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Potential Importance of Immune System Response to Exercise on Aging Muscle and Bone

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Abstract

Purpose of Review The age-related loss of skeletal muscle and bone tissue decreases functionality and increases the risk for falls and injuries. One contributing factor of muscle and bone loss over time is chronic low-grade inflammation. Exercise training is an effective countermeasure for decreasing the loss of muscle and bone tissue, possibly by enhancing immune system response. Herein, we discuss key interactions between the immune system, muscle, and bone in relation to exercise perturbations, and we identify that there is substantial "cross-talk" between muscle and bone and the immune system in response to exercise.

Recent Findings Recent advances in our understanding of the "cross-talk" between muscle and bone and the immune system indicate that exercise is likely to mediate many of the beneficial effects on muscle and bone via their interactions with the immune system.

Summary The age-related loss of muscle and bone tissue may be partially explained by an impaired immune system via chronic low-grade inflammation. Exercise training has a beneficial effect on immune system function and aging muscle and bone. Theoretically, the "cross-talk" between the immune system, muscle, and bone in response to exercise enhances aging musculoskeletal health.

Keywords Osteoporosis · Sarcopenia · Immune · Inflammation · Cytokine · Myokine

Introduction

Aging is associated with the development of a variety of non-communicable diseases with some of the most significant deteriorations to health happening in the musculoskeletal system. The age-related loss of skeletal muscle mass (i.e., one defining factor of sarcopenia) and bone tissue (i.e., one defining factor of osteoporosis) is highly prevalent, and the incidence of sarcopenia and osteoporosis will inevitably increase with the growing (and aging) population [1, 2]. One main contributing factor of muscle and bone loss over time is altered/impaired immune system function, referred to as "inflammaging" [3] which describes the low-level chronic inflammatory response that exists in many aged conditions and diseases [4]. Exercise training may act as a countermeasure; however, the mechanistic effects of exercise on "inflammaging" are relatively unknown.

Research is emerging regarding our understanding of the "cross-talk" between the immune system and muscle and bone [5, 6•, 7•]. Physical inactivity remains a major health concern for a large variety of diseases and modifying physical activity levels, and including more exercise as a lifestyle behavior, is viewed as beneficial for reducing the risk of chronic disease development [8]. This holds true for decreasing the risk of developing musculoskeletal diseases such as sarcopenia and osteoporosis [9, 10] as well as modifying the immunosenescence that occurs with aging [3]. The purpose of this brief review is to provide an overview of (1) the immune system response to acute and chronic exercise and the effects of exercise on chronic low-grade inflammation; (2) the

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effects of exercise on immune response and skeletal muscle; (3) the effects of exercise on immune response and bone; and (4) future directions for research in this area.

Immune System Response to Exercise

With acute bouts of exercise, either aerobic or resistance exercise, there is a cellular (leukocyte) immune response that occurs in the systemic circulation both in the innate (which is partly composed of cells such as monocytes/macrophages, neutrophils, and natural killer cells) and adaptive (which is composed predominantly of T cells and B cells) branches of the immune system [11, 12]. Within the innate immune response, there is generally neutrophilia (an increase in neutrophil numbers) which occurs immediately following exercise with a secondary increase hours later [13, 14]. There is a transitory increase in monocytes, circulating dendritic cells, and natural killer cells (which are all different types of leukocytes or white blood cells) [15]. In the adaptive branch of the immune system there is a biphasic response of lymphocytes (T cells and B cells) to acute exercise [16, 17]. A transient increase in circulating lymphocytes occurs in response to exercise which then subsides below baseline (resting) levels before gradually rising back to resting levels [16, 17]. Speculation exists that the transient decrease in lymphocytes may cause an "open-window" for opportunistic pathogens to infect the host, but the potential for lymphocytes to move to areas where pathogens may be encountered (like the gastrointestinal tract and lungs) seems highly probable, thus increasing the resistance to infections [18, 19].

The leukocyte response to chronic exercise training is well-documented [18, 19]. In general, if an exercise-trained individual is in a truly rested state (i.e., no exercise for the previous 24 h), there does not seem to be any significant effect on leukocyte or lymphocyte cell count in systemic circulation [20–24]. However, there is controversy about the effects of chronic exercise on the function of certain cells such as monocytes/macrophages, dendritic cells, and natural killer cells [11, 25] (see Table 1 for a brief summary of the different types of leukocytes and their primary function in the immune system [26]).

Chronic low-grade inflammation is defined as a 2- to 4-fold increase in circulating levels of inflammatory cytokines [27]. The chronic low-grade inflammatory condition may be combatted to a certain extent by participation in regular exercise training [11, 28]. In particular, during an acute bout of exercise, there is a substantial increase in interleukin-6 (IL-6), a multifunctional myokine/cytokine, that may act in both pro- and anti-inflammatory capacities [11, 29]. Skeletal muscle is able to produce myokines which are peptide/protein-based mediators that act in an autocrine, paracrine, and/or endocrine fashion to influence other tissues [30]. In the context of acute exercise, IL-6 is theorized to reduce the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) and increase the levels of anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra) and IL-10 [11]. The "cross-talk" between the immune system and muscle and bone is possibly influenced by myokines and cytokines [7•, 31, 32].

As mentioned above, chronic (regular) exercise training is associated with a reduction in low-grade inflammation, and both endurance (aerobic) and resistance training are associated with reductions in various biomarkers of systemic inflammation (such as IL-6, TNF-α, C-reactive protein (CRP), and serum amyloid A (SAA)) [3]. Furthermore, one of the main mechanisms whereby chronic exercise training may decrease inflammation is through a reduction in fat mass (and especially visceral fat mass) [29]. The next sections of this review will address the influence of exercise on the immune response in relation to muscle and bone health.

Effects of Exercise on Immune Response and Skeletal Muscle

Chronic low-grade inflammation may contribute to the development of sarcopenia, and maintaining muscle mass and

Table 1 Various types of leukocytes (white blood cells) and their main function in the immune system

Cell type	Main immune system function	Acute exercise	Chronic exercise
Neutrophils	Phagocytosis	↑	↔
Monocytes/macrophages	Phagocytosis, antigen presentation, cytokine production, cytotoxicity	↑	↔
Dendritic cells	Antigen presenting cells	↑	↔
Natural killer cells	Cytotoxicity	↑	↔
T cells	Lymphocyte regulation, antigen recognition, B-cell proliferation	↑ then ↓ (biphasic)	↔
B cells	Antibody production, memory cell production	↑ then ↓ (Biphasic)	↔

↑, increase in circulating cell numbers systemically; ↓, decrease in circulating cell numbers systemically; ↔, no change in circulating cell numbers systemically. Adapted from reference [26]

function throughout the aging process is viewed as a major health challenge [33]. The process of muscle hypertrophy and regeneration is highly regulated and involves communication between the immune system and muscle [5]. As mentioned above, myokines are released from contracting skeletal muscle, and these myokines are likely to play an essential role in coordinating the "cross-talk" which occurs between the muscle and the immune system [30].

In muscle, there are resident monocytes and macrophages (part of the innate immune system) that are normally quiescent, but when muscle is contracted forcefully and/or muscle damage occurs, resident leukocytes will become activated. The activated macrophages release chemokines that attract other leukocytes such as neutrophils to the region of muscle damage. The neutrophils' main function is to create a pro-inflammatory environment where pro-inflammatory cytokines such as IFN-γ and TNF-α predominate and attract further macrophages from the systemic circulation via extravasation (i.e., the movement of macrophages from the systemic circulation to areas within the tissue itself). These macrophages are phenotypically distinct and are named the M1 type. The M1 type of macrophage is known as the pro-inflammatory phenotype, whereas the M2 type of macrophage is involved in creating an anti-inflammatory environment and is involved with muscle regeneration. Thus, depending on the stage of muscle injury or repair, either the M1 or M2 type of macrophage will predominate which allows for a coordinated response of the immune system in the muscle [5, 29].

The link between the regulation of the immune system, the associated inflammatory response, and muscle has recently started to become apparent. There are a few cytokines that play an essential role in linking the inflammatory response of the immune system with the muscle regeneration that occurs. Included in this is IFN-γ, which acts to mediate the production of the M1 type of macrophage but also controls the expression of genes encoding major histocompatibility complex class II transactivator (CIITA) in myocytes. IFN-γ will activate muscle satellite cells to express the target genes for CIITA which essentially links the immune system with skeletal muscle [34–37]. Furthermore, TNF-α is intricately involved in linking the inflammatory response due to muscle injury and muscle regeneration following injury. Here, the TNF-α cytokine is linked to suppression of proliferation, but promotion of differentiation of muscle satellite cells as well as the activation of NF-κB in myeloid cells and myocytes (inducing an inflammatory response and muscle atrophy respectively) [38, 39]. Thus, it is evident that TNF-α plays multiple roles and influences the muscle and immune systems in a variety of ways. It is interesting to note that TNF-α is not released in substantial quantities into the systemic circulation with exercise but is increased at the gene level within skeletal muscle itself [40]. This suggests that TNF-α acts in an autocrine manner within the muscle tissue but may also communicate with resident macrophages in the muscle itself.

When M1 macrophages are transitioning to the M2 phenotype, there is concomitant increase in IL-10 (a cytokine that is predominantly considered to be anti-inflammatory). This cytokine is involved in both inflammatory modulation, via M1 to M2 phenotypic shifting, and regeneration of muscle following damaging injury by signaling myogenic satellite cells to transition from proliferation to differentiation [41, 42]. Remarkably, this links another cytokine (IL-10) with pleiotropic roles in the immune and muscle systems and demonstrates the cross-talk that occurs between these two physiological systems. The IL-10 cytokine/myokine is also released in substantial amounts into the systemic circulation via exercise and is thought to play an essential role in producing the anti-inflammatory effects of exercise (Fig. 1) [11, 40] which may contribute to improving muscle health in those with chronic low-grade inflammation. Transforming growth factor-β (TGFβ) is another cytokine that is intricately involved in the muscle and immune compartments within regenerating muscle tissue. Here, TNF-α expression is suppressed, and TGFβ expression is increased which shifts the phenotype of macrophages to the M2 type [43–45]; this promotes muscle regeneration following damage or injury.

Effects of Exercise on Immune Response and Bone

As already mentioned, chronic low-grade inflammation is highly associated with the development of bone loss (osteopenia, osteoporosis) as an individual ages. Many of the inflammatory signaling pathways and molecular mechanisms responsible for inflammation are countered by participating in regular exercise [7•]. For instance, IκBα kinase (IKK) phosphorylates nuclear factor-κB (NF-κB) which is a transcription factor that plays a key role in immunity and inflammation via the production of many pro-inflammatory regulators [46]. NF-κB is stimulated by the receptor activator of NF-κB ligand (RANKL) which binds with the receptor activator of NF-κB (RANK) on precursor osteoclast cells to eventually form osteoclast cells which results in bone resorption [47–49]. Many pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-7, IL-17, vascular endothelial growth factor (VEGF), and TNF-α will promote osteoclastogenesis as well as bone resorption via their stimulation of RANK through accumulative production of RANKL [49]. Osteoprotegerin (OPG) is a cytokine decoy receptor that binds with RANKL and inhibits its ability to bind with RANK which results in less osteoclast differentiation and consequently less bone resorption [48, 49]. The drug denosumab, a monoclonal antibody to RANKL, binds to RANKL in a similar manner as OPG and is now used in the treatment of

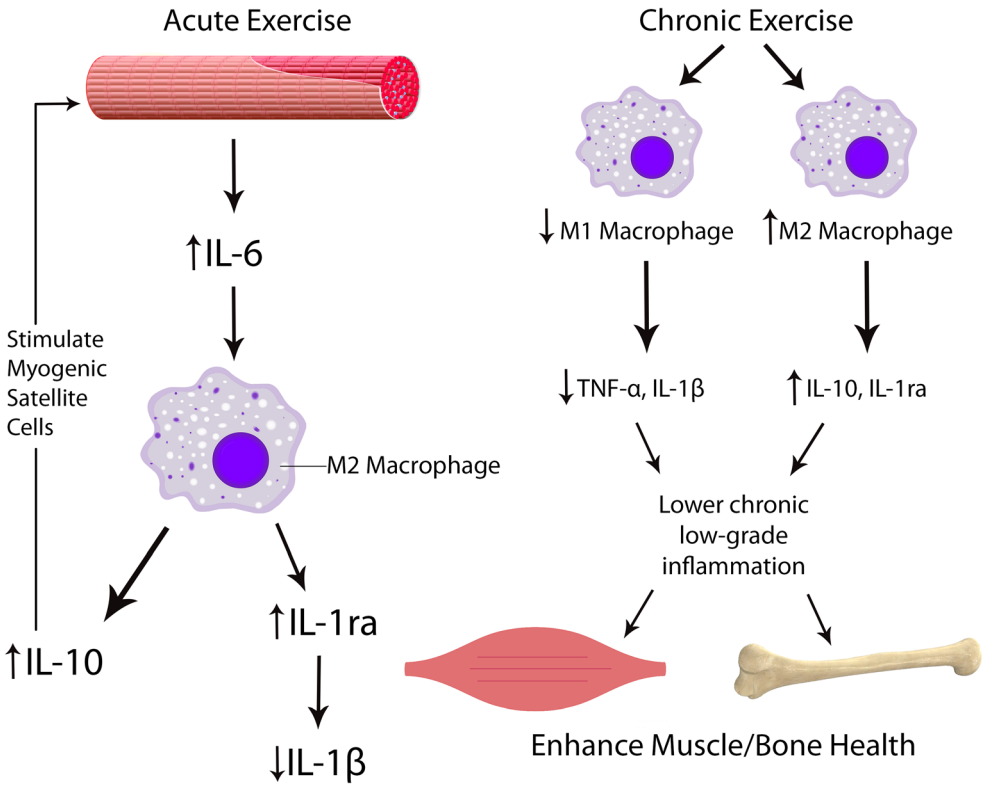

Fig. 1 Acute and chronic effects of exercise on some inflammatory cells and cytokines. IL-6, interleukin-6; IL-10, interleukin-10; IL-1ra, interleukin-1 receptor antagonist; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor alpha

osteoporosis [50]. The RANK receptor, which is typically associated with the immune system, clearly has profound influences on bone.

High-impact exercise (plyometric jumping) in girls, boys, and young men acutely stimulates a systemic increase in OPG which suggests that exercise of this type may have a beneficial effect on bone [51, 52]. Systemic RANKL was decreased after an acute plyometric exercise session in female children and adolescents; however, OPG remained unchanged in this cohort [53]. In contrast, two back-to-back days of high-intensity metabolic conditioning (that involved both cardiovascular conditioning and resistance exercise) resulted in a significant decrease in OPG 48-h post-exercise in a group of young adults [54]. Further work indicated that an acute session of high-intensity interval exercise on a cycle ergometer was able to significantly increase immediate post-exercise concentrations of bone alkaline phosphatase (a biomarker of bone formation), OPG, and RANKL but the effect was only sustained for bone alkaline phosphatase at 1-h post-exercise [55]. A biomarker of bone resorption (amino-terminal cross-linking propeptide) was reduced 24-h post-exercise [55].

The effects of chronic exercise training on OPG/RANK/RANK-L are mixed. Eight weeks of resistance training in middle aged women with metabolic syndrome (which is associated with low-level chronic inflammation) was able to raise the basal systemic levels of OPG compared with that of a control group; this suggests that chronic resistance training is able to raise OPG levels which may have a beneficial effect on bone [56]. In contrast, aerobic-based endurance exercise for 8 months in a cohort of 30–65-year-old adults had no effect on the systemic resting levels of OPG [57]. In a group of older women and men (mean age 68.2 years) who completed 32 weeks of 2 days per week of resistance training and 1 day per week of weight-bearing impact exercise training, there was a significant decrease in the inflammatory cytokines interferon-γ (IFN-γ) and IL-6 (in the men only) with no change in resting values of OPG, osteocalcin (a marker of bone formation), C-terminal telopeptide of type I collagen (a marker of bone resorption), or RANKL [58]. This type of exercise training may therefore be an effective anti-inflammatory modality; however, it may not have the desired chronic effect on bone biomarkers.

While OPG has received a high degree of attention as a potential mediator of bone metabolism, and may be stimulated with acute exercise interventions, there are a number of other cytokines that have an influence on bone from a variety of different research models. As previously discussed, IL-6 is elevated in chronic inflammatory states and stimulates bone resorption by augmenting osteoclast differentiation via RANKL stimulation [59, 60]. In a group of post-menopausal women diagnosed with osteopenia, the systemic concentration of IL-6 negatively correlated with bone mineral density (BMD) and hand-grip strength at baseline. Furthermore, the decrease in IL-6 with 6 months of alendronate-calcitriol therapy negatively correlated with baseline lumbar BMD and positively correlated with parathyroid hormone concentration

(PTH) [61]. This study concluded that the improvement in IL-6 concentrations over the 6 months was associated with the severity of bone loss at baseline and higher levels of PTH [61]. Muscle contraction (exercise) is known to stimulate the release of the myokine/cytokine IL-6 into the systemic circulation but the increase is only a temporary response with concentrations usually decreasing fairly rapidly after the exercise session is complete [11]. It is likely that the pulsatile nature of the acute exercise IL-6 response helps create the anti-inflammatory environment, whereas chronic elevation of IL-6 is viewed as pro-inflammatory with deleterious effects on a number of tissue types including bone [62]. Additional anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra) and IL-10 are released with acute bouts of exercise [11, 63]. It is theorized that this systemic cytokine response creates an anti-inflammatory environment for individuals who engage in regular exercise training.

There are a number of additional cytokines that may affect bone metabolism. IL-7 is a pleiotropic cytokine which has effects on both osteoclasts and osteoblasts, and thus, it remains a contentious issue as to what effects IL-7 has on bone metabolism [64]. Osteoblasts produce RANKL which is stimulated by TNF-α which is induced by IL-15; therefore, IL-15 is involved in osteoclastogenesis via the RANK/RANKL pathway [7•]. TNF-α is a major stimulator of osteoclastogenesis and therefore bone resorption [65]. Myostatin, which is considered a myokine that inhibits muscle hypertrophy, directly affects bone loss in a mouse model of rheumatoid arthritis and inhibition of myostatin resulted in preservation of bone [66]. Seven days of unloading in myostatin knockout mice decreased osteoblast cell numbers, and bone loss was not prevented in this model [67]. Finally, the myokine irisin is lower in post-menopausal women who had a previous fragility fracture when compared with those who had not had a fragility fracture [68]. In mice, injection of low-dose recombinant irisin stimulates an increase in cortical bone mass [69], prevents trabecular and cortical bone mineral density loss during hind-limb suspension, and restores bone mass once hind-limb suspension ceases [70]. These cytokines and myokines demonstrate the cross-talk that the immune system has on bone as well as the cross-talk that may be occurring when skeletal muscle releases myokines that could influence bone. More research evaluating the effects of various cytokines and myokines on bone tissue may lead to better therapeutic approaches to diseases and the understanding of the cross-talk between various physiological systems.

Conclusion

While there is some understanding of the inter-relationship between the immune system, muscle, and bone in response to exercise, research is limited and additional work is warranted. Specifically, identifying the types, doses, intensities, and frequencies of various exercise modalities on influencing the immune system response and how this influences bone and muscle is an area apt for future research. Also, identifying the similarities or differences in the acute response of the immune system, and its cross-talk with muscle and bone, between an un-trained and trained state is of interest. Will the strength of the response remain, or even be more robust, in a trained state? Understanding the effects of exercise training on the cross-talk between the immune system and bone or muscle in diseased populations is an area that should continue to undergo pre-clinical and clinical research efforts. These interactions are essential for maintaining musculoskeletal health as individuals' age.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflicts of interest with regards to this manuscript.

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