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Review Article

Exercise and Immunity: A Correlated Mechanism

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ABSTRACT

Sedentary lifestyles now become an incredible worldwide problem with the advancement of technologies over the past several decades. Physical inactivity has progressively increased now-a-days and potentially contributes the risk of numerous diseases/disorders. The initial body defensive mechanisms contribute the protective responses, effective against a diverse variety of threats. Regular physical activity, fitness and exercise are critically important for the good health and may have prevalence over immunological system. Prolonged bouts of exercise are correlated with depressed immune system to pick up opportunistic infections. Moderate exercise whereas elicit beneficial outcomes in both prevention and rehabilitation of many diseases. Nevertheless the cascades of exercise-induced cellular-molecular-signaling pathway may trigger antigen-receptor recognition gateway. Exercise and immunity henceforth, is a correlated mixed-message mechanism and has important potential implications on public health.

Key Words: Physical-activity; NK cells; ROS; SIgA; Myokine; Autophagy

INTRODUCTION

Physical activity is the bodily movement, constructed by skeletal muscles that outcomes in calorie expenditure. [1] Henceforth, physical activity is multidimensional, portrayed by frequency, duration, intensity and type of activity. [1,2] Exercise (or exercise-training), a subcategory of physical activity, is planned, structured, repetitive and intentional bodily movements intended to improve or maintain one or more components of physical fitness. [2-4] An important difference between physical activity and fitness is the intra-individual day-to-day variability. [1] Physical activity varies indubitably on a daily basis, whereas fitness remains relatively static and taking time to change.

Physical activity is an input to countless surveillance and epidemiological studies, considering trends and connections with disease. Public health initiatives intended at escalating physical activity, resort to monitor the measurement of physical activity. [1] Exercise, a subcategory of physical activity, relates to immunity is a combined memorandum. [5] Regular moderate-intensity exercise diminishes the risk of infection, [5,6] whereas prolonged or over-trained exercise is associated with immunosuppression. [7-9] Exercise may increase the production of macrophages that assaulting bacteria, associated with upper respiratory tract diseases (URTD). [5,7] Cross-sectional and longitudinal data recommend that regular moderate-intensity exercise uphold a reduced risk of self-reported respiratory symptoms. [7,10-12] Temporary rise in body temperature during exercise may inhibit bacterial growth as well as sluggish stress-related hormone. [5,13] However, over-exercise emerges to negatively affect immunity. Quinn [14] accounted that >90 minutes of high-

intensity exercise (marathons, triathlons, endurance races) makes a person more susceptible to illness for up to 72 hours after working out. During prolonged or high-intensity exercise, the body produces stress-hormones (cortisol and adrenaline), that raise blood pressure, elevate cholesterol levels and suppress the immune system. [5,14] Intense exercise before or during viral infection has been associated with greater morbidity and mortality. [7,15,16] It is well established by Nieman [17] "J-shaped" hypothesis, representing the relation between exercise and susceptibility to infection. This model suggests that immune function enhanced above sedentary levels with moderate activity while excessive amounts of prolonged, high-intensity exercise may impair immune function. Nevertheless, strenuous physical exercise executes increased-vulnerability to immunological mechanism is well defined by "open window" theory. [9,18-20] "Open window" for pathogen entrance may alter immunity via the risk of clinical infection after excessive exercise which can last between 3 to 72 hours. According to the International Society of Exercise and Immunology (ISEI), the immune dysfunction remarkably observed due to continuous and prolonged (> 1.5h) exercise and performed at an intensity ranging from moderate to high. [8]

The purpose of this article is to summarize current literatures regarding exercise and immunity as well as to provide a platform for further investigation into the mechanisms and reconciling the protective effect of exercise. The study narrates how an exercise stimulus may act upon the inter-dependent network to orchestrate the beneficial or reverse effects on patho-physiology as well as immunity.

Exercise and Immunological Features

Exercise of moderate intensity stimulates parameters related to cellular immunity to decrease the risk of infection, while high-intensity exercise may promote a reduction of these same parameters, increasing the risk of infectious diseases. [21,22] The line of defense engrosses white blood cells (leukocytes) that travel through the bloodstream and into tissues, searching for and attacking microorganisms and other invaders. [23] Nielsen, [20] Pederson & Hoffman-Goetz, [21] McCarthy & Dale [24] and Fry et al. [25] stated that the alteration in leukocyte numbers in circulating blood is the most studied aspects of exercise and immune system. During exercise the chief source of circulatory neutrophils are bone marrows, spleen, lymph nodes and gut. [20,26,27] Fry et al., [25] Nieman et al. [28] and Peake [29] scrutinized that intensity of exercise, duration and/or the fitness level can cooperate with the degree of leukocytosis occurring.

Leukocytes has two modes of actions in term of internal-physical defense- i) innate immunity and ii) acquired immunity.

Innate Immunity

Innate immunity, the first line of defense, responds to invaders instantly without learning to recognize them. It consists of anatomic, physiological and chemical barriers such as skin, body temperature, pH, complement systems. [20,22] Natural killer (NK) cells, neutrophils, macrophages, as well as microbicide molecules such as the nitric oxide (NO) and free radicals are the participants of innate immunity.

NK cells, one of the first innate lymphoid cell populations can display cytotoxicity by producing cytokine, IFγ. [30] NK cells present remarkable sensitivity to the stress induced by physical exercise, which promotes their redistribution from the peripheral blood to other tissues. [22] Timmons & Cieslak [30] suggested that the NK cells may be a potential link between regular physical activity and general health status. Mobilization of peripheral circulation of NK cells may transpire via mechanisms including, stress caused by a substantial increase in the peripheral blood flow and decreased expression of adhesion molecules like catecholamine, [31] by physical exercise. [32] Jones & Hoyne [33] observed a transient

increase of NK cells with a rapid egress, in the acute post-exercise phase 1 hour following completion of exercise. Gannon et al. [34] however, reported that the concentration of circulating NK cells may return to the pre-exercise level, or even become lower during excessive prolonged exercise (>3h).

Leukocytes circulate through the body and work in a coordinated manner to monitor the body for invaders. [20] Mainly two types of leukocytes (phagocytes and lymphocytes) engage with immunity. Neutrophils are phagocytes, involved in many of inflammatory processes of muscle fiber to raise calcium release and synthesis of pro-inflammatory cytokines (tumor-necrosis-factor-TNF-α and inter-leukine-IL-1β), promoted by exercise, playing an important role in the innate immune response. [22] Walsh [35] evaluated that intense physical exercise endorses degranulation of neutrophils to enhance the concentration of enzymes - myeloperoxidase (MPO), which acts as a marker of neutrophil migration into the muscle and of the degranulation in the serum. Morozov et al [36] concluded with an experiment that a single session of exhaustive exercise produces significant MPO in untrained group compared to the trained group, suggesting a possible protective effect from training in the muscle tissue.

Monocytes are effective phagocytes, responsible to differentiate into macrophages. Macrophages are liable to give innate immunity by phagocytosis, microbial killing and antitumor activity [37] but also predominant in triggering atherosclerosis. [20] Both moderate and exhaustive exercise enhances a variety of peritoneal macrophage capacities, including chemotaxis [38,39] adherence, [40] phagocytosis [41,42] and antitumor [43] activity. Potent effects of exercise on macrophage function may be interceded by exercise-induced alterations in the sympathetic-nervous-system or hypothalamic-pituitary-axis via neuroendocrine hormones in a local manner. [37,44] Kohut et al. [45] found that the exercise-induced suppression in intrinsic alveolar macrophage antiviral resistance can be abrogated by propranolol, a β-adrenergic antagonist. According to Woods et al. [46] monocyte numbers transiently increase (50-100%) in peripheral blood in response to acute exercise. Grabiel et al. [47] demonstrated that exercise intensity or duration-dependent changes in subpopulations of monocytes may migrate out of the vasculature following long-duration exercise. Woods et al. [37] evaluated that both moderate and exhaustive treadmill running over periods of 3-7 days increases the antitumor activity of thioglycolate (TG)-elicited or *Propionibacterium acnes*-activated peritoneal macrophages due to enhance production of TNFα and NO respectively though other peritoneal macrophage functions like antigen presentation may be suppressed by exercise.

This increase in molecular oxygen (O_2) consumption combined with the activation of specific metabolic pathways during and after exercise can result in free radicals or reactive-oxygen-species (ROS) formation. [48-51] ROS can be fabricated by different mechanisms during physical exercise, including the partial diminution of oxygen in the mitochondria (electron transport chain) and the inflammatory process. [51-54] ROS, produced by metabolically oxidative process are required for the activation of immune system. [55] ROS also can induce pro-inflammatory cytokines. [56] The intracellular ROS serve mainly for host defense against infectious agents, redox-sensitive signal transduction and other cellular processes, while the extracellular release of ROS may damage surrounding tissues, potentially promoting inflammatory processes. [56-58] Jin et al. [59] accounted that the elevated oxidative and physical stress reflected by the level of intracellular ROS and cortisol respectively, may contribute to immunosuppression. In addition, low levels of inflammatory markers observed in the elderly who

frequently exercise. [60] Acute exercise generates excessive ROS causing damage in the body, while regular exercise results in bodily adaptations leading to resistance against oxidative damage via antioxidant pathways. [61,62] Yavari et al. [61] reported that mitochondrial ROS generated during regular exercise are necessary for the activation of primary signaling pathways associated with muscle adaptation. Nuclear factor erythroid 2-related factor (Nrf2), a redox-sensing transcription factor, is the primary regulator of antioxidants as well as other cytoprotective cofactors that are responsible for the enhanced antioxidant defense system. [62-64]

Relation with Mucosal Immunity

The mucosal immune system protects mucosal surfaces of the respiratory tract, nasal passages and intestine. Saliva is the most commonly used secretion for measurement of secretory antibodies in the assessment of mucosal immune status. [65] The effect of acute exercise on mucosal immunity is mainly focused on changes in the secretion of immunoglobulin A (SIgA) as determined in saliva. [66,67] Secretory IgM (SIgM) antibodies contribute to a lesser extent in the normal adult but play a significant role in mucosal defense in the neonate and also in IgA-deficiency states. [65,68] Individuals with selective IgA deficiency suffer from upper respiratory tract infection (URTI). [69-71] Habitual exercise at an intense level can cause suppression of mucosal immune parameters, while moderate exercise may have positive effects. [65,72] According to Gleeson & Pyne [65] the diminished mucosal immunoglobulins after exercise do not appear to be the upshot of the mucosal plasma cells depletion but recovery to pre-exercise levels usually occurs within 24 hours, though after high-intensity exercise the levels may remain suppressed for longer period leading to increased-risk of infection. [8] Nieman (2000) [13] and Müns et al. [73] reported that nasal mucociliary transit time is significantly prolonged by abnormally functioning ciliated cells after a marathon race for several days. This situation impairs in nasal neutrophil function and nasal/ salivary IgA secretion rates, directing the suppressed host protection in the upper airway passages.

Adaptive Immunity

Lymphocytes (B cells and T cells) represent adaptive or acquired immunity to learn how to efficiently encounter an invader and remember the specific invader. [23] T lymphocytes including T-helper-cell-type-1 (Th1, with surface protein cluster of differentiation CD4+), T-helper-cell-type-2 (Th2, CD4+) and cytotoxic-T-cell (Tc, with surface protein cluster of differentiation CD8+) recognize invaders via antigen-presenting cells (APCs) like macrophages and dendritic cells for recognition, activation, mobilization, regulation and resolution to represent cellular adaptive immunity. [74] The ratio of CD4+: CD8 declines throughout exercise, reflecting a more remarkable enhancement of Tc cells [21] due to increase in numbers of NK cells more than any other T cell subpopulation. [30] Prolonged and extenuating aerobic exercises reduce the expression of Toll-like receptors (TLRs) in macrophages, compromising the presentation of antigens for the Th1 inflammatory response. [22] The Th1 anti-inflammatory effect evades the usual tissue damage and reduces the risk of chronic inflammatory diseases but raises the susceptibility to infections by intracellular microorganisms. [75]

B lymphocytes and their products antibodies and cytokines represent humoral adaptive immunity via neutralization, agglutination, precipitation, complement activation and lysis. [22,76] Acute Exercise induces muscle cell injury due to a sequential release of the pro-inflammatory cytokines TNF-α, IL-1b and IL-6 followed by anti-inflammatory cytokines. [18,77,78] Endurance exercise (marathon running) associated with muscle soreness, induces a greater inflammatory cytokine response than other modes like cycling or rowing. [18] Bruunsgaard et al. [79] evaluated that the delayed-type hypersensitivity (DTH)

reaction was suppressed in triathletes (60%), two days after competing in a half iron man triathlon (mean time 6.5 h).

Contracting muscle can produce and release a cytokine named myokine (IL-6), exerting autocrine, paracrine or endocrine effects. [80] Myokines provide a conceptual basis to explain how muscles communicate to other organs. [81] Pedersen & Febbraio [80] appraised that intramuscular IL-6 expression is modified by signaling network involving crosstalk between the Ca^{2+}/nuclear factor of activated T-cells (NFAT) and lycogen/p38 mitogen-activated protein kinase (MAPK) pathways. Consequently, macrophage-produced IL-6 leads to an inflammatory response, whereas muscle cells fabricate and release IL-6 without activating classical pro-inflammatory pathways.

Signaling Pathways Involved In Exercise Induced Immune Response

The ligand-receptor molecular interactions trigger biochemical cascade signaling pathways, resulting in the production of proteins, cytokines and the expression and proliferation of receptors. [22] The antigen-receptor aggregation leads to an activation of tyrosine kinase proteins by phosphorylation, associated with the receptors in the cellular membrane. [82] IL-6 activates the signaling pathway of the Janus-activated-kinase (JAK) as well as signal transducer and activator of transcription (STAT) protein complex by phosphorylation and activation of the mitogen-activated-protein-kinase (MAPK)/ extracellular-signal-regulated-kinase (ERK) signaling cascade with interference by adenosine-mono-phosphate-kinase (AMPK) and phosphoinositol-3-kinase - protein-kinase-B (PI3K-AKT) signaling. [80] In the immunological system, mammalian target of rapamycin (mTOR; serine/threonine kinase) protein signaling is triggered by the antigens ligation to their specific receptors in T and B cells or to TLR and by the ligation of interleukins to their receptors. [22,83,84]

Exercise may cause the production of growth factors and cytokines. [22] Exercise training strongly alters physical forces, exerting significant physiologic effects on endothelial and smooth muscle gene expression and function. [85,86] Exercise induced mechanotransduction mechanisms trigger many intracellular pathways like MAPK and sequential phosphorylation activating transcription factors and gene expression. [87,88] Thompson et al. [84] reported that exercise promotes cellular stress and DNA damage that may inhibit the type of mTOR activity, leading to a pro-inflammatory effect in phagocytic cells to produce cytokines (IL-6, IL-12 and IL-23) and decrease the production of anti-inflammatory cytokines (IL-10). This phenomenon triggers the cellular immunity. [89]

Exercise Induced Beneficial Effect of Cellular System

Exercise has numerous health benefits, including lifespan expansion and protection against cardiovascular diseases, diabetes, cancer and neurodegenerative diseases. [90,91] Many of these health benefits overlap with cellular programmed mechanism [92,93] triggering through various signaling pathways of cellular proteins and/or protein kinases. Autophagy (programmed cell death type II; PCDII), a high-capacity process, encloses selective elimination of vital organelles and/or proteins, instigating mechanisms of cytoprotection and homeostasis in biological systems under normal physiological and stress conditions. [94] Autophagy is an evolutionarily conserved adaptive ubiquitous cellular process governed by dynamic catabolic biochemical mechanisms to generate autophagosomes by engulfing intracellular components and ultimately fuse with lysosomes. [94-97]

He et al. [91] reported that acute exercise (30 min) can sufficiently induce autophagosome formation in skeletal and cardiac muscle, reaching a plateau phase after 80 min of exertion. Accordingly, by using several markers of autophagy, He et al. [91] also evaluated that there is a possible role of autophagy in metabolic regulation

during exercise in skeletal muscle, heart, liver, pancreatic β cells and adipose tissue. A single bout of long endurance exercise increases autophagic flux via the ubiquitin-proteasome and the autophagolysosome systems, associated with mTOR signaling. [98,99] Chronic exercise affects the basal level of the autophagy by increasing the transcription of several autophagic proteins/genes. Autophagy modulation by exercise is linked to the nutritional status, are also modulated by amino acid and glucose availability. [99,100] Exercise may elicit metabolic stress, oxidative stress, calcium imbalance and general disturbances in cellular homeostasis [101-103] which may contribute to autophagic activation. [91,97,104] Grumati et al. [105] suggested that the functional autophagy is required for the proper response to acute and chronic exercise. Moreover, life-long exercise, in mishmash with caloric restriction, improved the decline in autophagic-proteins with aging and dampened the age-related increase in oxidative damage. [106]

CONCLUSIONS

Life has changed dramatically over the last century. People have become less active, adopting more sedentary habits. A sedentary lifestyle potentially contributes the serious implications on human-health and produce chronic diseases such as cardiovascular diseases, obesity, type-2-diabetes and metabolic syndromes. In this scenario, regular practice of physical exercise should be beneficial to health by altering the metabolic state and also the immune system. Overall this review summarized that moderate exercise may have predominance over cellular and humoral immunity whereas high intensity exercise raises the concentration of anti-inflammatory cytokines, leading to cause infection by intracellular microorganisms. Exercise induced mechanotransduction mechanism triggers many intracellular pathways like signaling-cascades of MAPK/ERK, AMPK, PI3-AKT, mTOR, associated with antigen-receptor recognition gateway of immunology. Muscle can release important factors via activation of autophagy which may foster the pleiotropic health benefits of exercise. The current state of knowledge hereafter may shed a light on the alteration of immune response depending on the types of exercise.

Competing Interests

The authors declare that they have no competing interests.

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