40, 41). Neutrophil count may exhibit a biphasic response, characterized by an initial small increase, followed by a decline to resting values 30-60 minutes after the cessation of exercise. A delayed larger increase in neutrophil numbers could be observed

2 to 4 hours post-exercise (42). This leukocyte trafficking reflect recruitment into the circulation of neutrophils and could be related to hemodynamic changes as increased cardiac output, hyperthermia or could reflect changes in circulating stress hormones, particularly epinephrine and cortisol, released during exercise (42). Resting leukocyte number is generally normal in athletes, although long periods of high-volume training may be associated with long lasting suppression of circulating cell numbers, which may persist low over weeks (43). This may be attributed to migration of leukocytes out of the circulation to possible damaged skeletal muscle (44).

Disproportionate changes in lymphocyte subsets occur during exercise. Usually, during prolonged exercise the NK and CD8 T- cells increase far more than B cells and CD4 T- cells counts (40). Significant decline in the CD4:CD8 ratio was reported after 60 min of treadmill running. Although neutrophil counts may remain elevated for several hours after exercise cessation, lymphocyte number may decline bellow baseline values for up to 6 hours post exercise (7). Following vigorous exercise it was reported a transient fall of circulating natural killer (NK) cell count (45).

In summary, exercise increases neutrophil numbers and may reflect an appropriate response to exercise-induced stress rather than an impaired immunocompromised state. In contrast, the post-exercise decrease in the absolute lymphocyte counts, the NK decrease and the inversion of the CD4 to CD8 ratio, could indicate immunosuppresion.

It is remarkable that no significant changes were reported in B-cell circulating lymphocytes and only local salivary IgA reduction was shown following intense, prolonged exercise. The relationship between the leukocyte dynamics and the clinical implications is still unclear.

4. Immunological studies – Our experience

Scant information exists on exercise-induced changes in the immune system among children. We investigated the effect of aerobic exercise on several aspects of cellular and humoral functions among 10-12 year-old highly trained female gymnasts and untrained girls (46). All girls were pre-pubertal. Venous blood samples were drawn before, immediately after and 24 h following 20 min of treadmill running (heart rate 170-180 beats.min-1). White blood cells' number rose significantly following exercise and remained elevated for 24 h. The increase in leukocyte number was due to an increase in granulocytes as well as an increase in lymphocytes and monocytes. While neutrophil count returned to basal values after 24 h, lymphocytes and monocytes number remained elevated 24 h following exercise. Exercise resulted in a significant elevation of T cell lymphocytes, T helpers, T suppressors and natural killer cells. All values returned to normal after 24 h. There were no changes in B cell lymphocytes following exercise (Table 1). Exercise had no effect on serum immunoglobulin's and sub-types of IgG {IgG1, IgG2, IgG3 and IgG4} (Table 2). No differences were observed between gymnasts and untrained girls (46). The changes observed were similar to those found in adults (40).

Our laboratory for leukocyte functions focused within the last 30 years on granulocyte functions and dysfunctions in healthy subjects and in patients suffering from recurrent, severe, opportunistic infections. For the last 15 years, our group focused on neutrophil functions following a single bout of submaximal aerobic exercise (47-50). Neutrophil

functions as chemotaxis, oxidative burst, and bactericidal activity were unaffected immediately post-exercise, however neutrophil chemotactic activity was found significantly decreased 24 h after the cessation of the exercise (Table 3) (47).

		Pre exercise		Immediately after exercise		24 h following exercise	
		X	SD	X	SD	X	SD
WBC	gymnasts	5561	596	*7046	1306	*6505	436
	untrained	6340	1043	*8263	1225	*6738	1150
Neutrophils	gymnasts	2710	349	*3554	692	3126	498
	untrained	3570	1000	*4658	1184	3490	805
Lymphocytes	gymnasts	1930	235	*2690	360	*2365	524
	untrained	2106	544	*2671	834	*2464	401
T cell	gymnasts	1590	493	*1860	682	723	340
	untrained	1413	219	*1953	357	1677	458
Th cells	gymnasts	943	251	*1030	248	1003	155
	untrained	792	197	*1059	303	992	334
Ts cells	gymnasts	663	278	* 851	410	776	205
	untrained	550	98	* 784	193	669	173
B cells	gymnasts	306	101	320	96	344	93
	untrained	295	56	329	92	350	103
Natural killer cells	gymnasts	161	132	* 256	119	231	124
	untrained	124	47	* 267	85	139	43
Monocytes	gymnasts	293	61	* 391	127	# 424	72
	untrained	373	82	* 462	125	375	18

* significantly different from pre-exercise value in both groups
# significantly different from pre-exercise value in the gymnasts group only

Table 1. Changes in the cellular components of the immune system. WBC and lymphocyte subpopulations (cells/μl) following exercise in gymnasts and untrained girls (46).

	IgM (mg/dl)		IgA (mg/dl)		IgE (unit/ml)		IgG (mg/dl)		IgG-1 (mg/dl)		IgG-2 (mg/dl)		IgG-3 (mg/dl)		IgG-4 (mg/dl)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
pre exercise	207.0	83.3	120.6	26.1	81.6	53.2	1194.0	138.2	673.7	108.0	235.3	63.7	69.7	35.5	61.2	24.1
post exercise	199.3	67.6	120.4	21.6	81.1	49.8	1180.7	151.2	705.9	132.6	242.1	66.8	59.1	18.5	63.4	25.1
24 h post exercise	179.4	73.2	116.4	36.4	83.1	56.5	1181.4	147.3	669.9	144.3	232.4	69.0	63.6	22.1	61.4	24.2

Table 2. Immunoglobulin levels pre-exercise, immediately post-exercise among gymnasts (46).

		Pre-exercise (Basal)	Post-exercise	24 h post-exercise
Neutrophils (cells/μl)	**trained**	2710 ± 349	3554 ± 692	3126 ± 498
	untrained	3570 ± 1000	4658 ± 1184	3490 ± 805
Chemotaxis (cells /field)	**trained**	58 ± 11	55 ± 13	36 ± 11 *
	untrained	47 ± 7	52 ± 15	42 ± 8 *
Killing (log decrease of colonies) with autologous serum	**trained**	0.8 ± 0.3 #	0.8 ± 0.2 #	0.8 ± 0.1 #
	untrained	1.1 ± 0.1	1.1 ± 0.l	1.0 ± 0.2
Killing (log decrease of colonies) with homologous serum	**trained**	0.7 ± 0.2 #	0.8 ± 0.1 #	0.8 ± 0.2
	untrained	1.0 ± 0.1	1.0 ± 0.02	0.9 ± 0.2
Superoxide production (nmol 0_2-/10^6 PMNs/min) with PMA stimulation	**trained**	5.7 ± 0.4	4.4 ± 1.0 *	4.8 ± 1.0 *
	untrained	5.1 ± 0.7	4.7 ± 1.3	4.9 ± 1.2
Superoxide production (nmol 0_2-/10^6 PMNs/min) with fMLP stimulation	**trained**	3.4 ± 1.9	3.2 ± 1.3	2.6 ± 1.3
	untrained	4.1 ± 1.3	3.3 ± 0.5	3.7 ± 0.6

*⟩<0.05 compared with basal values (before vs. following exercise).
#⟩<0.05 compared with control group (trained vs. untrained).

Table 3. Effect of exercise on neutrophil count and neutrophil functions (mean+SD), Pre-exercise (basal), immediate post-exercise and 24 h post-exercise (47).

A consistent decrease of neutrophil migration was detected 24 h post-exercise in trained and untrained subjects, children and adults, male and female (47-50). The following studies focused on the recovery time of the impaired neutrophil chemotaxis, using various chemoattractans. We also aimed to learn about the possible mechanisms involved in the post exercise-associated chemotactic defect. We found that the transient impairment shown in the chemotactic activity 24 h post-exercise, returned to normal after 48 h (Figure 1) (49).

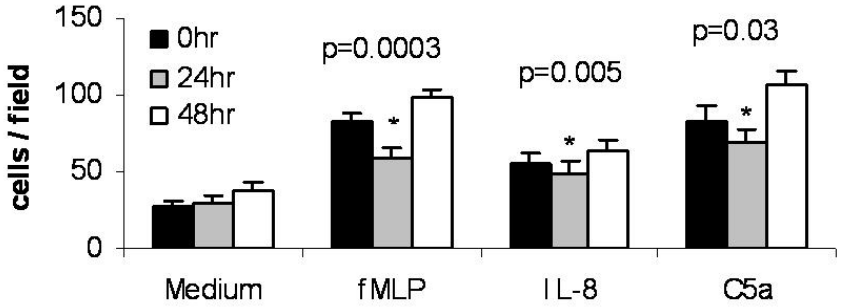

Fig. 1. Kinetics of the neutrophil chemotactic activity in 16 athletes; Pre-exercise, immediately post-exercise and 24 h post-exercise. The chemotaxis was induced by the chemoattractant: fMLP (1 μM), IL-8 (10 nM), or C5a (10 nM). Random migration was conducted in the presence of medium M199. The results were expressed as the number of migrating cells per field (mean±SE) (49).

Looking at the response of the neutrophil specific membrane receptors to the different chemoattractants, we repeatedly found reduction of the chemotaxis following intense exercise, regardless of the chemoattractant used, including Formylated peptides (fMLP), the

chemokine IL-8, and the activated complement component(C5a) (49). These chemokines attach to their specific receptors, fMLP-R (N- formyl-Met-Leu-Phe), IL-8-R (CXCR1 and CXCR2), and C5aR, which belong to the seven-transmembrane helix surface receptor family ("serpentine receptors") that transduces signals downstream the cytoskeleton by coupling to heterotrimeric G-proteins (51). Once the signal has been triggered, rapid cytoskeletal rearrangement and chemotaxis take place. "Target" chemoattractants (fMLP, C5a) function primarily through a common signal-transduction pathway by stimulating p38 MAPK, whereas "host" intermediary chemoattractants (IL-8, LTB4) primarily function via the PI3K/Akt pathway (52). The surface density of the chemotactic receptor (C5aR), which serves as a representative model of receptor availability, was not affected 24 h after exercise. Moreover, the integrin CD11b/CD18, which represent one of the main receptors for neutrophil adhesiveness and crucial for normal chemotaxis, was also unaffected by exercise. Therefore, the chemotactic defect is not dependent on the specific receptor of activation, or on its specific pathway of transduction. We could speculate that the chemotactic impairment was related to a common defect at the membrane level, leading to decreased receptor availability or to other factors yet to be elucidated. For achieving appropriate chemotactic responses, an intact cytoskeleton structures are necessary (53,54). Continuous reorganization of the cytoskeleton is required for efficient F-actin polymerization and polarization. Both are important steps in the skeletal rearrangement during migration (55). Consequently, we studied the neutrophil F-actin neutrophil polarization and polymerization (49). Following fMLP stimulation, the cell undergoes sequential morphological changes from round to elongated geometrical forms (figure 2A). These changes reflect the cell activation and the ability to migrate against the chemotactic gradients toward the target (49,53). Using the green phalloidin test we found no correlation between the chemotactic defect and the ability to polymerize F-actin, indicating that the reduction in chemotaxis following exercise was not a result of the F-actin dysfunction. Despite the fact that positive correlation between chemotaxis and F-actin polymerization usually occurs, a lack of correlation in certain conditions has been reported (55).

To elucidate other cell skeletal responses to aerobic exercise, we studied the neutrophil polarization, known to be in tight correlation with the chemotactic activity.

Indeed, the neutrophil polarization was significantly decreased 24 h following aerobic exercise. This change also correlated with the decrease in chemotactic activity ($r= 0.945$; $P= 0.001$) (figure 2B) (49,50).

Since the neutrophil bactericidal activity and the oxidative burst were found to be normal, it seems that the signal transduction pathways are not affected following 30 min of intense aerobic exercise. Rather, it seems that aerobic exercise causes a skeletal impairment, and this eventually could leads to a reduction of the chemotactic activity. Most probably the impaired chemotaxis event, following a short bout of submaximal exercise, occurred at the effectors' machinery level, rather than at the level of the neutrophil membrane receptors. Others found no change in chemotaxis 24 h after a graded exercise to exhaustion (56). Giraldo et. al. reported increased chemotaxis immediately after moderate (45 min of 55% VO2max) and intense (1 hr of 70% VO2max) aerobic exercise that returned to basal values after 24 h (57). These discrepancies are probably related to differences in the type, intensity, and duration of exercise, timing of blood sampling, or use of different laboratory assays.

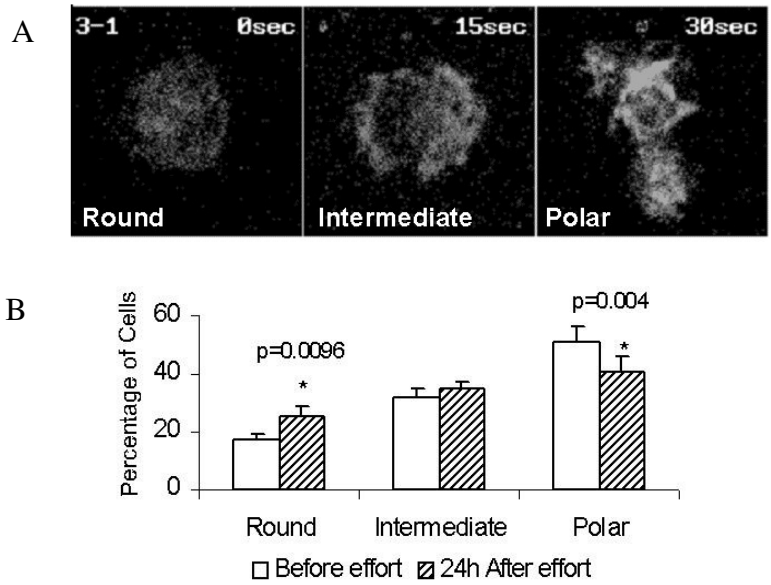

Fig. 2. Neutrophil polarization. A. The cell shape changes that occur following fMLP-stimulation. Three different cell shapes were recorded: non-activated - round cells (R), partially activated - intermediate cells (I), and fully activated - polarized cells (P).
B. Analysis of the cells' morphological changes following fMLP-stimulation, in 11 athletes, before and after effort (mean±SE) (49).

5. Therapeutic approach to exercise-induced immune suppression

Dietary and drug intervention have been reported to boost performance in athletes (58). They could block the transient immune changes, to prevent the oxidative stress and the inflammation induced by prolonged, intense exercise or excessive training. Some supplements as flavonoids were reported to benefit the immune system (59). In endurance events, iron and mineral supplements, together with antioxidant vitamins, help to prevent muscle damage (60). Carbohydrates enhance muscle glycogen stores. Glutamine and aminoacid supplementation did not prove to be beneficial (61).

Vitamin E (VE) and vitamin C, as antioxidants, play an important role in protecting the cells and muscles from damage (62-65). It is well-established that exercise exerts imbalance on the oxidative state by increasing Reactive Oxygen Species (ROS) and decreasing the level of antioxidants (63). As previously shown, intense or prolonged exercise can adversely affect the function of the immune system. It was found that submaximal aerobic activity (1h swim at 75-80% of VO2max) could produce oxidative damage within the neutrophils (64), which lose the appropriate antioxidant defense mechanisms, leading to a defective chemotactic ability (65). This impairment could rise from the increased levels of ROS and lipid peroxidation; both potentially could damage neutrophil function. The enhanced production of ROS, mainly by mitochondria, is associated with excessive oxidation of lipids, proteins, and nucleic acids, causing damage to cell membranes and to the physiological function of proteins and DNA (66-68). To defend themselves from ROS induced damage, cells contain

complex antioxidant mechanisms including enzymatic (e.g. superoxide dismutase, glutathione peroxidase, catalase) and non-enzymatic antioxidants (e.g., vitamin E (VE), vitamin C, beta-carotene). VE is the most important lipid-soluble antioxidant due to its abundance in cell and mitochondrial membranes and its ability to act directly on ROS and stop lipid peroxidation. This antioxidant is known to decrease the exercise-induced oxidative stress (69-71) and has been shown to protect against exercise-induced muscle damage (70). Neutrophils play a dual role in exercise-induced oxidative damage. On the one hand, they contribute to ROS formation during intense or prolonged exercise; on the other hand, intense exercise can produce oxidative damage within neutrophils. VE has an important role as anti-oxidant and an important role in maintaining normal neutrophil function. Chemotaxis, adherence, and phagocytic capacities of neutrophils were shown to be reduced in VE deficiency, improving after antioxidant treatment (65,72,73).

Our research focused on the phagocytic immune response to exercise, showing prevention of the impairments by vitamin E supplementation. The results of chemotaxis and polarization are shown in Figure 3, representing the mean +/- SEM of 7 trained men pre- and post-exercise, before and after 28 days of daily VE supplementation (74). We can see that daily supplementation of 800 IU d-alpha tocopheryl succinate, indeed corrected the defective neutrophil chemotaxis and polarization observed 24 hr post-exercise.

A relatively small number of studies have dealt with the effect of VE on neutrophil functions following exercise. To the best of our knowledge, there are no studies addressing the effect of VE on exercise-induced impaired chemotaxis. However, a beneficial effect of VE on chemotaxis was shown in other populations, such as healthy elderly men and women and elderly women with coronary heart disease or major depressive disorder (72,73). Improvement in chemotactic ability after VE supplementation was also found in rats with VE deficiency and in periparturient dairy cows (75,76).

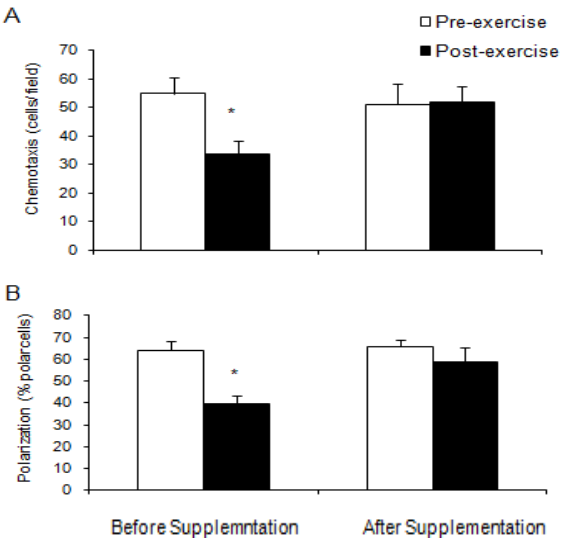

Fig. 3. A. Correction of the defective neutrophil chemotactic activity (observed 24 h post-exercise) by vitamin E supplementation. B. Correction of the defective neutrophil polarization (observed 24 h post-exercise) by vitamin E supplementation (74).

Of note is that recent reports have emphasized that ROS production, through the reversible oxidation of thiol groups, has also important physiological influences on gene transcription and protein synthesis, as part of the adaptive processes that occurs after exercise. High dose antioxidant supplementation may interfere with these processes. Cooper's Group reported gene reorganization after intense exercise (77, 78).

In recent years, it has been reported that regular physical activity can have beneficial role in cancer's prevention and therapy (79,80). There is evidence of a protective effect of physical activity on colon and postmenopausal breast cancer (81). Further, it is also mounting that physical activity reduces risks of lung tumor metastases (82). It has been reported that exercise prevent the loss of muscle mass and functional capacity in chronic deteriorating conditions, beyond the beneficial psychological effects, which certainly improve the quality of life (83-85).

Athletes are not immunocompromised by clinical definition, but could suffer from transitory, persistent immunosuppression, eventually leading to subclinical or clinical diseases. Recovery time is imperative in elite athletes involved in intense training and competitions. The temporary, sometimes multiple, mild impairments of the immune system could change into a chronic more severe immune dysfunction.

The approach should be multidisciplinary, including all care givers as sport medicine physicians, physiologists, immunologists, physiotherapists, nutritionists, psychologists and coaches. To achieve the main goals, an integrated model with programmed activities and clear guidelines for any specific type of sport is imperative. Recommendations should be directed to elite athletes and recreational sports, for sedentary individuals, for moderate and well trained subjects. The target is to maintain the balance of the immune system for the health of the athlete and his optimal performance.

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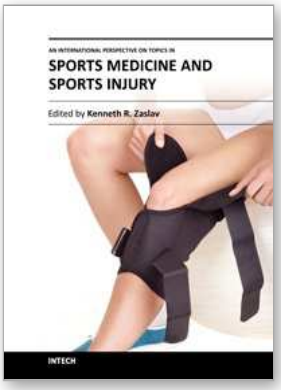

An International Perspective on Topics in Sports Medicine and Sports Injury

Edited by Dr. Kenneth R. Zaslav

ISBN 978-953-51-0005-8
Hard cover, 534 pages
Publisher InTech
Published online 17, February, 2012
Published in print edition February, 2012

For the past two decades, Sports Medicine has been a burgeoning science in the USA and Western Europe. Great strides have been made in understanding the basic physiology of exercise, energy consumption and the mechanisms of sports injury. Additionally, through advances in minimally invasive surgical treatment and physical rehabilitation, athletes have been returning to sports quicker and at higher levels after injury. This book contains new information from basic scientists on the physiology of exercise and sports performance, updates on medical diseases treated in athletes and excellent summaries of treatment options for common sports-related injuries to the skeletal system.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Baruch Wolach (2012). Exercise and the Immune System – Focusing on the Effect of Exercise on Neutrophil Functions, An International Perspective on Topics in Sports Medicine and Sports Injury, Dr. Kenneth R. Zaslav (Ed.), ISBN: 978-953-51-0005-8, InTech, Available from: http://www.intechopen.com/books/an-international-perspective-on-topics-in-sports-medicine-and-sports-injury/exercise-and-the-immune-system-focusing-on-the-effect-of-exercise-on-neutrophil-functions

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