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MUSCLE AND BONE (A BONETTO AND M BROTTO, SECTION EDITORS)

Muscle, Bone, and Fat Crosstalk: the Biological Role of Myokines, Osteokines, and Adipokines

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Abstract

Purpose of Review Skeletal muscle and bone are connected anatomically and physiologically, and play a crucial role in human locomotion and metabolism. Historically, the coupling between muscle and bone has been viewed in light of mechanotransduction, which dictates that the mechanical forces applied to muscle are transmitted to the skeleton to initiate bone formation. However, these organs also communicate through the endocrine system, orchestrated by a family of cytokines namely myokines (derived from myocytes) and osteokines (derived from bone cells). A third player in this biochemical crosstalk is adipose tissue and the secretion of adipokines (derived from adipocytes). In this review, we discuss the bidirectional effects of myokines and osteokines on muscle and bone metabolism, and the impact of adipokines on both of these secretory organs.

Recent Findings Several myokines, notably, IL6, irisin, IGF-1, BDNF, myostatin, and FGF2 exert anabolic/catabolic effects on bone, while the osteokines osteocalcin and sclerostin have shown to induce muscle anabolism and catabolism, respectively. Adipokines, such as leptin, resistin, adiponectin, and TNFα (released from adipose tissue), can also modulate muscle and bone metabolism. Contrarily, exercise-mediated release of lipolytic myokines (IL6, irisin, and LIF) stimulates thermogenesis by promoting the browning of adipocytes.

Summary Myokines, osteokines, and adipokines exert autocrine/paracrine effects locally as well as through the endocrine system, to regulate muscle, bone, and fat metabolism. Reductions in physical activity and increases in energy intake, both linked with aging, leads to adipocyte hypertrophy and the recruitment of immunological cells (macrophages). In turn, this releases pro-inflammatory adipokines which induces chronic low-grade inflammation (LGI), a key player in the pathology of several diseases. However, exercise-induced stimulation of bioactive cytokines, through muscle-bone-fat crosstalk, increases muscle anabolism, bone formation, mitochondrial biogenesis, glucose utilization, and fatty acid oxidation, and attenuates chronic LGI.

Keywords Muscle · Bone · Fat · Myokines · Osteokines · Adipokines · Osteosarcopenia

Introduction

The musculoskeletal system, comprising primarily of muscle and bone, encompasses a significant portion of whole-body mass (~55% of a healthy adult) and plays a fundamental role in human movement and metabolic health. Aside from the biomechanical role of bone (in supporting the skeleton) [1] and muscle (enabling locomotion through contractile proteins (sarcomeres)) [2], both tissues also regulate whole-body metabolism via the utilization, distribution, and delivery of nutrients and other substrates [3, 4]. For instance, bone provides the largest storage site for calcium/phosphate, production of mesenchymal stem cells (MSC), and hematopoiesis [1], while muscle is the largest depot for glucose disposal, storage of amino acids, and is a major contributor to basal metabolic rate [3].

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The maintenance of muscle and bone homeostasis is dependent on endogenous (hormonal, inflammatory) and exogenous (physical loading, nutrition) factors [5], which act in synergy to regulate its structure and function [6]. Bone turnover is modulated by the coupling of bone formation and resorption, with the former mediated by MSC-derived osteoblasts which deposit new extracellular matrix in response to biochemical stimuli, and the latter facilitated by monocyte-derived osteoclasts which remove poor-quality bone generated by states of inactivity, disuse, or trauma/injury [6]. On the other hand, muscle protein metabolism is governed by the net balance between protein synthesis and degradation (i.e., if degradation exceeds synthesis catabolism occurs and vice versa) [7]. In the presence of anabolic stimuli (i.e., physical loading and/or protein-derived amino acids), myogenesis occurs allowing the proliferation and differentiation of myoblasts into myotubes/myofibers [7]. Both tissues hold great plasticity; in healthy adults, muscle protein turnover occurs at ~ 1–2% per day [7] while bone turnover occurs at an attenuated rate (cortical bone ~ 5% per year, trabecular bone ~ 25% per year) [8]. Beginning between the 4 and 5th decades of life, the structure and function of muscle and bone slowly decline (bone density (~ 1–1.5% per year); muscle mass (~ 1.5–2% per year); muscle strength (~ 2.5–3% per year) [9, 10]), and by age 80, this may translate into a significant loss of muscle mass (~ 30%) [10], strength (~ 50%) [11], and bone density (30–50%) [8].

Hormonal factors particularly estrogen, testosterone (in men), parathyroid hormone (PTH), leptin, growth hormone, and its constituent insulin-like growth factor-1 (IGF-1) [12] play a role in the accretion of muscle and bone in early life, maintenance in midlife, and the preservation of these tissues in late life [13]. Nutritional factors, notably dietary protein, vitamin D and calcium modulate bone metabolism [14, 15], and protein (and possibly vitamin D), activate anabolic signaling (i.e., IGF-1, mTOR pathways) and downregulation of catabolic systems (i.e., ubiquitin proteasome pathway) [16–18]. Epidemiological data support these findings by demonstrating that a higher dietary intake of protein correlates with bone density [19], and both protein and vitamin D are associated with higher lean mass, strength, and function [16, 20–23]. Finally, genome-wide associations demonstrate that genetic factors are predictive of peak bone density and lean body mass [24], and single-nucleotide polymorphisms in the genes regulating myostatin and the vitamin D receptor have been associated with muscle and bone loss [25].

Overall, aging induces changes in serum levels and cellular response to most of these factors. In addition, factors secreted by other tissues—such as fat—start playing an important role as inducers of tissue degeneration. Herein, we discuss the directional effects of myokines on bone metabolism and osteokines on muscle metabolism, and the impact of adipokines on both of these secretory organs. We also highlight the role of cytokines in the manifestation of various age- and metabolically related diseases, and highlight how exercise can combat chronic low-grade inflammation associated with these pathological states.

Effects of Aging, Physical Inactivity, Obesity, and Inflammation

As muscle and bone metabolism are tightly regulated, any imbalance between bone-forming osteoblasts/bone-resorbing osteoclasts and muscle protein synthesis/degradation, as observed with physical inactivity (aging/daily step reductions) or de-loading (prolonged bed rest/spaceflight) [13] results in the loss of bone strength and microarchitecture and muscle mass and function, and increases the risk of osteopenia/osteoporosis, sarcopenia, and/or osteosarcopenia [26]. All three conditions are strong risk factors for falls, fractures, and adverse outcomes in older persons [27]. Muscle loss has metabolic consequences too, just 2 weeks of step reduction induces a marked decline in muscle protein synthesis rates which, in turn, increases insulin resistance and transitions older men from a pre-diabetic to a diabetes state [28]. In bone too, declines in microarchitecture are linked to stem cell exhaustion [29]. To exacerbate this process, a chronic energy surplus (i.e., increases in food intake and/or reductions in physical activity) common in aging increases adiposity and deposition of lipids within bone marrow and myofibers, releasing free fatty acids which are lipotoxic [30, 31] to osteocytes, osteoblasts, and myocytes in the vicinity [32]. In a vicious cycle, systemic low-grade inflammation (LGI) ensues [33] and results in a host of metabolic consequences.

Biomechanical and Biochemical Interactions

Muscle and bone interact to maintain their structure and function [12]. Studies demonstrate the load applied to skeletal muscle (SKM) in response to resistance exercise is transferred to bone, which not only initiates muscle protein synthesis but also signals a high-energy demand to facilitate bone formation, providing evidence of a biomechanical interaction [6]. Systemic factors such as growth hormone (GH), insulin-like growth factor-1 (IGF-1), and leptin can also initiate muscle hypertrophy and bone formation [12], demonstrating that these tissues are also able to receive endocrine signals. Indeed, it is now recognized that muscle and bone can receive, as well as secrete, biochemical signals in a bidirectional manner, thus affecting the metabolism of both tissues as well as the whole body [4, 6, 34, 35]. These signals are orchestrated by a panel of cytokines and growth-like factors, namely myokines secreted from myocytes and osteokines from osteocytes, both of which can exert autocrine, paracrine, and endocrine effects.

In addition, adipose tissue (AT)-derived adipokines (secreted by adipocytes) interact in concert with myokines and osteokines to regulate muscle and bone metabolism.

Myokines and Bone Metabolism

Myokines that influence bone metabolism include some interleukins (ILs) and myostatin; however, burgeoning evidence has implicated several other factors capable of influencing bone metabolism. The interleukin (IL) families of cytokines are pro-inflammatory mediators and are secreted from a variety of cell types across the body. Several ILs are secreted by SKM, with wide ranging and occasionally contrary effects. One of the most significant of these is IL6, though IL7 and IL15 have also been observed in muscle. Most IL6 is synthesized by the liver, and is strongly pro-inflammatory; however, exercise has been shown to stimulate a large amount of muscle-derived IL6 [36••], which in fact acts as an anti-inflammatory compound and increases glucose uptake and sensitivity [37, 38]. Despite these beneficial effects, the impacts of IL6 on bone are less positive. Systemic inflammation or estrogen deficiency and IL6 drive osteoclastogenesis by inducing the release of receptor activator of nuclear factor kappa-B (RANK) by osteoblasts, osteocytes, and leukocytes and increase expression of its ligand (RANKL) by osteoclasts leading to a net resorptive effect [39]. Muscle-derived IL6 has been shown to drive a resorptive state in bone via osteoblast signaling in co-culture experiments of IL6 receptor (IL6R)-deficient cells. When IL6 is added to cultures of osteoblasts and osteoclast progenitors, there is an increase in bone-resorbing cells. However, when osteoblasts in culture lack the IL6R, the addition of IL6 does not have this effect. IL7 and IL8 are also strongly related to inflammatory responses and have been shown to be expressed in muscle. IL7 is a mediator of the acquired immune system [40], and IL15 is a potent proliferator of innate immune cells [41]. Both have a strong action on bone resorption, increasing osteoclastogenesis largely via RANKL stimulation, leading to catabolism.

Myostatin is a member of the transforming growth factor β (TGFβ) family of cytokines, and is a negative regulator of muscle mass. Increased levels of myostatin correlate with states of muscle disuse, injury, and sarcopenia [42]. In a similar theme, myostatin negatively impacts bone remodelling, driving a catabolic, resorptive state, with increased osteoclastogenesis, and limiting bone formation [43•]. Strengthening this association, treatment with follistatin, an inhibitor of TGFβ cytokines, leads to improved bone regeneration in animal models of type 2 diabetes mellitus (T2DM) [44], and suppression of the myostatin signalling pathway may underpin the pro-osteogenic effects of pulsed ultrasound therapy for fracture healing [45]. While myostatin has a clear effect on bone remodelling, the underlying mechanism remains unclear. Research has indicated a role for osteocyte signalling and exosome production as a potential underlying mechanism for the effects of myostatin in bone [6]. Myostatin was shown to suppress the expression of miRNA-218 in osteocyte-derived exosomes, as well as increased production of the anti-anabolic factors sclerostin (Sost), RANKL, and Dickkopf Wnt signalling pathway inhibitor 1 (DKK1). miRNA-218 is a Wnt signalling inhibitor, and as osteocyte-derived exosomes undergo rapid uptake by local osteoblasts, this leads to a decrease in osteoblastogenesis and bone formation [43•].

While myostatin has been the most extensively studied myokine regarding its deleterious impact on bone remodelling, there are a number of myokine growth factors that have been shown to have an anabolic effect on bone. SKM expresses a number of growth factors, including IGF-1 and the fibroblast growth factors 2 (FGF2) and 21 (FGF21). IGF-1 is predominantly synthesized by the liver and has well-documented anabolic effects in almost all body tissues. It is also expressed by SKM, particularly after exercise [46]. IGF-1 is well known to be a strong mediator of bone anabolism through increased osteoblast survival and proliferation [47]. FGF2 has a similar effect on bone as IGF1, though its secretion has been suggested to be a function of disruption to muscle plasma membranes either from exercise or injury, rather than exocytosis [46], though newer evidence has identified a non-typical method for the release of FGF2 [48]. Irrespective of its secretion, FGF2 causes similar effects in osteoblasts to IGF1 with increased proliferation, and accelerated bone formation [46]. More recently, however, FGF2 has been shown to mitigate the resorptive effects of glucocorticoids on bone, through inhibition of Sost signalling [49], providing evidence of another putative pathway for its anabolic effects. FGF21 was first documented as a mediator of glucose uptake in a range of tissues including the liver, AT, and SKM. In muscle, it is expressed in response to insulin, and causes increased uptake of glucose, and in bone, it has been purported to lead to bone resorption. Loss of function mutations of the FGF21 gene in mice leads to the development of a high bone mass phenotype, mediated by the peroxisome proliferator-activated receptor γ (PPARγ). Additionally, increased expression of the FGF21 gene leads to osteoporosis, further suggesting a role in bone homeostasis [50]. Recently, however, the in vivo importance of this effect has been disputed, with administration of exogenous FGF21 causing no change in bone formation or resorption in mice, leaving little clarity as to its physiological role [51].

Another agent gathering interest due to its role in AT, muscle, and bone is the adipomyokine irisin. Irisin is one of the more newly discovered hormones and is a fragment resulting from the proteolytic cleavage of fibronectin type III domain 5 (FNDC5), which is secreted by both muscle and fat tissue [52]. Irisin has been shown to have effects across multiple

body systems, including increasing insulin sensitivity and glucose uptake in the liver, muscle, and AT. It was initially shown that low circulating levels of irisin were correlated with decreased bone mass in people with T2DM [53] and osteoporotic fractures [54]. More recently, it has also been shown to have an anabolic effect on bone, improving osteoblastogenesis [55] and improving bone mass [56, 57] in animal models when administered exogenously. Despite this positive evidence for an impact in both metabolic function and bone mass, there is as yet, no clear mechanism for the action of irisin in vivo, though it has been suggested that the improvement in osteogenesis is due to stimulation of MAP kinase signalling pathways [58]. It has been demonstrated by a number of laboratories that it increases after exercise [59–61], and plays a role in the insulin-mediated glucose response; however, other studies have contradicted this finding [62].

Osteokines and Muscle Metabolism

Recently, a small number of factors secreted by bone have been identified as having effects systemically, on a range of tissues, including muscle. While several candidates have been suggested, osteocalcin (OCN) and Sost have exclusively shown to have an endocrine impact on SKM.

OCN is a hormone secreted principally by osteoblasts and is present in the circulation in carboxylated, undercarboxylated, and uncarboxylated forms. Since it was shown that the un- or undercarboxylated forms (ucOCN) increased insulin sensitivity and secretion through direct effects on the pancreas [63•], it has been the center of most research. Multiple clinical studies have shown that ucOCN increases after exercise [64–66], and this has been associated with a number of metabolic effects with the overall effect of increasing insulin secretion and sensitivity, and in glucose uptake. While direct binding has never been observed, both knock out models [67, 68] and computational modelling [69] have suggested the GPRC6A as the putative receptor for ucOCN. In muscle, ucOCN causes an insulin-dependent increase in glucose uptake post-contraction in animal models [70, 71], with an associated increase in GPRC6A [72]. From a more functional perspective, ucOCN has also been implicated in muscle hypertrophy and strength. Mice with OCN deletions have lower muscle mass [67, 73], and administration of ucOCN increased muscle mass in older mice [74]. Recent evidence has uncovered a novel mechanism of bone-muscle crosstalk surrounding OCN and IL6 signaling. After observation of significant increases in both muscle-derived IL6 and ucOCN post-endurance exercise, it was found that these changes are dependent on one another [36••]. IL6-deficient mice did not show the typical increase in OCN post-exercise, indicating that the chemokine was required for this crosstalk. This effect was corrected via application of injected IL6, providing strong evidence for the underlying mechanisms. As discussed above, it was shown that the bone effects of IL6 occur through osteoblast signaling, with a resultant increase in RANKL expression and osteoclastogenesis, and it appears that muscle performance benefits of IL6 are mediated through the skeleton [36••]. While IL6-deficient mice have been repeatedly shown to have compromised muscle response to exercise, mice lacking the IL6R in myofibers did not suffer from the deficit. Instead, mice lacking IL6R in osteoblasts mimicked the effect of total IL6 deficiency, indicating that OCN was a mediator of the muscle response to the chemokine [36]. Finally, this mechanism was shown to underpin the effects of OCN on muscle, by increasing the uptake and metabolism of glucose.

Despite these promising animal models, human trials are lacking and are less conclusive. Cross-sectional studies have shown that resistance training causes an increase in ucOCN, alongside a decrease in HbA1c, insulin resistance, and blood glucose [75] as well as quadricep strength [76]. This exercise-mediated increase in OCN has also been shown to rely on IL6 secretion from muscle [36••]. Use of the IL6 antibody drug tocilizumab caused an almost complete erasure of the exercise-induced OCN increase after a 12-week endurance training regimen [36••], indicating that the relationships found in animal studies also translate to human. Despite these associations, no interventional trials have provided causative evidence in vivo for the effects of ucOCN on muscle metabolism or function.

While ucOCN is the most extensively studied osteokine, a small body of recent evidence has investigated other bone-derived factors for their role in muscle function. Studies have investigated the secretome of the osteocyte, showing that it inhibits SKM cell differentiation, although no specific agent has been identified [77]. This has prompted investigation into osteocyte-secreted factors, including the anti-anabolic Sost which acts to inhibit osteoblastogenesis. This action occurs through the inhibition of Wnt signalling upon binding with the receptors LRP5 and LRP6, thus limiting osteogenesis. Identification of LRP5/6 in muscle cells [78] led to investigation into whether Sost had effects in muscle. Some in vitro and ex vivo evidence suggests that osteocytes in culture can stimulate myogenesis and contractile function [79], suggesting a contrary anabolic response when compared with its role in bone. However, a recent cross-sectional study found the opposite, with serum Sost levels negatively correlating with SKM mass in older Koreans with sarcopenia [80••], implying a similar anti-anabolic effect as seen in bone. To further complicate the picture, an animal model has shown that treatment with anti-Sost antibody therapy (commonly used in osteoporosis treatment) did not stop, or slow the atrophy associated with spinal cord injury, as would be expected were Sost a strong inhibitor of muscle hypertrophy [81].

Adipokines Impact on Muscle and Bone Metabolism

Adipokines are AT-derived cytokines and hormone-like factors regulating the metabolic response throughout autocrine, paracrine, and endocrine signalling [82]. Typically, visceral AT accumulation (i.e., positive energy balance) is associated with adipocyte hypertrophy that recruit infiltrating immune cells [83]. The resulting release of adipokines leads to the development of systemic low-grade inflammation (LGI) [84] that can induce dysmetabolic conditions (e.g., insulin resistance) [59, 85]. Contrarily, enhanced energy consumption associated with fat mobilization from AT (e.g., exercise), together with the effect of SKM-derived lipolytic myokines (IL6, irisin, LIF), stimulates thermogenesis and, by reducing LGI, improves whole-body metabolism [37].

Besides their involvement in the pathogenesis of metabolic diseases, adipokines modulate bone turnover and bone mineral density (BMD) (e.g., enhanced bone marrow adiposity in osteoporosis associates with accelerated bone resorption) as well as SKM catabolism in aging (e.g., sarcopenia) [6].

In LGI, as in obesity, leptin upregulates IL6 and TNFα and altogether downregulate adiponectin; hyperleptinemia causes leptin resistance that limits muscle fatty acid (FA) oxidation and reduced lipolysis in AT [86] an effect that is effectively counteracted by exercise [84]. Adiponectin expression is inversely associated with AT mass; it has an anti-inflammatory effect, increases FA oxidation and glucose uptake in SKM, and inhibits hepatic gluconeogenesis. It is also expressed by SKM [87], although it is not affected by acute exercise but it is upregulated in SKM of severely obese subjects in response to endurance training, as are adiponectin receptors (AdipoR1 and R2) [88]. IL6, C-reactive protein, leptin, resistin, and visfatin/NAMP that features, among the other adipokines, increased adiposity and LGI inversely associates with BMD [89, 90] and this phenotype can be reverted by exercise training [37, 91–94] (Fig. 1).

Age-associated muscle wasting and sarcopenia associate with SKM disuse and catabolism, endocrine alterations, chronic inflammation, nutritional deficiencies, and insulin resistance [95]. In sarcopenic older person, LGI and increased plasma levels of IL6, TNFα, and CRP [96] associate with loss in muscle strength [97]. For instance, chronically elevated IL6 activates the JAK/STAT3 pathway that leads to SKM atrophy [98] and in turn induces IL6 resistance, a condition that share similar patterns with insulin or leptin resistance in diseases [99].

In a vicious cycle, the metabolic and inflammatory effects of obesity can be exacerbated by the presence of sarcopenia, in a condition called sarcopenic obesity [59]. Also, bone loss (osteopenia/osteoporosis) is often associated with sarcopenia since they share common risk factors and molecular mechanisms; their combination has been termed osteosarcopenia [26]. Diabetes and obesity, associated with an unhealthy inactive lifestyle, together with aging thyroid dysfunctions, GH/IGF-1 alteration, and malnutrition, are main risk factors for osteosarcopenia since they alter the metabolic balance toward catabolism [100]. Often, increased adiposity and LGI reflects into fat infiltration of SKM and bone; the established local inflammation sustains the systemic inflammation. Moreover, the pro-inflammatory phenotype expressed by these tissues feeds the catabolism and results in an aberrant crosstalk that exacerbates the progression of the disease [100, 101].

Inducing Changes in Tissue-Specific Factors and Their Effects on Muscle, Bone, and Fat

Exercise profoundly affects all tissues and organs: the more intense and greater volume is the activity, the greater is the response. Different kinds of exercise (e.g., endurance vs. resistance, aerobic vs. anaerobic, continuous vs. intermittent) differently affect the homeostasis and, hence, the adaptive response [102]. Adaptation to exercise contemplates the integration of primary (direct response) and secondary (response to soluble factors released by a third tissue) mechanical, endocrine, metabolic, and inflammatory responses each one proper of a different tissue. Then, these responses differ between acute and chronic exercise (training), since long-term adaptation implies changes in cell functions [103]. From a therapeutic point of view, the current most effective and easily applicable strategy to treat sarcopenia and osteosarcopenia is to intervene on lifestyle, e.g., exercise and nutrition. Regular exercising limits chronic LGI by reducing the basal inflammatory status and, also, the acute inflammatory response arising from a flogistic stimulus [104] (Fig. 2).

The primary bone response to acute exercise depends upon the mechanical stimulation and is mainly mediated by osteocytes. These specialized osteoblasts, buried into the complex canalicular system within bone matrix, sense the exercise-driven changes in the canalicular environment (e.g., fluid shear stress, electrolyte concentration, shape modification) and inhibit the constitutive secretion of Sost. Mechanical stimulation of bone (i.e., loading) eliminates the Sost inhibition and allows the activation of osteoblasts. Exercise-induced osteocyte-derived prostaglandin E2 (PGE2) exerts similar effects by stimulating the transcriptional activity of β-catenin, a downstream factor in Wnt signalling [103] However, as actual exercise "consumes" calcium, bone is resorbed regardless the loading level of the activity [105]. The release of osteokines from both the direct stimulation of osteocytes/osteoblasts and the resorption-dependent release/cleavage of matrix-buried factors generates a secondary response in bone itself and other tissues by acting autocrinally, paracrinally, and endocrinally. On the contrary, the response to chronic exercise is mainly dependent upon the loading level with weight-

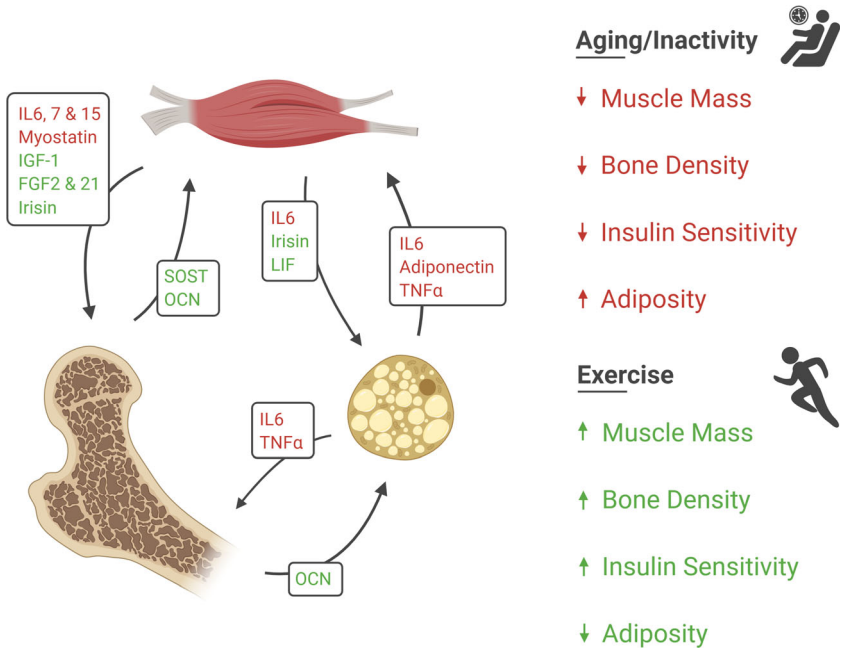

Fig. 1 The biological role of myokines, osteokines, and adipokines in muscle, bone, and fat crosstalk. Interleukin, IL; insulin-like growth factor-1, IGF-1; fibroblast growth factor, FGF; leukemia inhibitory factor, LIF; tumor necrosis factor, TNF; osteocalcin, OCN; sclerostin, SOST

bearing and high impact activities (running, jumping, resistance) generating an anabolic response and loading-free activities (cycling, swimming) associated with a more prominent catabolic response of the bone [103, 106].

The loading-induced Sost inhibition and the consequent activation of Wnt signalling, for instance, increases the MSC pool, induces osteogenesis, and inhibits adipogenesis [107]. Serum Sost positively associates with age and body mass index (BMI) and negatively with bone formation marker levels and physically active status [108]; indeed, Sost has emerged as a regulator of glucose and fat metabolism [109, 110].

In unloading conditions (e.g., bed rest, immobility, not weight-bearing training), osteocytes also express FGF23, a phosphatonin that increases the release of phosphorous in urine (by inhibiting its reabsorption in the kidney tubule), in order to maintain the blood concentrations of phosphorous that are increased as a consequence of increased bone resorption. FGF23 inhibits the activation of vitamin D in the kidney and decreases PTH secretion, with the aim to keep the calcium-phosphate homeostasis [103]. FGF23 is also expressed by the trained SKM, at least in mice, where it may limit the exercise-associated production of radicals [111].

Bone morphogenetic protein (BMP)7, osteocalcin, and lipocalin (LCN)2 are expressed by active osteoblasts but can be released from the matrix during bone resorption (BMP7, ucOC). They act as osteokines with prominent effects on energy metabolism [4, 38]. BMP7 is involved in browning of AT [112] and enhanced thermogenesis other than stimulating

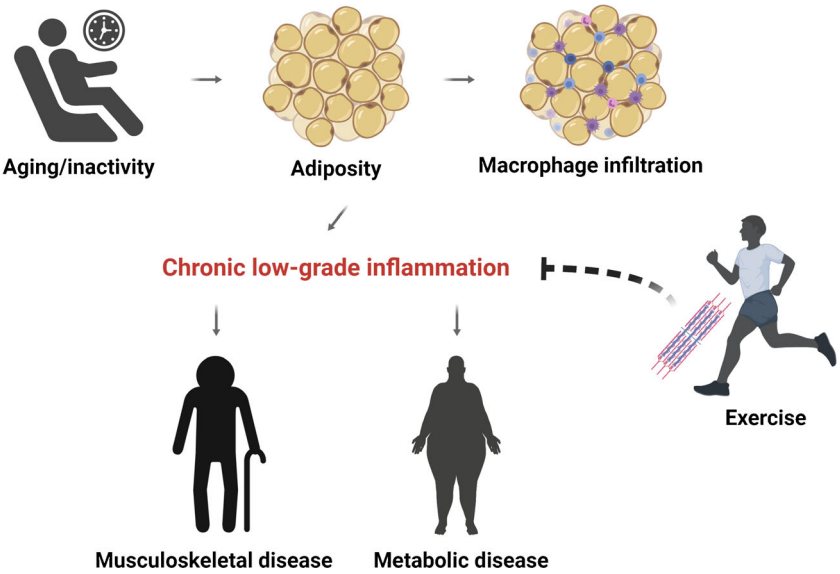

Fig. 2 Physical inactivity and/or a positive energy balance, both associated with aging, lead to adipocyte hypertrophy and the recruitment of immunological cells (macrophages). This releases pro-inflammatory cytokines from adipose tissue and causes chronic low-grade inflammation (LGI), which plays a pathological role in various age- and metabolically related diseases. However, exercise-induced contraction of sarcomeres releases anti-inflammatory myokines that combat chronic LGI

insulin secretion by pancreatic insulae [113, 114]. In mice, ucOC (but not carboxylated OC [cOC]) improves insulin sensitivity, and metabolic status in high-fat diet models [115], glucose uptake and IL6 sensitivity in SKM [116•], and possibly infertility [117, 118] in mice. However, the relative effects of cOC and ucOC are definitely unclear in humans: vitamin K treatment increases cOC and decreases ucOC but associates with an improved metabolic status; total OC, and not ucOC, associates with the metabolic profile in osteoporotic women; weight-bearing (cOC enhancing) and not weight-bearing (ucOC enhancing) training activities associate with an improved metabolic status, although with bone anabolism the former and bone catabolism the latter [4].

LCN2, first recognized as adipokine, is expressed by osteoblasts and regulates feeding contributing to postprandial satiety and stimulates energy expenditure [119••]; obese subjects can develop LCN2 resistance [120]. Like sclerostin, LCN2 responds to mechanical stimulation and is overexpressed under unloading (e.g., bed rest, microgravity) but not in unloading-independent bone loss conditions (e.g., ovariectomy). LCN2 serum levels increases with aging and are reduced by energy expenditure [121].

SKM is the effector of exercise and throughout a voluntary contraction driven by central nervous system signals. Movement of sarcomeres and sarcomere-associated structures also results in the generation of biochemical signals (myokines) that are released by the SKM and act autocrinally/paracrinally on the myofibers and endocrinally on other tissues. Moreover, SKM activity is secondarily regulated by biochemical signals released by other tissues (e.g., bone, AT) in response to exercise themselves [37, 122]. Most of these muscle-derived biochemical signals are shared with AT-generated signals, but the net result of their action mainly depends upon the different kinetics of release. A main example is given by IL6: chronically, even slightly elevated, AT-derived IL6 has pro-inflammatory effects (LGI) while pulsatile, even very high in amplitude, levels of SK-derived IL6 (i.e., during exercise) have anti-inflammatory effects. While AT-derived IL6 associates with glucose intolerance [37] and stimulates bone resorption by inducing RANKL and PGE2 expression [123, 124], SKM-derived IL6 increases glucose and FA uptake in SKM cells and improves the metabolic status and bone metabolism due to an inhibitory effect on LGI-associated IL6 [37, 122].

LIF (leukemia inhibitory factor), a myokine belonging to the IL6 superfamily, stimulates the post-injury satellite cell (SC) proliferation for muscle regeneration (e.g., exercise-induced muscle damage, EIMD) and SKM hypertrophy [125]. It is induced by acute exercise (aerobic and resistance) [126] and, in bone, stimulates turnover, osteoblast proliferation in periosteal pre-osteoblast while it inhibits osteoblastic functions in mature cells. It is also responsible for enhanced PG-induced bone resorption [127]. IL7 is also involved in SKM regeneration by stimulating the migration of SCs [128], and although as for IL6, T cell-derived IL7 has pro-osteoclastogenic effects in bone (it is a mediator of ovariectomy-induced osteoporosis) [129], when expressed in a pulsatile fashion by exercising SKM stimulate turnover [37].

IL15 is a myokine involved in the first phase of adaptation to exercise [130] and it powerfully induces TNFα and RANKL expression in osteoblasts and stromal cells, thus stimulating osteoclastogenesis [131]. These acute exercise-dependent SKM-generated signals, hence, seem to have pro-regenerating and pro-anabolic effects on SKM itself while, on bone, they stimulate turnover and, hence, the release of calcium, useful for muscular contraction and neuromuscular function, and osteokines for regulation of the energy substrate management.

On a chronic point of view, instead, SKM disuse, atrophy, sarcopenia, and aging are associated with myostatin expression [34, 132] which also enhances osteoclastogenesis [133]. Follistatin (FST) and its related factors (FSTL1, FSTL3, decorin), inhibitors of myostatin, are induced by acute endurance exercise [134] and chronic combined strength and endurance training [135]. The phenotypes from their mutation evidenced their importance in bone and muscle development. $Fstl3^{-/-}$ mice undergo frequent fractures and loss of osteocyte mechanosensitivity (i.e., loss of loading-dependent bone gain and Sost inhibition) [34].

Brain-derived neurotrophic factor (BDNF) is induced by acute and chronic endurance and moderate-to-high intensity, regardless the gender [136–142]. BDNF acts, throughout its receptor (TrkB), on metabolically active osteoblast and by hypertrophic chondrocytes of the growth plate during intramembranous ossification, and in osteoblasts and endothelial cells in fracture healing site [143].

MCP-1 expression in SKM is strongly induced by acute and chronic resistance and endurance exercise, in an intensity-dependent manner, regardless the metabolic and training statuses [144–146]. MCP-1 (also known as CCL2) is the primary ligand for the CCR2 receptor, which is expressed by monocyte/macrophages and, as such, it is a key regulator of osteoclastogenesis and has a pivotal role in inflammation and tumor-induced osteolysis [147]. Besides its expression in AT, it promptly responds to acute exercise regardless the type of activity, while it is not affected by chronic exercise [146].

AT responds to exercise mainly secondarily to the increased energy needs, signaled by the SKM first but also by liver, brain, and bone. This response consists in the release of energy substrates (FA and glycerol) and, as reported above, adipokines that may hesitate, on log-term basis, into reduced adiposity and improved inflammatory (LGI) status. In general terms, while acute exercise may stimulate adipokine release, training causes a decrease in their expression and secretion, thus limiting the basal flogistic level, as discussed above. Only adiponectin, whose anti-inflammatory properties have been

already discussed, increases during exercise training. The exercise training-associated pro-inflammatory-to-anti-inflammatory shift limits the catabolic potential while increasing the anabolic one. The net result is an improved status of bone and SKM [4, 6].

Closing Remarks and Future Directions

The recent rediscovery of SKM, AT, and bone as endocrine organs has revolutionized several concepts in biomedicine by widening the concept of integration. As described above, without the claim to be exhaustive, the structure and function of these tissues strikingly depends on the metabolic function of others. However, this is just a part of the story since this first, although multilevel, integration is, in turn, integrated within the whole-body system, thus pushing the complexity of the interactions. The evidence comes from several metabolic diseases: as the phenotype of a metabolic disease mainly expresses toward the modification of the functions/metabolism of one or two organs, it secondarily affects the others. For instance, in T2DM, the primary metabolic dysfunction of AT and SKM associates with the increased fracture risk; in osteoporosis, the increased fracture risk often associates with metabolic dysfunctions, sarcopenia, and obesity. It emerges that by therapeutically acting on one of these organs (e.g., to treat a metabolic dysfunction), one can get results on the others; better, by acting on all these organs, the net result may be even potentiated [103]. This is the case of exercise interventions, currently considered a "polypill" to treat multimorbidities and to improve health status given its favorable pleiotropic effects on all organs and systems [148]. Thanks to this endocrine-based view, the exercise biology studies, prior neglected and mostly relegated as "recreational science", have gained relevance as conventional and effective interventions. Future researches must invariably base on this integrative view in order to effectively explain the biological mechanisms underlying the physiological and pathophysiological interactions among muscle, bone, and adipose tissue.

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Compliance with Ethical Standards

Conflicts of Interest BK, JF, GL, and GD have no conflicts of interest to declare.

Ethical Approval This review article does not present any previously unpublished original research, and ethical approval is therefore not applicable.

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