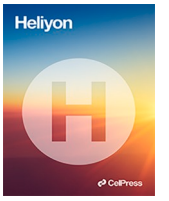
Heliyon 10 (2024) e22547

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Advances in the research on myokine-driven regulation of bone metabolism

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ARTICLE INFO

Keywords:
Myokine
Sarcopenia
Bone metabolism
Osteoporosis
Osteoblasts
Osteoclasts

ABSTRACT

The traditional view posits that bones and muscles interact primarily through mechanical coupling. However, recent studies have revealed that myokines, proteins secreted by skeletal muscle cells, play a crucial role in the regulation of bone metabolism. Myokines are widely involved in bone metabolism, influencing bone resorption and formation by interacting with factors related to bone cell secretion or influencing bone metabolic pathways. Here, we review the research progress on the myokine regulation of bone metabolism, discuss the mechanism of myokine regulation of bone metabolism, explore the pathophysiological relationship between sarcopenia and osteoporosis, and provide future perspectives on myokine research, with the aim of identify potential specific diagnostic markers and therapeutic entry points.

1. Introduction

Sarcopenia is an age-related disease characterized by progressive and systemic loss of skeletal muscle mass and strength [1]. The risk of death in patients with sarcopenia is four times higher than that in individuals without sarcopenia [2]. Osteoporosis is a common disease among the elderly and is one of the most prevalent public health issues today, affecting hundreds of millions of people worldwide. The muscle mass and strength loss is frequently accompanied by a loss of bone mass, implying that sarcopenia and osteoporosis often coexist, forming a "dangerous duo" that increases the risk of fractures [3]. As the global population ages, the prevalence of these two diseases increases, causing significant social and economic burdens and endangering the lives and health of the elderly.

Aging and a lack of exercise are essential factors in the development of osteoporosis and sarcopenia. After the age of 30, most people begin to lose bone mass, and some individuals develop osteoporosis, defined by reduced bone density [4]. Similarly, skeletal muscle mass peaks at 30 years of age, and then declines at a rate of 1–2% per year thereafter [5]. After 70 years of age, this degeneration becomes more severe, and sarcopenia, defined mainly by a decrease in skeletal muscle mass and strength, may develop [6]. This condition may have grievous consequences such as fractures, disability, and even death. It is projected that by 2050, the global prevalence of sarcopenia in people over 60 years of age will reach 20 % and will increase to more than 33 % by 2150 [7]. Research studies on osteoporosis and sarcopenia progression have demonstrated that they share a remarkably similar cycle of disease and

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https://doi.org/10.1016/j.heliyon.2023.e22547
Received 19 June 2023; Received in revised form 14 November 2023; Accepted 14 November 2023
Available online 20 November 2023

pathogenicity; osteoporosis commonly coexists with sarcopenia or cachexia, and the coexistence of osteoporosis and sarcopenia has been lately considered as a syndrome named "osteosarcopenia" [8]. These disorders significantly decreases the survival period and quality of life of the patients [9]. There are numerous indications that skeletal- and muscle-related disorders do not occur independently, that increases in skeletal muscle mass and strength can improve bone mass and strength, and that they are inextricably linked [10].

Bone metabolism is greatly affected by cytokines synthesized by skeletal muscle cells; these "myokines" are important factors in bone remodeling regulation (formation and/or resorption). The main objective of this review is to discuss the role of myokines in bone metabolism (bone formation and resorption) and identify molecular targets for the diagnosis and management of sarcopenia and osteoporosis. Fig. 1 depicts the mechanism by which skeletal muscles secrete the factors that regulate bone metabolism.

2. Myokines and bone metabolism

Skeletal muscle is the largest endocrine organ in the human body, accounting for 40–50 % of the total body weight. During exercise, muscle fiber cells express and release over 3000 cytokines and polypeptide molecules, known as "myokines," which act on the skeletal muscle itself and mediate communication between muscles, liver, bones, and other organs, as well as regulate the metabolism of tissues and organs [11]. Myokines positively affect satellite cell development and skeletal muscle hypertrophy. It also regulates the metabolic activities of the bone, liver, heart, and other organs via endocrine mechanisms [12].

Muscle and skeletal tissues are both mesenchymal in origin, and a close biochemical link between muscles and bones is observed at the embryonic stage. Maintenance of muscle and bone homeostasis is regulated by complex endocrine mechanisms. Muscle-secreted myokines form the basis of muscle–bone communication and are essential for the remodeling of the bone extracellular matrix as well as proliferation, migration, and differentiation of osteoblasts and osteoclasts.

Skeletal muscles secrete a large number of myokines into the circulation in response to exercise, which are transported to the whole body through extracellular carriers and mediate communication between skeletal muscles and organs throughout the body. Some myokines are involved in the regulation of skeletal muscle proliferation and differentiation as well as in the mediation of energy supply during acute bouts of exercise. However, most myokine functions of myokines remain unclear; in particular, there are still many questions regarding the regulatory role of myokines in the skeleton. Exercise leads to increased secretion of myokines and elevated bone mass, with whole-body metabolic levels increasing by more than 20-fold. For example, running promotes oxidative fibers and is related to a lower bone mineral density (BMD) in comparison to resistance exercises, such as weightlifting, which increase muscle mass and are related to greater BMD. Muscle plays an important role in fracture healing. In a mouse model of open tibial fractures, the effects of muscle and fascial skin tissue coverage on fracture healing were observed. Twenty-eight days post-fracture, the muscle-covered fracture site group showed an almost 50 % increase in cortical bone content and a 3-fold increase in submuscular healing strength compared to the skin- and fascial tissue-covered fracture site groups alone, along with faster fracture recovery and higher repair quality [13].

Another study that collected skeletal microstructural data from soldiers undergoing eight weeks of combat training found that the distal tibial metaphysis, cortical thickness, trabecular thickness, trabecular number, bone volume/total volume, and total and

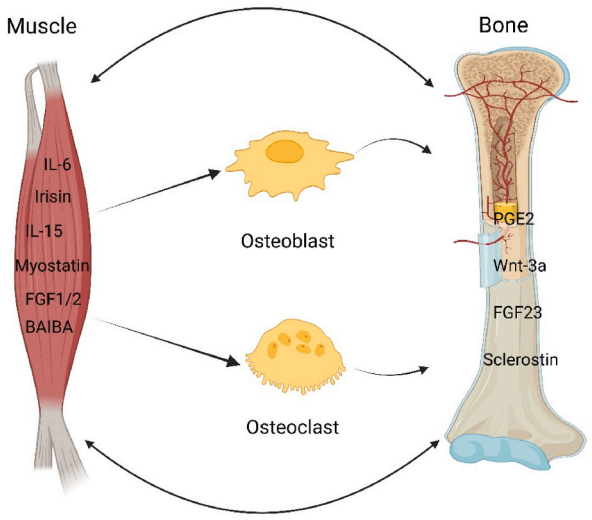

Fig. 1. Crosstalk between skeletal muscle and bone
Schematic diagram of muscle and bone acting as endocrine organs to secrete a variety of cytokines that mediate muscle and bone communication. Muscle secretes myokines, such as IL-6, irisin, BAIBA, and myostatin, that affect bone metabolism by regulating osteoblast and osteoclast functions. Bone secretes OPG, wnt-3a, sclerostin, FGF-23, and other osteokines that regulate muscle metabolism. IL-6, interleukin 6; BAIBA, β-aminoisobutyric acid; OPG, osteoprotegerin; FGF-23, fibroblast growth factor 23; PGE2, prostaglandin E2.

trabecular volumetric bone density showed a significant elevation of 1–2%, bone strength, and estimated elevation by 2.5 % and 0.7 % at the distal tibial metaphysis and diaphysis, respectively [14]. In addition, sustained exercise maintains bone mass and strength over time, which can prevent osteoporosis, whereas muscle disuse and/or muscle atrophy results in osteoporosis [15]. In the inactive population, skeletal muscle atrophy exceeds 30 %, systemic metabolic dysmetabolism, and bone mass and strength are significantly reduced but can be improved with exercise training [16]. It shows that increased myokine secretion appears to strongly correlate with bone mass growth.

The secretome of skeletal muscles has emerged as an important nexus for the in-depth study of the metabolic interaction between muscles and bone health in aging and may provide new insights and potential medical strategies for treating metabolic diseases [17]. The main myokines widely reported to regulate bone metabolism in recent years include interleukin 6 (IL-6), irisin, β-aminoisobutyric acid (L-BAIBA), myostatin, and brain-derived neurotrophic factor (BDNF). Accurate knowledge of myokine functions in the interplay between muscles and bones can help formulate detailed prevention or treatment plans for related diseases. Fig. 2 illustrates the mechanisms by which myokines regulate bone metabolism.

2.1. Myokines related to bone formation

(Table 1 illustrates the Myokines regulate bone formation in Muscle–bone crosstalk).

2.1.1. Irisin

Irisin is a small 12 kDa peptide created by the cleavage of fibronectin III domain protein 5 (FNDC5) and is expressed in several tissues and organs. Irisin is a myokine released by contracting skeletal muscles. Circulating irisin levels are positively correlated with muscle mass, strength, and metabolism. Irisin promotes myogenesis and prevents dexamethasone-induced atrophy of C2C12 myotubes [18,19]. Irisin activates the PPAR-r co-activated receptor 1a (pgc1a) during endurance training, which can stimulate FNDC5 expression in skeletal muscle cells, thus increasing circulating irisin. Irisin has been shown to have critical effects on bone, adipose tissues, and the brain. Irisin binds to αV-integrin-class proteins and improves osteocytic survival and sclerostin synthesis, thereby reducing bone loss [20]. Moreover, irisin regulates bone metabolism by promoting osteoblast function and inhibiting osteoclast function [21].

Some researchers have shown that irisin injection can increase the density and quality of the cortical bone in mice. This effect is achieved through a significant increase in the functional activity of osteoblasts, promotion of osteoblast gene upregulation, and reduction in osteoblast inhibitors. Renal failure reduced irisin expression in the gastrocnemius muscle of mice and may have contributed to cortical bone loss due to renal failure [22]. These observations suggest that irisin primarily regulates bone metabolism by increasing osteoblast activity and is a key mediator of bone–muscle communication [23]. Irisin also increased the expression of

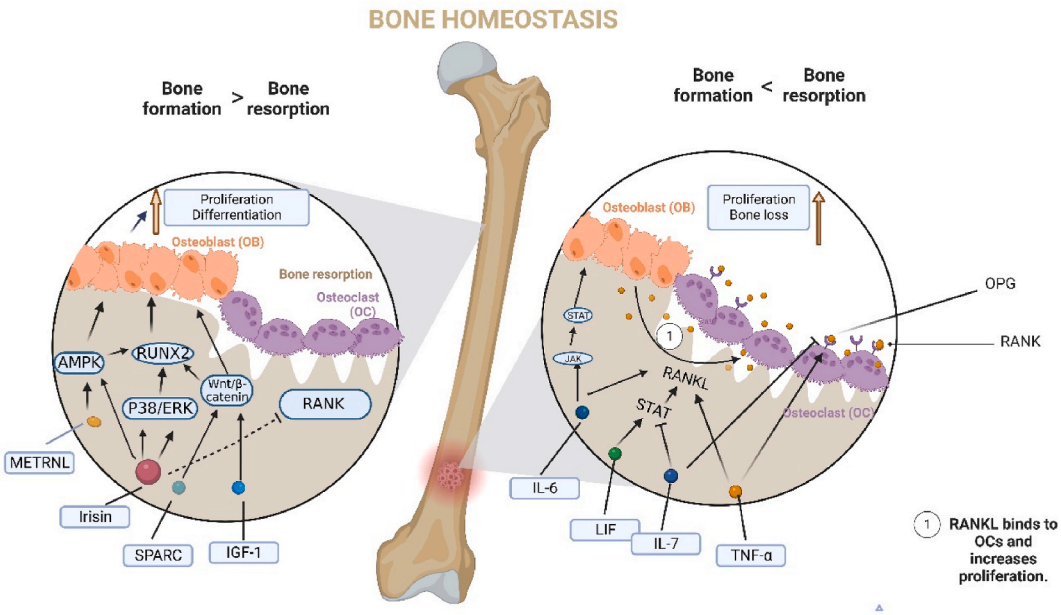

Fig. 2. Mechanisms by which myokines regulate bone metabolism.
METRNL, irisin, SPARC, and LIF-1 regulate the proliferation and differentiation of osteoblasts and inhibit the function of osteoclasts through the MAPK, P38/ERK, Wnt/β-catenin, and RANKL pathways, resulting in greater bone formation than bone resorption. IL-6, IL-7, LIF, and TNF-α promote osteoclast proliferation and accelerate bone loss by regulating the binding of RANKL to RANK and OPG, resulting in greater bone resorption than bone formation. AMPK, AMP-activated protein kinase; METRNL, meteorin-like protein; SPARC, secreted protein acidic and rich in cysteine; LIF-1, leukemia inhibitory factor 1; IL, interleukin; TNF-α, tumor necrosis factor-alpha; OPG, osteoprotegerin; IGF-1, insulin-like growth factor 1.

Table 1
Myokines regulate bone formation in muscle–bone crosstalk.

Muscle-to-bone formation	
FGF21	Inhibit bone formation
LIF	Promote osteoclast differentiation
IL-6	Increases osteoclastogenesis
IL-7	Upregulates RANKL expression
Myostatin	Promotes osteoclastogenesis
TNF-α	Induce osteoclast differentiation

activating transcription factor 4 (ATF4), Runt-related transcription factor 2 (RUNX2), and alkaline phosphatase (ALP) by activating the phosphorylation and signal transduction of ERK and p38, implying that irisin may promote osteoblast proliferation and differentiation through the p38/ERK signaling pathway [24,25]. Furthermore, irisin activates the Wnt/β-catenin pathway, increases RUNX2 expression, and promotes bone cell proliferation and differentiation. Irisin can induce the up-regulation of the osteopontin-encoding gene SSP-1 under mechanical load, indicating that irisin is an osteopontin regulator; concurrently, irisin inhibits the expression of SOST, a Wnt/β-catenin pathway inhibitor, thus negatively regulating bone formation [23,26–28]. Irisin also inhibits osteoclast differentiation by reducing RANKL-induced osteoclast induction and phosphorylation of downstream effectors of the RANKL signaling pathway. Irisin reduces the expression of osteoclast-specific genes by inhibiting RANK expression [27]. Mechanistically, irisin activates the Wnt, p38/ERK, and MAPK signaling pathways, increasing both runx2 expression and osteoblast proliferation [24,27,29].

Moreover, irisin stimulates MSC-derived osteogenesis by binding to αV-integrin and activating BMP/SMAD signaling, consequently regulating bone mass [30]. Studies in athletes have indicated that irisin levels positively correlate with strength and bone density [31]. Irisin is crucial for the regulation of bone metabolism. Currently, research is mainly based on healthy individuals and is a static study. Few dynamic studies have been conducted on irisin secretion and regulation during exercise. Given the essential role of irisin in the development of sarcopenia and osteoporosis, it is expected to be used as a specific target for the detection and treatment of osteoporosis and sarcopenia-related diseases as research progresses. Fig. 3 illustrates the Mechanisms by Irisin's regulation of bone metabolism.

2.1.2. L-BAIBA

L-BAIBA, a new minor-molecule metabolite, enhances muscular contraction and strength in a sex-dependent manner and is involved in a number of bone and muscle processes [32]. L-BAIBA is a muscle-derived osteocyte survival factor that facilitates the proliferation and differentiation of MC3T3-E1 cells by moderately activating reactive oxygen species (ROS) signaling [33]. ROS are critical for the maintenance of mitochondrial function [34]. Excessive ROS levels cause mitochondrial decomposition and bone cell apoptosis with age [35]. Recent research has shown that L-BAIBA can inhibit the apoptosis of ROS-induced bone cells and protect bone cells by binding to the glycine receptor MRGPRD. MRGPRD is highly expressed in young bone cells, but its expression decreases with age, indicating that MRGPRD expression is strongly correlated with age. This explains the association between osteoporosis and age [36]. In addition, L-BAIBA may maintain bone mass by retaining the muscle that directly bears the tibia, as well as bone cell vitality under conditions of disuse and oxidative stress [36]. In vitro L-BAIBA treatment of bone cells has been shown to protect against apoptosis caused by ROS (H_2O_2) [37]. L-BAIBA, like other myokines, is thought to influence osteoblasts and osteoclasts to regulate

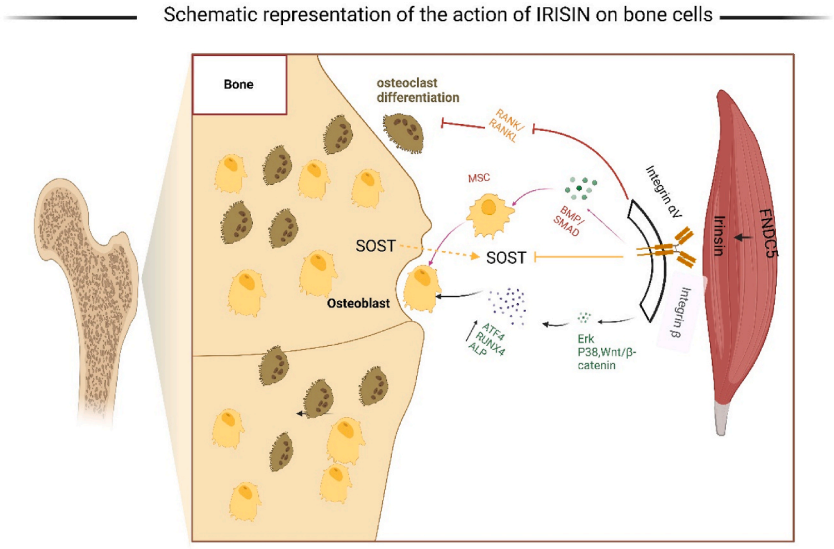

Fig. 3. Mechanisms by Irisin's regulation of bone metabolism The irisin-binding receptor integrin αV/β, regulates osteoblast and osteoclast function through RANK/RANKL, BMP/SMAD, P38/ERK, and Wnt/β-catenin pathways.

bone remodeling. A previous study where L-BAIBA was added to drinking water to treat hindlimb unloaded mice for more than two weeks, their bone mass increased; this increase was more noticeable in males than females and could be because males have a higher number of trabecular bones. In addition, compared to the mice treated with L-BAIBA, the bone cells of the control group showed more significant apoptosis, but the expression of related bone secretory proteins did not increase significantly. Moreover, the level of MRGPRD expressed by the bone cells was much higher. L-BAIBA is thought to increase bone cell activity and directly influence osteoblast function [36,38].

However, the research on L-BAIBA is still in the early stages and the mechanism of its action on osteoblasts and osteoclasts is unknown. The mechanism by which L-BAIBA tunes bone mass by influencing load-bearing muscles also warrants further investigation.

2.1.3. Insulin-like growth factor 1 (IGF-1)

IGF-1 is a critical bone growth factor. Evidence indicates that IGF-1 plays a significant role in regulating skeletal muscle growth and differentiation and is locally expressed in muscle cells. Muscle-derived IGF-1 can act on local osteoblasts that express the IGF-1 receptor and promote bone formation [39]. IGF-1 promotes osteoblast proliferation, improves mature osteoblast function, and stimulates bone formation. IGF-1 can also increase collagen synthesis while decreasing collagen degradation and maintaining an appropriate bone matrix level and bone mass [40]. When bone cells, osteoblasts, and bone marrow mesenchymal cells are mechanically stimulated, IGF-1 binds to the IGF receptor tyrosine kinase via IGF-binding proteins (IGFBPS) to transmit mechanical stimulation to downstream effectors, initiate P13K and MAPK signaling cascades, and promote bone growth [41,42]. IGF-1 can promote osteoblast proliferation and differentiation by stimulating the expression of mammalian targets of rapamycin complex 1 (mTOR) via the PI3K-Akt pathway [43,44]. IGF-1 can also increase RUNX2 expression by stimulating the Wnt/β-catenin pathway, promoting osteoblast synthesis, and reducing apoptosis [45]. In addition, IGF-1 increases RANKL activity, induces osteoclast differentiation, and promotes bone resorption under certain conditions [46]. In summary, IGF-1 exerts its anabolic effects primarily by improving bone cell function and survival.

IGF-1 has a regulatory function in bones and chondrocytes at different growth stages and has a broad impact on both intramembranous osteogenesis and endochondral osteogenesis. Recent research has suggested that IGF-1 influences osteoclast metabolism by protecting bone cells; however, the precise mechanism remains unknown.

2.1.4. Meteorin-like protein (METRNL)

METRNL is a secreted adipokine that is induced in skeletal muscles and white adipose tissue upon exercise and exposure to cold, respectively [47]. METRNL is a critical regulator of muscle regeneration; mice genetically lacking METRNL have impaired muscle regeneration, and joining wild-type and whole-body METRNL knockout mice returns METRNL expression in the injured muscle, improving muscle repair [48]. METRNL inhibits inflammation via the AMP-activated protein kinase (AMPK) [49]. METRNL and IL-10 are both linked to the inflammatory function of METRNL-β. METRNL increases the expression of IL-10, thereby enhancing its anti-inflammatory effects [50]. Researchers have demonstrated that METRNL inhibits the formation of mineralized nodules, as well as the expression of osteoprotegerin (OPG) and OCN. METRNL can also influence bone and chondrocyte function by interacting with the AP-1 molecular complex; however, its specific mechanism and pathway remain unknown [51]. Metabolic diseases are associated with low-grade inflammation. Considering the powerful anti-inflammatory effects of METRNL, further research on METRNL and low-grade inflammation may pave the way for the treatment of metabolic diseases associated with musculoskeletal aging.

2.1.5. BDNF

BDNF is a neurotrophic factor that is primarily secreted by brain cells. BDNF and its receptor tropomyosin-related kinase receptor type B (TrkB) mRNA are expressed in rat bone tissue and play a role in the regulation of rat bone tissue development and transformation [52]. BDNF and TrkB are overexpressed in osteoblasts, which are active in intramembranous ossification and trabecular bone formation, and in chondrocytes in the epiphysis growth plate, indicating the involvement of BDNF in rat skeletal development and bone remodeling [53]. Particularly, treatment with recombinant human brain-derived neurotrophic factor can activate the AMPKα-PGCα signaling pathway and acetyl-CoA carboxylase function, enhance fatty acid oxidation, and significantly improve skeletal muscle exercise capacity [54]. Further research has found that exercise and electrical stimulation of skeletal muscles increase the release of BDNF, promote cortical and trabecular bone growth, and improve bone quality [55]. BDNF has also been shown to promote the development of axial and appendage bones, as well as to participate in blood vessel formation and osteogenesis during the fracture healing process [56]. Additionally, in bone metastases, such as multiple myeloma and gastric cancer, BDNF is considered a bone-resorbing factor that leads to osteolytic lesions. BDNF stimulates RANKL expression in osteoblasts, leading to osteoclast formation and promotion of osteolytic lesion formation [57,58].

BDNF is thought to play a role in the mutual regulation of fat, muscle, and bone, which could lead to new avenues of research on systemic metabolic diseases.

2.1.6. Secreted protein acidic and rich in cysteine (SPARC)

Osteonectin, a glycoprotein found in bone, is involved in tissue development, tissue remodeling, bone mineralization, and bone cancer metastasis. In 2013, it was experimentally confirmed for the first time that human plasma SPARC levels increased two-fold after aerobic exercise. This finding was subsequently replicated in an electrically stimulated C2C12 myoblast experiment [59,60]. Since then, SPARC has been widely recognized as a myokine secreted by the skeletal muscles during acute exercise.

SPARC is a key indicator of bone formation and plays a critical role in the osteogenic differentiation of stem cells during the initial crystal growth phase [61]. Moreover, SPARC is involved in regulating the proliferation and differentiation of osteoblasts, promoting calcium deposition, and regulating bone mineralization during wound healing and bone formation [62]. Heterotopic ossification (HO)

is a pathological condition characterized by the formation of bones outside the skeleton, which can result in severe consequences such as disability and even death. SPARC expression was upregulated in the Achilles tendon tissue of HO rats However, silencing SPARC reduced the phosphorylation of ERK, JNK, p38, NF-κB, and IKKβ by inhibiting the MAPK signaling pathway. This, in turn, led to a decrease in ALP activity, the number of mineralized nodules, and OCN content, ultimately inhibiting the occurrence of HO [63]. These findings suggest that SPARC plays a crucial role in the development of HO and that inhibiting its expression could be a potential therapeutic strategy for preventing and treating this debilitating condition.

Furthermore, stable SPARC expression significantly inhibits bone metastasis from malignant tumors, such as breast and prostate cancers, and may be a potential diagnostic and therapeutic target [64,65]. However, there are few studies on osteonectin-induced regulation of bone metabolism and tumor bone metastasis, and more evidence is needed to explain the exact effect.

2.2. Myokines

(Table 2 illustrates the Myokines regulate bone resorption in Muscle–bone crosstalk).

2.2.1. IL-6

IL-6 is a classic inflammatory and well-studied muscle factor. It has long been assumed that IL-6 is primarily secreted after muscle injury and is regarded as a distinct marker of muscle injury. Recent studies have demonstrated that IL-6 secretion increases during exercise and is related to the exercise mode, intensity, and duration [66]. Moreover, IL-6 mRNA and protein expression in monocytes did not increase during exercise, demonstrating that IL-6 is secreted independent of muscle damage [67].

IL-6 is essential for muscle stem cell-mediated hypertrophy, while IL-6 deficiency decreases muscle hypertrophy by suppressing muscle stem cell proliferation and fusion with previously existing myofibers [68]. IL-6 does not play the same role at different times of action or molecular concentrations; however, it can regulate bone resorption and formation [69]. A study of the effects of IL-6 on skeletal development using an IL-6-overexpressing transgenic mice model revealed a decrease in osteoblasts, an increase in the number and activity of osteoclasts, a decrease in bone mass, severe structural changes, impaired development of growth plates and epiphyseal ossification centers, a significant effect on both intramembranous osteogenesis and endochondral ossification and mineralization rates, and a severe ossification defect. These observations indicated that IL-6 plays an essential role in bone growth and development [70]. Further research into its regulatory mechanism revealed that IL-6 mainly acts by inducing RANK expression, increasing cell activity, inducing prostaglandin E2 (PGE2)-dependent osteoclast activation in osteoblasts, and damaging trabecular bone formation [71–73]. Moreover, estrogen can increase IL-6 expression. Mounting evidence has shown that elevated bone resorption resulting from ovariectomy can be explained by the combined effects of IL-6 and other factors [74,75]. In vitro studies demonstrated that osteoblasts express IL-6Ra and promote bone formation by activating the JAK/STAT signaling cascade, thereby stimulating the expression of transcription factors that induce osteoblast differentiation [76,77].

IL-6 is involved in many aspects of inflammation and material metabolism, and affects musculoskeletal function by regulating muscle, bone, and fat metabolism. Currently, IL-6 inhibitors have shown potential anti-inflammatory effects. Breakthroughs in the treatment of age-related metabolic diseases are expected in the future.

2.2.2. Fibroblast growth factor 21 (FGF-21)

Nishimura et al. discovered FGF-21 in 2000. FGF-21 does not participate in muscle homeostasis under basal conditions; however, elevated FGF-21 expression during fasting is essential for muscle atrophy and weakness [78]. The administration of recombinant FGF-21 in mice was associated with a reduction in the quantity and size of osteoblasts, an elevation in the quantity and size of osteoclasts, and a consequent significant bone loss [79].

FGF-21 inhibits mineralized nodule formation and expression of OPG and OCN. Furthermore, FGF-21 can increase the activity of the peroxisome proliferator-activated receptor γ (PPAR-γ), inhibit osteoblast differentiation, stimulate the adipogenesis of bone marrow mesenchymal stem cells, and inhibit bone formation [79]. Currently, the effect of FGF-21 on bone density remains controversial. Some studies have shown a positive correlation with female spine bone density, but no difference between men and women; however, some studies in China have shown a negative correlation with femoral neck bone density, with no difference between men and women. These contradictory findings could be attributed to difference in race or bone parts. FGF-21 regulates bone resorption, giving us reasons to believe that it is a key connecting factor between sarcopenia and osteoporosis.

2.2.3. IL-7

IL-7 is a lymphocyte factor secreted by the bone and skeletal muscle cells. Early research has suggested that IL-7 stimulates the

Table 2
Myokines regulate bone resorption in muscle–bone crosstalk.

Muscle-to-bone resorption	
BDNF	Stimulates osteoclast formation
IGF-1	Promotes osteoclastogenesis and stimulates bone formation
Irisin	Increase bone resorption
L-BAIBA	Promotes osteoblast
SPARC	Promotes osteoblasts proliferation and differentiation

proliferation of B220 cells, which are considered osteoclast precursors, and causes bone loss [80]. Several recent studies have suggested that the IL-7/IL-7R pathway has dual regulatory effects on osteoclasts. As a bone growth factor, IL-7 promotes osteoclast differentiation by increasing the expression of RANKL, a key T cell source; however, IL-7 blocks osteoclast differentiation by directly inhibiting the STAT5 pathway in the RANKL-induced system [81,82]. IL-7 may also suppress the bait receptor of RANKL, OPG to promote osteoclastogenesis and mediate estrogen-induced bone loss [83]. Current research shows that IL-7 mainly regulates bone resorption. Notably, the IL-7/IL-7R axis plays a role in the development of rheumatoid arthritis, and this process is also involves osteoclasts. Related studies have demonstrated a greater practical impact on the treatment of RA and other diseases.

2.2.4. Leukemia inhibitory factor (LIF)

LIF is a muscle cytokine belonging to the IL-6 family. LIF is produced and released from muscle cells in vitro and from intact skeletal muscles in vivo. During exercise, skeletal muscles potently upregulate LIF mRNA expression. LIF stimulates the proliferation of muscle satellite cells and is involved in muscle hypertrophy and regeneration [84]. LIF is thought to act as a coupling factor between osteoblasts and osteoclasts, thereby regulating metabolism and bone mass during exercise [85]. LIF increases STAT3 phosphorylation, promotes osteoclast differentiation, and suppresses osteoblast differentiation [86]. However, there is no consensus regarding the effect of LIF on bone mass to maintain normal bone growth under pathological and inflammatory conditions.

2.2.5. Myostatin

In 1997, Shizhen et al. discovered myostatin, also known as the growth differentiation factor 8 (GDF8). Myostatin is a negative regulator of skeletal muscle mass and is defined by drastically elevated muscle mass due to a mutation in its gene. Muscular atrophy and hypertrophy are caused by its elevated expression and lack of expression, respectively [87]. Studies in mice have shown that the inhibition of myostatin increases muscle and bone mass [88]. In addition, in tumor necrosis factor-alpha (TNF-α) mice with rheumatoid arthritis, myostatin interfered with osteoclast formation, and bone destruction was reduced [89]. GDF8 can cause bone remodeling when it acts on bone cells, and mature myostatin is negatively correlated with bone mineral density in middle-aged and older individuals [90]. Myostatin inhibits the differentiation of mesenchymal stem cells and osteoblasts during the early stages of fracture healing. After two weeks, myostatin levels were negatively correlated with callus size, and myostatin negatively regulated the fracture healing process [91]. Myostatin also increased the expression of sclerostin SOST, Dickkopf-1 (DKK1), and RANKL, and decreased osteocyte-derived exosome Mir-218 by inhibiting muscle growth, thus inhibiting osteoblast differentiation [92,93]. Collectively, myostatin inhibits muscle and bone growth and metabolism; therefore, elucidating specific pathways and signaling mechanisms will help researchers better understand musculoskeletal aging diseases.

2.2.6. TNF-α

TNF-α belongs to the tumor necrosis factor family. TNF-α induces osteoclast differentiation in the presence of macrophage colony-stimulating factor (M-CSF) by interacting with cytokines, such as RANKL and osteoprotegerin-ligand, to stimulate the formation of mononuclear preosteoblast-like cells (POCs) and multinucleated osteoclast-like cells (MNCs). TNF-α was shown to significantly increase the expression of nuclear factor kappa B mRNA receptor activator. Addition of RANKL to preformed POCs was found to potentially effectively induce MNC differentiation [94,95]. RANKL cytokines also induce osteoclast differentiation by degrading TRAF3 in osteoclast precursors [96]. Thus, TNF-α interacts with RANK to induce osteoclast differentiation, dramatically reducing the expression of osteogenic markers. However, most studies have mainly focused on osteoclasts, with only a few studies focusing on osteoblasts.

3. Osteokines and muscle metabolism

In 2006, osteocytes were proposed to be endocrine cells. FGF-23 expression was found to be significantly elevated in osteocytes of patients with hypophosphatemic rickets, targeting the kidney to regulate phosphate homeostasis [97]. Since then, an increasing number of studies have shown that osteocytes produce a variety of cytokines such as osteocalcin, OPG, DKK1, stromal extracellular phosphoglycoprotein (MEPE), and PGE2. Osteokines mainly affect skeletal function but are also involved in the regulation of muscle metabolism and function.

Osteocalcin receptor Gprc6a knockout mice exhibit a phenotype of reduced muscle mass, whereas ESP (a phosphatase that inhibits osteocalcin function) knockout mice exhibit increased muscle mass. Osteocalcin supplementation increased muscle mass and restored exercise capacity in mice [98]. Transforming growth factor-beta (TGF-β), a key mediator of muscle weakness, is mainly secreted by bone. In patients with bone metastases from breast cancer, it was found that bone secretes large amounts of TGF-β that reduced Ca^{2+}, leading to the onset of muscle weakness. In addition, body mass and skeletal muscle atrophy were enhanced by targeting TGF-β signaling with the TGF-β receptor I kinase inhibitor SD-208 or bone-targeted bisphosphonates azole. In addition, osteokines, including tumor necrosis factor ligand superfamily 11 (TNFSF11), wnt3a, wnt1, and PGE2, regulate the differentiation of myogenic cells [99]. As our understanding of the biochemical communication between osteokines and muscles has gradually increased, osteokines appear to have potential uses in the treatment and prevention of sarcopenia.

4. Conclusion

Muscles not only interact mechanically with bones, but also as endocrine organs. Muscle cells secrete numerous myokines. Myokines are vital regulators of bone metabolism and exert a wide range of effects on bone cell proliferation and differentiation. They

play essential roles in maintaining the integrity and functional stability of bones. Myokines also exert a negative effect by promoting bone destruction. Thus, myokines may play an important role in the onset and progression of osteoporosis and provide new strategies for treating osteoporosis. Based on the above discussion, a conclusion can be reached that muscle cell-secreted IL-6, irisin, myostatin, and FGF-21 are active in the process of bone remodeling regulation, with the potential to become specific targets for treating musculoskeletal age-related diseases in the future; RANK/RANKL/OPG as well as metabolic pathways mediated by AMPK and other molecules are crucial in the process of bone remodeling and could serve as potential targets for the development of therapeutic drugs. However, at present, relevant drug investigations mainly focus on cell and animal experiments, and more human experimental data are needed to further verify the clinical therapeutic effects. Currently, research on myokines is in infancy, and the functions of a large number of myokines remains unknown. The present review introduces several studies on myokines. However, many myokines that are closely related to bone remodeling and have a complex mechanism of action are yet to be discovered, warranting further in-depth analysis.

The discovery of myokines has provided much hope in the fight against age-related diseases. The role of myokines in bone remodeling and the treatment of related diseases is an important area for future research. Recent studies have shown that noncoding RNA and exosomes are overexpressed in patients with sarcopenia and osteoporosis. They are currently being used as potential markers for disease diagnosis and treatment and show tremendous potential; therefore, they will be a research hotspot in the future.

In addition, we cannot ignore the brain–bone–muscle interactions and focus on the mechanisms of neuromodulation in musculoskeletal metabolism, which may help us fully understand the upstream mechanisms by which muscle factors regulate bone metabolism [100]. We hope that this review will further the understanding of the roles of myokines in the regulation of bone metabolism and provide strategies for investigating specific markers for the diagnosis and treatment of sarcopenia and osteoporosis.

Funding

This work was supported by the Yunnan Provincial Key Laboratory of Digital Orthopedics (202005AG070004); Yunnan Orthopaedic and Sports Rehabilitation Clinical Medical Research Center (202102AA310068); Yunnan Spinal Cord Disease Clinical Medical Center (ZX2022000101); Yunnan Provincial Department of Science and Technology, Applied Basic Surface Project (202201AT070278); The First People's Hospital of Yunnan Province, High-level Talent Introduction Program (2022-KHRCBZ-B06); The First People's Hospital of Yunnan Province, Doctoral Research Fund (KHBS-2022-20); Yunnan Provincial Department of Science and Technology, Kunming Medical Joint Special-Project (202201AC070436).

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

MingHong Shao: Writing – original draft. **QiYang Wang:** Writing – original draft. **QiuNan Lv:** Writing – review & editing. **YuQiong Zhang:** Writing – review & editing. **GuoXi Gao:** Writing – review & editing. **Sheng Lu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The figures were partially created with BioRender.com with an academic license.

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Glossary

Akt: protein kinase B
ALP: Alkaline phosphatase
ATF4: Activating transcription factor 4
BAIBA: β-aminoisobutyric acid
BDNF: brain-derived neurotrophic factor
BMD: Bone mineral density
BMP: bone morphogenetic protein
Dkk1: Dickkopf-1
DNAM-1: DNAX accessory molecule-1
FAs: fatty acids
FNDC5: fibronectin III domain protein 5
FGF-1: Fibroblast Growth Factor 1
FGF-2: Fibroblast Growth Factor 2
FGF-21: fibroblast growth factor 21
FGF-23: fibroblast growth factor 23
GSK3: glycogen synthase kinase 3
LFA-1: lymphocyte function-associated antigen-1
IGF-1: insulin-like growth factor
IGF-1R: insulin-like growth factor-1 receptor
IGFBPS: IGF-binding proteins
IGFBPs: insulin-like growth factor–binding proteins
IL-6: interleukin 6
IL-7: interleukin 7
IL-8: interleukin 8
IL-15: interleukin 15
LIF: leukemia inhibitory factor
METRNL: Meteorin-Like Protein
MEPE: stromal extracellular phosphoglycoprotein
mTOR: mammalian target of rapamycin
MNCs: multinucleated osteoclast-like cells
NF-κB: Nuclear factor-κB
OPG: osteoprotegerin
OPGL: osteoprotegerin-ligand
OVX: ovariectomy
OPN: osteopontin
OC: osteocalcin
PGE2: Prostaglandin E2
Runx2: Runt-related transcription factor 2
SPARC: secreted protein acidic and rich in cysteine
RANKL: receptor activator of nuclear factor kappa-B ligand

TGF-β: transforming growth factor β
TNFSF11: tumor necrosis factor ligand superfamily 11
TRAIL: tumor necrosis factor-related apoptosis-inducing ligand
TrkB: tropomyosin-related kinase receptor type B