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REVIEW ARTICLE

Exercise Immunology: Involved Components and Varieties in Different Types of Physical Exercise

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Abstract

Physical exercise induces modifications in the immune system influencing either positively or negatively on health depending on its frequency, duration and intensity. Acute or moderate physical exercise increases appreciably the immune cells, including cytokine levels while decreasing other components like NK cells, leading to a stronger response to pathogens as well as decreasing liability to allergic reactions. The expression of Toll-like receptors (TLR) is elevated as well, augmenting the positive effect. Exhaustive physical exercise, by contrast, modifies the immune system adversely. This review explores the links between physical exercise, immune cells and cytokines, and the immunological effects that have been studied by the performance of different kinds of physical exercise.

Keywords: Physical exercise, acute exercise, moderate exercise, immune system, exhaustive exercise, strenuous exercise.

Introduction

It has been put forward that physical exercise induces immune modifications which have either positive or negative influence on health [1, 2]. Physical exercise is an activity that is planned, structured, repetitive, with the purpose of improving or maintaining one or more health-related components of physical fitness. Examples of these components are cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility [3]. Physical exercise can be said to be acute or moderate (require less effort and short-lived) such as cycling for 30 minutes, and exhaustive or strenuous exercise (requires more effort and takes much time), such as cycling for 2 hours.

Moderate amount of exercise provides an overall "boost" to the immune system but strenuous exercise results in dampening [4]. Strenuous exercise shows a remarkable increase in the levels of pro-inflammatory and anti-inflammatory cytokines along with naturally occurring cytokine inhibitors and chemokines. Regular exercise has demonstrated increase resistance to mild infections such as the common cold, whereas strenuous exercise is associated with increased upper respiratory tract infections [5,6].

Exercise influences both innate and acquired immunity [4]. Innate immunity involves the participation of cells such as macrophages, neutrophils, dendritic cells, natural killer (NK) cells. The adaptive immune response involves B-cells and T-cells (CD4+ and CD8+) [7]. Different immune cell types are affected differently in relation to physical exercise.

This review seeks to establish the link between exercise and how it modulates the immune system.

Primary cells of immunity

Natural Killer Cells

Natural Killer (NK) cells, a major component of the inflammatory response, which upon activation, play a crucial role in the host defence without expressing any antigen-receptor in their membrane [8, 9]. The cytolytic activity of NK cells is enhanced by interferon (IFN)-γ [10] and IL-2 [11,12] whereas prostaglandin E-2 down-regulates the function of NK cells [13]. NK cells show a striking increase during exercise, while the cell count drops to below half the normal level after exercise [14, 15]. The increase in NK cells as measured in terms of concentration as a percentage of lymphocytes in peripheral blood [18] enhances the cytolytic capacity. Decreased level of NK cells results in suppressed cytolytic activity, which may indicate an enhanced period of susceptibility to infections [16]. NK cells present remarkable sensitivity to the stress induced by physical exercise, which promotes their redistribution from the peripheral blood to other tissues after exercise. The likely increase in NK cells in the peripheral blood to the other tissues during physical exercise due to induced stress signals (could result from muscle injuries), and should be reached before the cessation of the physical exercise,

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with the blood serving as highway to traffic NK cells and other immune cells to the sites of stress signalling [16,17].

Neutrophils

Neutrophils are crucial for host defence, protecting the host against infections, and are active in the pathology of various inflammatory conditions, as all immune cells [18]. Physical exercise has been studied to have both short- and long-term effects on neutrophils with either inducing or hindering neutrophils response to infections. The main function of neutrophils includes adherence, chemotaxis, phagocytosis, oxidative burst, degranulation, and microbial killing. Moderate exercise boosts the neutrophil functions including chemotaxis, phagocytosis, and oxidative burst while chemotaxis and degranulation are not affected. Extreme exercise, on the other hand, reduces the function of protecting the host against bacterial infections [19, 20, 21, 22]. Several elements are involved in the function of neutrophils and immune response to exercise. Physical exercise increases the release of calcium (Ca^{2+}), resulting in the synthesis of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α) and IL-1β. These regulate the expression of selections by the endothelial cells that attract circulating neutrophils to the stress signalling sites [59, 60]

Macrophages

Macrophages are important cells in the immune system for phagocytosis, cytokine production as well as antigen presentation [23]. It is well known that physical activity leads to an activation of endogenic opioid peptides [23], which probably play a role in the immune system [24]. It has also been reported that the increase in macrophage function induced by exercise is supported by enhanced glutamine consumption and metabolism [25].

Dendritic Cells

Dendritic cells (DCs) are the key specialist antigen-presenting cells that initiate and direct immune responses [26, 27]. When tissues are damaged by trauma, infection or are altered by malignant transformation, inflammatory cytokines and other cellular products are released. These stimuli, whether from the tissues (endogenous) or from microbial products (exogenous), leads to activation of resident DCs and recruitment of circulating DCs to the site [28]. DCs actively capture and process antigens and then migrate via the lymphatics to draining nodes. Here, they present processed antigens to T-cells to initiate primary or stimulate secondary (memory) immune responses. As such, they play a central role in immune surveillance, an essential part of the defence and protective mechanism against infections and malignancy [29]. Ho *et al*., 2001, reported a significant and reproducible increase in DC counts as part of the acute response to surgical and physical exercise [30]. According to Liao *et al.,* 2006, periodic physical exercise training promotes the number of DCs and enhance the activity of DCs against tumour cells [31].

Lymphocytes (B-cells, CD4+ T-cells and CD8+ T-cells)

T-cells are involved in the fundamental role of orchestration and regulation of the cell-mediated immune response. A crucial consequence of a defect in T-cell function is an increased incidence of viral infections [32]. B-cells produce antibodies, which are released to destroy the invading viruses and bacteria [33]. The CD4+T cells function in activating cells of the innate immune system such as the B-lymphocytes, and the cytotoxic T cells. CD4+ T cells are involved also in the suppression of immune reaction [63]. Whereas CD8+ T cells play a critical role in the immune defence against intracellular pathogens, including viruses and bacteria, as well as perform tumour surveillance [64]. During physical exercise, CD4+ and CD8+ T-cells, helper and cytotoxic T-cells, and CD19+ B-cells are recruited to the peripheral blood, resulting in increased concentrations of lymphocytes. Strenuous exercise, but not moderate exercise, is followed by decreased concentrations of lymphocytes in blood that results in low levels of lymphocytes in tissues [34]. After intense long duration exercise, the functions of B-cells are suppressed [35]. Lymphocyte concentrations have been shown to increase during acute exercise and fall below pre-values after long-duration physical work [18]. However, after acute exercise, the total lymphocyte concentration declines, and the proliferation response is unchanged from values obtained before exercise [6]. Physical exercise induces a greater early rise of catecholamine that affects the different lymphocytes, causing their mobilization in the blood, according to Natale *et al*., [62].

Cytokines affected by physical exercise

Cytokines being the major component in innate immunity, induce a direct and indirect mechanism of immune modulation in response to invading infection-causing agents and activating NK cells, monocytes and macrophages [36]. Exertion, like other physical stress, induces high levels of different cytokines (IL-6, IL-8, TNFα, IL-1ra) during and after exercise in the plasma [43]. These cytokines facilitate the influx of other immune cells including lymphocytes, neutrophils, and monocytes which participate in the clearance of the antigen and healing in response to an infection or tissue injury. IL-1 and TNFα upregulate major inflammatory mediators such as nitric oxide or matrix metalloproteinases [4]. Cytokines which are produced during moderate exercise, play a beneficial role. During strenuous exercise, overproduction of certain cytokines indirectly leads to muscle damage, and symbolize detrimental effects to the body. Important cytokine with respect to physical exercise is the IL-6 which is produced initially and increases enormously, functions as both an anti-inflammatory and pro-inflammatory cytokine simultaneously [61]. Strenuous exercise induces overproduction of IL-6 locally in skeletal muscles which in turn cause the damaging of muscles [37,38]. Other cytokines such as IL-1 show an initial increase but reduces later with regards to increase in IL-1ra, a natural inhibitor of IL-145-47. TNFα receptors 1, 2 and chemokine IL-8 shows an increase in response to strenuous exercise and macrophage inflammatory proteins also show increased levels during the exercise. Furthermore, it has been studied that exercise induces a strong anti-inflammatory response [42,43]. In long-term strenuous exercise, levels of cytokines vary, but later levels reach normal level [44, 39].

Immunological effects of different physical exercise

High volume exercise

In this review paper, we explored the resulting impact of various physical exercise on the components of the immune system. High volume exercises such as water rowing practice, running and resistance training has been studied in athletes and non-athlete participants. The exercise was performed 6.2 ± 1 days a week with an average time of 125.3 ± 41.5 minutes per day for 13 ± 4.2 years (Mean ± standard deviation). The intensity of the training was 60% easy-moderate, 30% intense and 10% very intense/competition [53]. The different intensities were defined by increased heart rate as a percentage of maximum heart rate: easy: 40%-54% of maximum heart rate; moderate: 55%-69% of maximum heart rate; intense: 70%-90% of maximum heart rate; very intense: 91%-100% of maximum heart rate [53]. Regarding the haematological and immune phenotype, high volume exercise significantly decreased the number of leukocytes as well as the number and percentage of neutrophils and lymphocytes in young and elderly athletes [53].

In the Leukocyte differentiation, mentionable was an increase in number of Effector memory RA T cells (TEMRA) cells, in young and in elderly athletes. Central Memory (CM) T-cells was reduced, but only in elderly athletes. Concerning thymic function, no difference in T-cell receptor excision circles (TREC) levels in CD4+ but not CD8+ T-cells of the younger individuals was examined [53]. It can be elucidated that there is a reduction in output of CD8+ T-cells from the thymus and varieties in the distribution of subpopulations of TEMRA subsets in the mentioned CD4+ respectively CD8+ T-cells [53]. The young non-athlete group more often expressed CD69 in both, CD4+ and CD8+ T-cells compared to the young athlete group, indicating that the functional capacity of T-lymphocytes of young non-athletes is lower compared to the young athletes [53]. The levels of activation and degranulation of NK-cells were significantly higher in young athletes than in young non-athletes. This could be "a compensatory mechanism for the functional defects of the T-lymphocytes" according to the research group [53]. Nevertheless, significant elevations of other immunological cells including NK cells and cytokines were demonstrated in this study, concurring to a previous study [55]. In elucidating tri-set resistance training (two times three exercises of the same muscle group, six to eight repetitions), no significant alteration in inflammatory response like circulating cytokines and cortisol was determined [56].

Treadmill running

Studies suggest that cytokines, chemokines and lymphocyte subsets are seen in the plasma of the individuals after the treadmill exercise [45]. The participants of the treadmill exercise did not take any medication and were overnight fasted (allowed to take water ad libitum) and were abstained from doing any other exercise for 2 weeks. Pulmonary blood level was measured for 0.5 hours, 1.5 hours during exercise and 2.5 hours at the end of the exercise. The treadmill exercise increased the total number of circulating lymphocytes, CD4+and CD8+ T cells during the exercise but declined below the level of pre-exercise during the resting or recovery phase after the exercise [45]. The IFN-γ showed decreased level after exercise and remained low for 2 hours after exercise when compared with the pre-exercise value. IL-6 showed a remarkable increase by 30-fold at the end and reached the pre-exercise value during the recovery or resting phase whereas other cytokines IL-2, IL-4, IL-12 showed fluctuating level in that some decreased below the detection level and pre-exercise value, some slightly increased during exercise and some did not show any change [48].

Cycling

Study of bicycle exercise effect with perspective to immune system revealed significant observations about the manipulation of immune cells during exerting in different intensities. The study conducted on six volunteers who exerted bicycle ergometer for 1 hour at 25%, 50%, 75% of VO2max with an interval of 2-3 weeks. Observations were based on the blood collected during basal state, at the end of the exercise and 2 hours later. Evidence obtained from blood which was collected in 3 different stages revealed that, during the initial stage (25%) of exercise, total concentration of all lymphocyte subsets where increased and declined after exercise at 50% and 75% of VO2max. However, the changes were more significant in 75% of VO2max. At all the levels, the percentage of CD3+ blood mononuclear cells were decreased due to the decrease in the fraction of CD4+ cells. NK cells showed increased level during the exercise and expressed a decline to pre-values after 2 hours. There is a drastic dropping down below the base level of all the cells at 75% VO2max. The level of IL-1 in plasma shows increased after 3hrs of cycling this shows that IL-1 is rapidly induced by the cycling exercise. Some observations state that IL-1 was neutralized by the antibody to IL-1 when measured 3 hours after 1 hour cycling by Thymocyte proliferation bioassay [46, 47, 49, 50].

Yoga

Evidence observed in previous studies suggest that yoga could induce immune modulation. Yoga, a mental, physical and spiritual practice, is performed with the equal participation of the body and mind. The art of this exercise lies in the patience and method of performing. Different modes of yoga have different stimulation over the body. There is an observable manipulation of immune cells by yoga exercise especially transcendental meditation (a special form of mantra meditation). There is an increased level of CD4 and CD8 lymphocytes, B lymphocytes and NK cells compared to the normal group [51]. According to Rajbhoj *et al.*, 2015, there is a beneficiary modulation of the immune system in industrial patience by the intervention of yoga, which leads to decrease in pro-inflammatory cytokines and increase in anti-inflammatory cytokines in industrial workers [52]. The group which performed yoga (9 subjects) had higher values of CD 4 and CD8 lymphocytes, B lymphocytes and Natural killer cells than the control group. There is evidence which proves that IL-10 is also increased in plasma level during yoga intervention [51,52].

Discussion

Studies have shown that there is a beneficial and detrimental relationship between physical exercise and the immune system. Immune cells (NK, CD4+, CD8+ lymphocytes and macrophages) are stimulated and show appreciable levels in an exercising individual than a non-exercising individual [56]. Further, performing a moderate amount of exercise, regardless of the type of exercise, provides beneficial stimulation of the immune system, which can facilitate the cure of mild diseases such as common cold, and diseases such as diabetes which showed a neutral level in excreting individuals [4]. On the contrary, some studies suggest that strenuous exercise affect the immune system in a detrimental way. For instance, overproduction of IL-6 in marathon participants may lead to muscle damage [56]. During an acute exercise, all lymphocyte subpopulations NK and T-cells function and cytokines (IL-6, IL-1, IL-2, TNF-α) were observed to be induced after a prolonged intense exercise. The cytokine IL-6 showed a great increase level in the plasma during exercise [56].

The high-volume training study shows phenotypic and functional changes in the adaptive immune response such as more differentiation but less functional responsiveness, inducing a more mature immune system. This is maintained throughout life, even though it decreases partly when growing older. Moreover, recent studies also suggest that such high-volume training is beneficial to the individuals' immune system, even if the individuals start in a progressed age (that is, 61 - 76 years) [58].

It can be elucidated that regular physical exercise initially leads to a general suppression of inflammatory lymphocyte activation with decrease in natural killer T-cell and NK cell numbers [4], making host vulnerable to infections [35]. The suppression of inflammatory lymphocyte activation can lead to the development of inflammatory conditions such as allergy and autoimmune disease [54]. Again, the antigen-presenting function of dendritic cells is higher than normal because of an augmentation in the high level of Toll-like receptors, resulting in an enhanced resistance to infective pathogens. Moderate physical exercise thus enhances the immune defence against external pathogens and probably diminishes hyperimmune reactions where it improves the health of individuals with chronic immune disturbances [57].

Conclusion

Available literature has shown that physical exercise has a crucial influence on the immune system of an individual. It has been established that moderate physical exercise has an appreciable positive influence on the immune system through down-regulation of the levels of NK cells, increasing the number of Toll-like receptors and in general generating a more differentiated immune system. This tends to improve the good health standing of the individual performing the physical exercise. Exhaustive exercise, however, results in decreased immune functions directly after the training and making the physical exercise participant at risk of infections. Damage to muscles due to aggressive concentrations of IL-6 have been a studied negative impact from exhaustive physical exercises. To further improve the knowledge on this subject, future studies should explore the environmental influence on different individuals participating in physical exercises and the effect these factors have on the immune system.

Conflict of interest

None

List of abbreviations

B-cells: Bursa cells
CD: Cluster of differentiation
CMT-cells: Central memory T-cells
DCs: Dendritic cells
TEMRA: Effector memory RA T cells
IFNγ: Interferon-gamma
IL: Interleukin
NK cells: Natural Killer cells
NK T-cells: Natural Killer T-cells
T-cells: Thymus cells
TLR: Toll-like receptor

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