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The Role of Physical Activity in Reducing Inflammation: Implications for Preventive Medicine

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ABSTRACT
Physical activity is an accessible and free, modifiable factor which influences our health and wellbeing. Increased physical activity (PA) and exercise are associated with reduced chronic disease risk. The prevalence of physical inactivity is constantly increasing. Physical inactivity is associated with the development of various chronic diseases including cancer, cardiovascular, metabolic and neurodegenerative diseases [1].
All countries should adopt policies focused on encouraging people to move at all stages of life. Understanding the links that exist between PA and inflammation can bring new vision on common chronic disease.

There is no doubt it would favorably impact global society on the economic as well as productivity side. This review highlights anti-inflammatory effects of PA and exercise training in selected, frequent illnesses our time.
Purpose of the work: The purpose of this review is to explore and synthesize current scientific evidence on the anti-inflammatory effects of PA and exercise training, focusing on their impact on the prevention and management of chronic diseases.
Materials and Methods: We conducted a literature search on the MEDLINE database in October 2024, utilizing keywords including 'physical activity', 'inflammation', ‘exercise’ and 'exerkine' to identify pertinent documents. The inclusion criterion was that the article addresses the following issues: the relationship between PA and inflammation in chronic diseases, the biochemical mechanisms linking physical activity to anti-inflammatory effects. Non-English language, or without full-text available articles, and publications not addressing the issues described in the inclusion criteria and were excluded from the analysis.

Keywords: physical activity, inflammation, exerkine, exercise

INTRODUCTION

The ever-increasing prevalence of physical inactivity and involved consequences of this trend have made this topic a great interest to researchers. Knowledge about bio-chemical etiology of common diseases and their inflammatory background with newest finds about anti-inflammatory effects due to physical activity make this aspect even more curious. In order to bring those correlations to light, through rigorous synthesis of current findings, this review seeks to provide evidence-based insight to the anti-inflammatory effect of physical activity and the correlation with dementia, obesity, cancer, osteoarthritis and cardio-vascular diseases.

PHYSICAL ACTIVITY BASIC INFORMATION

Physical Activity Guidelines conducted clear recommendations. In this context, exercise training is defined as the planned and structured recurrence of exercise with the aim to maintain or increase physical aptitude [2]. Adults should do at least 150 minutes to 300 minutes a week of moderate-intensity, or 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. They should also do muscle-strengthening activities on 2 or more days a week [3]. Considering PA, we also have to note the benefits of non-exercise activity thermogenesis (NEAT) [4]. NEAT consists of continuous and vital movements with postural changes that do not involve moderate- to vigorous-intensity exercise. These activities involve for example walking, cleaning, climbing stars, standing, laughing, cooking, manual work, typing, performing yard work, and gesturing. Those additive activities are associated with energy expenditure beyond the basal metabolic activity and account for significant thermogenesis and energy consumption [5].
The biochemical benefits of NEAT have been shown in humans with type 2 diabetes [6], in interventions with the childhood obesity epidemic [7] and it is a well-known factor which reduces the long-term risk of cardiovascular disease events and all-cause mortality [8].
PA economic benefits are associated with lower all-cause mortality and with higher levels of workplace productivity [9].

Strain et al., in their pooled analysis of 507 populations with 5.7 million participants, show that the global age-standardised prevalence of insufficient physical activity is constantly increasing [10].

EXERCISE-DRIVEN EXERKINES

According to Lisa S chow et al., exerkines are defined as cytokines secreted in response to acute and chronic exercise, functioning through endocrine, paracrine or autocrine pathways [11]. Since then, researchers have focused a lot on this topic. A variety of organs, cells, and tissues release these factors, including skeletal muscle (myokines), white adipose tissue (adipokines), brown adipose tissue (baptokines), the heart (cardiokines), the liver (hepatokines), and neurons (neurokines). The classic exerkines are cytokines, in which IL-6 is the best known myokine. Apelin is another exerkine which increases during muscle contraction. It is responsible for glucose homeostasis, anti-inflammatory effect and insulin secretion [12] Irisin is also myokine. It enhances the process which is known as browning. As a result, energy expenditure increases and improves insulin sensitivity [13]. Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin, is from muscle and adipose tissue. SPARC can act as an immunomodulatory factor during exercise-induced inflammation. It regulates the recruitment and activation of immune cells, such as macrophages [14]. Acute and chronic exercise can increase brain-derived neurotrophic factor (BDNF) levels in the brain and peripheral tissues. The systemic effect of this factor is very wide. It is responsible for pleiotropic effects on neural function, metabolism, and inflammation. It promotes the conversion of M1 to M2 macrophages and inhibits the secretion of inflammatory cytokines. It is essential for maintaining energy balance during exercise by activating activated protein kinase [15] [16] [17]. Understanding the role of exercise and exerkines in anti-inflammatory responses has significant clinical implications.

CONNECTIONS BETWEEN PHYSICAL ACTIVITY AND INFLAMMATION

Systemic inflammation is a tightly regulated process. Inflammation is described as a stereotypical response as part of the tissues' biological responses to harmful stimuli, such as damaged cells, pathogens, or irritants. It is required for our existence [18].

The connection between exercise and inflammation has intrigued researchers ever since the early 20th-century. This time Larabee showed a spike of white cells in the blood of Boston marathon runners following the race [19]. After that time, researchers made a huge step forward and dive into this cellular process.

IL-6

During exercise, IL-6 is the first detectable cytokine released into the blood from the contracting skeletal muscle. Subsequently increase the production of IL-1 receptor antagonist (IL-1ra) and IL-10 by blood mononuclear cells, thus promoting an anti-inflammatory effect [20]. Moreover, in literature appears a concept that IL-6 resistance exists as a biological phenomenon. During exercise, hepatosplanchnic viscera remove IL-6 from the circulation. Researchers report a negative association between the amount of regular PA and basal plasma IL-6 levels. The more physically active, the lower the basal plasma IL-6.

While plasma IL-6 level decreases in response to endurance training, the basal IL-6Rα mRNA content in muscle is increased by approximately 100% [21]. Whether this phenomenon springs from muscle adaptation or it is another unknown process, more studies are needed. Nevertheless, the latest research brings more information about other also very important cells.

Regulatory T cells

A natural way to boost the body's immune responses and reduce inflammation is provided by exercise. Using acute and chronic models of exercise in mice, Langston *et al*. found that regulatory T cells (Tregs) suppress exercise-induced skeletal muscle inflammation that is counterproductive for performance enhancement [22]. Skeletal muscle regeneration after hard, demanding training results from the activation and differentiation of myogenic stem cells, called satellite cells. Inflammatory and immune cells have a crucial role in this process. Acute muscle injury causes a wave of neutrophils followed by a more persistent infiltration of M1 (proinflammatory) and M2 (anti-inflammatory/proregenerative) macrophages. M1 macrophages remove necrotic muscle fibers and apoptotic leukocytes, whereas M2 macrophages act on muscle satellite cells promoting muscle differentiation and growth. Muscle damage is sensed by cells resembling FAPs (FAP-like), which release IL-33. IL-33 recruits and activates Treg cells. Tregs promote muscle growth by releasing growth factors, such as amphiregulin. Tregs are also promoting muscle metabolic reprogramming by protecting mitochondria from interferon-γ–driven damage [23].

In mdx dystrophin-deficient mice, a model of human Duchenne muscular dystrophy, muscle injury, and inflammation is mitigated by expansion of the Treg-cell population but exacerbated by Treg-cell depletion. These findings open new perspectives for boosting muscle growth in chronic muscle disease. It may be a chance to find a completely new solution for diseases in which the science has been helpless [24].

What is more, congenital deficiency in Treg cells due to mutations of *Foxp3* causes fatal autoimmunity in mice, the *scurfy* phenotype and the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) in humans [25].

Natural killer cells

Natural killer cells (NK cells) constitute 5–15% of all circulating lymphocytes [26]. The main function of NK cells is to kill transformed (malignant) cells or kill infected (e.g., virus) and to trigger the adaptive immune response through cytokine release. Exercise-mediated increase in natural killer cell frequency is a well-known and significant phenomenon. Maximal mobilization of NK cells is achieved within 30min of endurance training. After this period of time, longer activity does not increase the level of NK cells in plasma [27].

Epinephrine and norepinephrine have been shown to drive NK cell mobilization in humans. This process is linked with catecholamine concentration [28].

ANTI-INFLAMMATORY IMPACT OF PHYSICAL ACTIVITY ON DISEASES

Physical activity and dementia

Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common cause of dementia. This is characterized by the decline in cognitive and function and neuronal loss. This progressive neurodegenerative disorder is caused by the accumulation of abnormal misfolded protein deposits in the brain including tau tangles, beta-amyloid plaques, and Hirano bodies. A recent investigation also highlighted the connection between AD and inflammation [29] [30]. The relationship between inflammation and AD is complex. Inflammation influences both the tau protein and the Aβ pathway. Inflammation stimulates the production of β-secretase and γ-secretase, enzymes that generate Aβ proteins. By activation of various kinases, such as mitogen-activated protein kinase and CDK5, hyperphosphorylation of tau protein is happening, resulting in the formation of intracellular neurofibrillary tangles. As a result, it causes structural abnormalities, neuronal cell death, and ultimately, the progression of AD. Key cytokines that induce both Aβ and tau pathways include pro-inflammatory cytokines, such as IL-1β and IL-18 [31]. Another study showed the impact of the myokines in regulating synaptic function and improving cognitive function in a mouse model of AD [32]. Irisin, the secreted form of fibronectin type III domain-containing protein-5 through the stimulation of BDNF in the hippocampus influences neural differentiation, neurogenesis and memory formation [33] [34].
Anti-inflammatory effects of PA give us an opportunity to prevent or delay by modifiable factors, cognitive decline, including dementia of the Alzheimer’s type [35].
What is more, studies have shown links between activity and reduced dementia risk by increased brain volumes in more active participants of the study [36].

Cardiovascular disease

According to the Centers for Disease Control and Prevention, Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide [37]. Atherosclerosis, which is initiated with a high serum low-density lipoprotein cholesterol level, is responsible for initiating the pathogenesis of this disease [38].
Inflammation plays a critical role in the genesis, progression, and manifestation of CVD as it is a vital role in the pathophysiology of atherosclerosis [39] [40].
What is more, exerkines released after exercise affect the cardiometabolic system. As just an example, vascular endothelial growth factor and nitric oxide has been shown to influence vascular tone, inflammation, regeneration and thrombosis, and has an important role in cardiovascular and overall resilience [41]. Cardiokines enhance vascularization and angiogenesis, as well as improve blood pressure, endothelial function [42]. Along with proper physical activity, inflammation can be muted. This policy could complement traditional targets, such as lipids and hypertension, to make new inroads into the management of atherosclerotic risk [43].

Cancer development and progression

A number of clinical studies have confirmed that survival rate may be improved in patients with breast cancer, colorectal cancer and prostate cancer by moderate-intensity exercise (60–70%VO2max).

Physical exercise reduces cancer risks, improves the prognoses of patients with cancer, and enhances quality of life [44] [45] [46]. In contrast, heavy exercise can have a carcinogenic effect [47]. Tumor control could be achieved through an epinephrine-dependent mobilization of NK cells, together with subsequent IL-6-induced redistribution and activation of NK cells. Pedersen et al. have found a link between 'flight or fight' response, exercise, epinephrine and IL-6 to NK cell redistribution after mobilization. In turn this process is responsible for controlling the tumor growth in mice [48] [49].

Some studies also showed the connection between exercise and cancer cells apoptosis. Mauro et Santin et al. showed that exercise-conditioned serum could be used in three-dimensional *in vitro* culture to evaluate the potential of exercise on cancer progression control. In this pilot study, a triple-negative breast cancer cell line was cultured with exercise-conditioned serum [50] [51].

Osteoarthritis

Osteoarthritis (OA) is the most prevalent chronic joint disease [52]. It has been widely described that inflammation promotes catabolic and degradative processes in bone and cartilage that affect their normal function [53].

Beside drug therapies such as non-steroidal anti-inflammatory drugs and joint replacement for advanced-stage disease, recent clinical guidelines advocate for physical- activity as frontline treatment [54]. By short-term moderate aerobic exercise, the visfatin, another exerkine is significantly increased [55]. It has a pronounced role in the pathophysiology of OA. It exhibits local effects on joints during the progression of the disease. Visfatin promotes inflammatory effects, inducing the expression of cytokines, metalloproteinases, and synthesis of prostaglandin E2. Visfatin also works as an epigenetic regulator through its interaction with Sirtuin 1. Furthermore, visfatin inhibits chondrocyte anabolism [56].

All in all, visfatin functions as a central catabolic agent in OA pathogenesis, mediating the deterioration of osteoarthritic cartilage [57].

Studies also report a significant increase in IL-33 levels in OA chondrocytes. This interleukin is primarily secreted by cardiac fibroblasts in response to mechanical strain [58]. Cartilage degeneration is caused through the Tool Like Receptor 3/IL-33 pathway [59]. Targeting IL-33 and enhancing IL-37 function may synergistically dampen inflammation [60].

INDIRECT ANTI-INFLAMMATORY EFFECT

Reduced fat tissue, reduced inflammation

Adipose tissue expansion in obesity is accompanied by inflammatory changes, within adipose tissue, contributing to chronic low-grade systemic inflammation. This state is characterized by mildly elevated levels of circulating cytokines, chemokines, and acute phase reactants [61]. We can easily ascertain this process by measuring C-reactive protein [62].

Obesity through visceral adipose tissue yields elevated levels of IL-6, tumor necrosis factor alpha, resistin and leptin [63]. Skeletal muscle can influence the adipose tissue response to exercise via lactate secretion. The study found that in a mouse model of chronic exercise, with specific lactate exposure in vitro and in vivo, increased adipocyte levels of transforming growth factor-β2 (TGFβ2).

TGFβ2 expression and secretion was associated with improvements in glucose metabolism, lipid oxidation and a possible reduction of adipose tissue inflammation [64]. There is no doubt, physical activity, no matter planned as a specific training or NEAT, supports anti-inflammatory effects by leading to reduced weight [65].

MANAGEMENT STRATEGIES

In response to the urgent need to address physical inactivity levels worldwide, the World Health Organisation (WHO) developed the Global action plan on physical activity 2018–2030: more active people for a healthier world [66].

According to the WHO, the rate of population ageing is much faster than in the past. Between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22% [67]. It is important to implement policy strategies which can extend healthy life years. Physical activity, in this context, is unique. In the cohort study including more than 2 million individuals aged 20 to 97 years, PA was consistently associated with a lower risk of mortality across all age groups. For other modifiable health factors such as high educational level, not smoking, not regularly consuming alcohol, healthy body weight, and living without hypertension and diabetes, the associations were remarkably smaller as age increased [68].

CONCLUSIONS

The health benefits of physical activity and exercise are clear. Physical activity is important not only for general health and wellbeing, but also in the prevention of diseases. Knowing the molecular mechanisms underlying exercise can bring new solutions in disease prevention and treatment. As a result of an improved inflammatory profile, the risk for chronic diseases is reduced. Since we know, physical inactivity is associated with persistent systemic low-grade inflammation, it is important to continue scientific research aimed at better understanding our impact on this process [69].

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