Research advances in crosstalk between muscle and bone in osteosarcopenia (Review)

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Abstract. Osteosarcopenia is a burgeoning geriatric syndrome and a familiar disease among older individuals. It is characterized by reduced skeletal muscle mass and bone mineral density due to osteoporosis and sarcopenia. Its clinical manifestations include reduced physical performance and individuals becoming prone to falls during the aging process resulting in fractures and hospitalization, which seriously affects the quality of life of patients and increases the risk of death. Due to the aging social structure of the global population, the morbidity of osteosarcopenia is expected to continue to increase. Both muscle and bone belong to the motor system and originate from the mesoderm; therefore, sarcopenia and osteoporosis also share similar pathogenical factors, which influence and regulate each other. Studying the pathogenesis and treatment of osteosarcopenia is of great significance to improve the quality of life of patients. Therefore, the present study reviewed the research progress on sarcopenia and osteoporosis in osteosarcopenia from the standpoints of its definition, epidemiology, clinical manifestations and diagnosis, prevention and treatment.

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Contents

1. Introduction

As individuals live longer, natural manifestations of aging such as sagging skin, cardiac function decline and decreased bone mineral density (BMD) become more evident (1). For older individuals, the incidence of chronic degenerative diseases inevitably increases with age (2). The decline in the musculoskeletal system in older adults can cause muscle atrophy, osteopenia and then muscle weakness and decreased exercise ability (3). Osteoporosis and sarcopenia are two common chronic musculoskeletal disorders in older adults. With the increase in the aging of the global population, the prevalence of osteoporosis and sarcopenia is increasing each year, thereby considerably increasing the risk of falls, fractures and hospitalization in older individuals (4,5).

Both muscle and bone develop from the mesoderm and have common interstitial precursors (6). Both belong to the motor system. Anatomically, bones are connected by muscles that are attached to bones to function. Previous studies have revealed that both bone and muscle have a certain endocrine function and that muscle factors secreted by muscles can

affect bone growth and development (7-9). At the same time, bone factors can also affect muscle strength and muscle mass to a certain extent (10). In addition, numerous studies have suggested that there may be molecular signaling pathways that regulate both muscle and bone or local signaling factors that link muscle and bone growth and development (11,12). Therefore, muscle and bone are not only regulated by several factors at the same time but also regulate each other to some level (10).

Sarcopenia and osteoporosis are closely related degenerative diseases, mainly through the interaction between muscle and bone. For example, both muscle strength and muscle mass influence BMD, and the amount of muscle changes as BMD increases and decreases (13,14). In the process of human aging, muscle and bone also influence each other, which in turn affects the occurrence and development of osteoporosis and sarcopenia (15). The decrease in the number of muscles will accelerate the loss of bone and trabeculae, and the decline of bone quality will also lead to the atrophy of muscle shape and decline of function (16,17). Therefore, understanding the relationship between muscle and bone and effective intervention on bone and muscle degeneration can improve muscle mass, muscle strength, body balance, bone mass and bone quality; avoid falls; and reduce bone fracture rates. The present article explores the concept, pathogenesis, clinical manifestation, evaluation criteria, intervention and treatment of sarcopenia and osteoporosis

2. Sarcopenia

Definition of sarcopenia. The muscle content of an adult generally reaches its peak at 25 years of age, and the number of muscle fibers starts to decrease thereafter by a total of 5% until 50 years of age; after 50 years, the muscle content reduces by 1-2% every year, and in total by 30-40% until the age of 70 years; and by ~3% every year after 70 years of age (18). Hence, sarcopenia, the concept of which was first introduced by Rosenberg in 1989, is defined as, in general, the loss of muscle mass and strength associated with aging (19). With increasing knowledge of sarcopenia, it has been defined as 'progressive and generalized loss of skeletal muscle mass and strength' by the International Working Group on Sarcopenia in 2010 (20). In October 2016, sarcopenia was officially included in the International Classification of Diseases (ICD-10) disease code, marking its recognition by the medical community as a separate disease with individual characteristics (M62.8) (21).

Epidemiology. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) conducted a screening of individuals aged >60 years old according to the definition of sarcopenia and found that 13% of those aged 60-70 years and 50% of those aged >80 years experienced sarcopenia, among whom women outnumbered men (15). According to a meta-analysis in 2021, the probability of sarcopenia in individuals <60 years old is 8-36%, and the prevalence of sarcopenia ≥60 years old is 10-27% (22).

Clinical manifestations and diagnostic criteria. Despite the lack of specific clinical manifestations of sarcopenia, its symptoms include proneness to falls, difficulty in walking, weakness of the limbs, mobility degradation, decreased physical performance and osteoporosis or fracture (23). The diagnosis of sarcopenia is based on a comprehensive assessment of muscle strength, muscle quality and physical performance (24). Currently, there are several diagnostic criteria for sarcopenia and they have not been fully standardized (25-31). The EWGSOP recommends that muscle strength be measured by the handgrip or chair stand test and that muscle weight be measured by dual energy X-ray absorptiometer (DXA) or bioelectrical impedance analysis (BIA) (32). BIA can evaluate total muscle mass and limb skeletal muscle mass, respectively (33). Muscle function represents the functional state of the whole body and is an objective index of body motor function, involving muscle, central and peripheral nerve function and balance function (34). The commonly used methods are walking speed and the Short physical performance battery scale (35). The initial diagnosis of sarcopenia can only be made using a step-by-step diagnostic method proposed by EWGSOP2: The possibility of sarcopenia is considered when the patient has low muscle strength, while low muscle strength combined with low muscle content is diagnosed as sarcopenia (36). At the same time, severe sarcopenia is diagnosed with hypofunction (22). Instead, the pathogenesis of sarcopenia is studied by directly diagnosing sarcopenia indirectly by using the individual definitions of sarcopenia.

3. Osteoporosis

Definition. Osteoporosis refers to systemic bone loss and is manifested by reduced BMD and deteriorative bone microarchitecture, leading to an increased risk of fracture (37,38). The reason for bone loss and reduced BMD is that bone absorption prevails over osteogenesis during bone remodeling (39,40). Osteoporosis can be divided into primary and secondary types (41,42), of which the primary type results from increasing age and changes in hormone levels, including senile and idiopathic osteoporosis, while the secondary type occurs secondary to other diseases such as rheumatic and immune diseases, blood disease and metabolic disease (43-45).

Epidemiology. Bone mass increases with age when individuals are young, generally reaches the peak between the ages of 30 and 40 years old, and then decreases each year to ~30% of the peak by the age of 70 years old (46). In postmenopausal women, bone mass decreases even faster by ~20% at 5-7 years after menopause (18). As global aging gradually intensifies, it is predicted that fractures caused by osteoporosis will grow exponentially by 2050 (47,48). A study show that the number of osteoporotic fracture patients worldwide will exceed to 21 million by 2050 (49). According to 2020 statistical data, the incidence of osteoporotic fractures in individuals aged >50 years in Europe and the United States is 4-6% (50), while that in Asia is >15%. Therefore, along with the social structure of population aging, osteoporosis has become a major public health problem (51).

Diagnosis criteria. Showing no obvious clinical symptoms, the majority of patients can be diagnosed with osteoporosis only when serious complications, such as osteoporotic fractures, occur (44). According to the osteoporosis diagnosis criteria

issued by the World Health Organization (WHO), BMD can be measured by DXA, where the T value (SD), which reflects the BMD of the lumbar and femoral necks, is used to diagnose osteoporosis (52). T≥-1.0 SD indicates normal BMD; -2.5 SD<T<-1.0 SD indicates osteopenia; while T≤-2.5 SD indicates osteoporosis (53). Additionally, the WHO fracture risk assessment tool is deemed effective for the evaluation of long-term fracture risk (54).

Osteosarcopenia. In 2009, Binkley proposed the concept of 'osteosarcopenia', which refers to the appearance of the clinical manifestation of osteoporosis or low BMD accompanied by low muscle quality and/or function (55). A study on the relevance of the decrease in muscle mass with osteoporosis showed that when the relative appendicular skeletal muscle mass increases by 1 unit, the risk of osteoporosis will decrease by 36%, and the probability of the patient with sarcopenia exhibiting osteoporosis is two times higher compared with that of healthy individuals (56). However, to the best of our knowledge, an epidemiological survey on the correlation between osteoporosis and sarcopenia shows that there is a two-way relationship between osteoporosis and sarcopenia, leading to the development of osteoporosis (57).

4. Interaction and mutual regulation between sarcopenia and osteoporosis

Biomechanical relationship between muscle and bone. Muscle is made up of myocytes that are activated under the control of the kinetic system. However, regulated by calcium ions, muscle cells will release acetylcholine, which leads to the decomposition of triphosadenine and the release of energy, providing energy for human muscles and bones (58). Bone is composed of bone cells and minerals such as calcium and phosphate. Bone cells can be divided into osteoblasts and osteoclasts, which exist in a large quantity and have a certain self-repairing capability (59). With the development and growth of the human body, the number of muscle cells and the volume of muscle will increase, and to compensate for the increasing load, the mass, size and strength of the bones will increase (5). However, after middle age, the muscle mass of the human body begins to decrease, and during old age muscular atrophy may even occur, and atrophic muscles cannot generate a strong load to the bones (60). This leads to disuse-atrophy of the bones and to the loss of original biological functions and effects of the inner structure of bone, including bone trabecula (61). Change in muscle can cause changes in skeletal form and function, and changes in bone strength can also cause alter the biomechanical characteristics and the quantity, shape and function of muscle (62,63).

Chemical crosstalk between muscle and bone. A study has confirmed that skeletal and muscle tissues not only receive upstream endocrine regulation from distal organs and tissues, but also secrete chemical factors responsible for crosstalk (64). Upstream endocrine regulators contain hormones of the somatotropin-insulin-like growth factor 1 (IGF-1) axis, sex steroid hormones, certain adipose tissue hormones and vitamin D (65). Muscles locally secrete cytokines, such as myokines, which stimulate bone formation independently of mechanical action, and bones secrete soluble factors that can act through the periosteum and into the muscle.

Effect of muscle on bone. The effects of muscle on bone mainly include mechanical and chemical effects. The mechanical effects refer to the signal to bone through muscle contraction, which affects bone growth and development and changes BMD and bone strength (66). A previous study has shown that muscle contraction caused by dynamic electric stimulus can inhibit bone loss and trabecular structure degradation to some extent, indicating that muscle contraction can also inhibit some bone loss (67). The chemical effects of muscle on bone refers to the effects of chemical substances generated by muscle such as cytokines, inflammatory factors and hormones on osteoblasts or osteoclasts through a paracrine or endocrine mechanism, which promotes osteoblast or inhibits osteoclast formation (68,69). For example, skeletal muscle can secrete myostatin, which may lead to a decrease in BMD, but muscle hypertrophy and increase in bone mass when its expression is inhibited (70).

Effect of bone regulation on muscle. The regulatory effect of bone on muscle is also achieved through mechanical and chemical activity. Connexin43 (Cx43), a gap junction protein that is rich in osteoblasts and osteocytes and plays an important role in mechanotransduction, is an example (71). When Cx43 expression is knocked out in mouse models, the muscle mass and strength of the mice decrease (72); however, injection of undercarboxylated osteocalcin into the mouse can delay or prevent the decline in muscle mass and grip strength, indicating that bone can affect muscle functions through biochemical activity (73).

Special form of regulation of bones and muscles via diffusion. Skeletal muscle and bone are the two major components of the musculoskeletal system. They have a close mechanical relationship, where bone acts as a lever and muscle acts as a pulley to move the organism. The two tissues, bone and muscle, are interdependent and mutually influenced, and the most important layer of the barrier is the periosteum, which surrounds the cellular layer of bone and muscle and is ~60 μm thick. Lai *et al* suggest that soluble factors that are <40 kDa, such as NO and PGE2, can diffuse directly and passively through the periosteum to reach the tissue microenvironment and eventually into adjacent tissues (74). However, molecules such as bone factor or muscle factor, which are >40 kDa, are likely to be transported through the circulatory system or as exosome-carried factors.

Regulation of common signal pathways of bone and muscle
Wnt/β-catenin pathway. The Wnt/β-catenin signal pathway can regulate bone and muscle growth and metabolism simultaneously (75). The Wnt ligand can be combined with the low-density lipoprotein receptor-related proteins(LRP)5/6 receptor and stop the degradation of β-catenin, leading to an excessively high level of β-catenin in the body and, thus, regulating the expression of osteoblasts (76). One study has shown that osteoblasts can promote osteoclast differentiation by activating the ROR2 receptor and secreting Wnt5a (77). Meanwhile, the Wnt family can regulate the expression of Pax3/7, myoblast determination protein 1 and myogenic

factor 5 in embryonic myogenic progenitor cells (78). These transcription factors are important in stimulating, regulating and advancing myogenesis (79,80). Furthermore, it has been shown that activation of the classic Wnt pathway can help induce proliferation of satellite cells during skeletal muscle regeneration (81).

NF-κB pathway. NF-κB is the heterodimer of p50/p65 in the body (82). When exposed to an external stimulus, NF-κB-α will be separated from the compound p50/p65 and NF-κB will be activated to enter the cell nucleus and regulate expression through combination with a specific locus of DNA (83,84). A typical indication of sarcopenia is increased reactive oxygen species secretion in myoblasts, which can activate the NF-κB pathway to improve the level of S100 calcium-binding protein B in muscle fibers, and finally to inhibit myocyte proliferation and differentiation into brown fat cells (85,86). Another study on aging demonstrates that young men have only a quarter of the amount of NF-κB in the vastus medialis muscle as compared with older men (87). Results from mouse genome sequencing have shown that the binding activity of NF-κB DNA in the anterior tibial muscle of the senile mouse is notably enhanced (88). Meanwhile, NF-κB DNA can be involved in NF-κB receptor activator of nuclear factor NF-κB ligand (RANKL)-induced osteoclast differentiation in bone tissue, thus affecting bone mass.

Other pathways. Studies have also shown that other signaling pathways can influence muscle and bone differentiation and inhibition simultaneously. For example, IGF-1 can activate the MAPK/ERK and PI3K-Akt pathways to regulate muscles and bones and promote their anabolism (89). Studies on other pathways are ongoing, and it is predicted that new treatment methods will be developed through newly discovered pathways such as JAK/STAT, Akt-FoxO and PKB-mTOR (90-92).

5. Pathogenesis of osteosarcopenia

Both sarcopenia and osteoporosis are symbolized by the hypofunction of the motor system with aging, of which sarcopenia is related to bones while osteoporosis is related to muscles (93,94). Muscles and bones have the same origin and adjacent anatomical positions; therefore, the signal crosstalk between them is closely associated (68). In the whole life process, muscles and bones regulate each other to maintain the normal functional status of the human body (95). Therefore, signal crosstalk may become the pathogenesis of osteosarcopenia (96). Since both sarcopenia and osteoporosis are caused by similar multifactorial factors, such as genetics, endocrine and fat infiltration, it can therefore be said that they are the same disease manifested in different physiological systems (97).

Hereditary factors. Hereditary factors play an important role in peak bone mass (PBM), which is the maximum bone mass that a person can acquire (98). The lower the PBM, the higher the risk of developing osteoporosis. Furthermore, according to UK Biobank data, hereditary factors also influence muscle strength to some extent (99). A genome-wide association study revealed that the genes encoding myostatin, α-actin-3, peroxisome proliferator-activated receptor-γ coactivator-1α, myocyte-specific enhancer factor 2C, glycine N-acyltransferase and METTL21C are closely associated with sarcopenia and osteoporosis (100-102). At present, it is generally considered that important heritable variations in muscle and bone tissues will provide new insights into the physiopathological mechanism of synthesis and catabolism of muscle and bone tissues (103).

Endocrine and paracrine regulation factor. Current studies show that muscles and bones are regulated by numerous signaling factors that influence one another through regulatory endocrine and paracrine mechanisms (104).

Endocrine regulation. Systemic hormones regulate the growth and metabolism of bones and muscles through the endocrine network (105). For example, growth hormones (GH), sex hormones and vitamin D can regulate bones and muscles simultaneously (106-108). The combined action of GH and IGF-1 can induce muscle hypertrophy and help maintain bone mass, while IGF-1 activity alone can promote myoblast proliferation and integration of existing muscle fibers (109). In addition, the regulation of sex hormone in bones and muscles can be summarized as the effects of androgen and estrogen (110). Androgen plays an important role in maintaining bone and muscle mass, with testosterone positively correlated with BMD and muscle strength (111). Meanwhile, estrogen, as the membrane stabilizer of muscle fiber, can not only protect muscle functions but also promote differentiation of bone mesenchymal stem cells into osteoblasts, thus maintaining the dynamic balance of bone formation and bone resorption (112).

Paracrine regulation. With the improvement in the understanding of osteosarcopenia, both bone and muscle tissues have secretory function and can secrete numerous factors that regulate one another. These factors are called muscle-derived and bone-derived factors, respectively (113,114). Cells in muscle tissues can secrete multiple muscle-derived factors, including myostatin, osteoglycin, follistatin-like protein 1 and interleukins (IL) (IL-6, -7, -8 and -15) (90). For example, myostatin, as a member of transforming growth factor β family, cannot only activate the Smad and MAPK signaling pathways to inhibit muscle growth but also directly regulates osteoclast differentiation and reduces bone growth (115,116).

Bone-derived factors include osteocalcin (OCN), sclerostin (SOST) and fibroblast growth factor 23 (117). The competitive binding of SOST secreted by bone cells to LRP5 can inhibit osteoblast differentiation, thus reducing bone mass (118,119). Meanwhile, studies have demonstrated that SOST can promote myogenic differentiation of C2C12 *in vitro*, indicating that SOST may have a dual influence on the growth and metabolism of bones and muscles in the body (105,120). In addition, OCN can not only inhibit osteogenesis but also act as a hormone to regulate pancreatic glucose metabolism, testosterone synthesis and muscle mass (73).

Fatty infiltration. One of the most obvious changes caused by aging is the change in body composition and tissue distribution. With the basal metabolic rate decreasing by 5-25% and with reduced athletic ability, older individuals have increased body mass and body fat content, and their subcutaneous fat infiltrates bone and muscle tissues. A previous clinical study showed that the percentage of body fat is negatively correlated

with total body BMD and muscle content (121). Other studies confirm that fatty tissue can influence the metabolism of bones and muscles to an extent (8,122). For example, increased fatty tissue will promote the generation of inflammatory factors, and increased inflammatory factors can not only stimulate osteoclast proliferation and differentiation through RANKL and osteoprotegerin signaling pathways, thereby improving bone destruction, but also influence the mass and function of skeletal muscle (123,124). By contrast, adiponectin (ADPN) secreted by adipocytes can not only promote osteoblast differentiation and inhibit osteoclast function but also increase sugar absorption of skeletal muscle cells, thus increasing bone mass (125,126). In previous years, it has also been revealed that a high level of inflammatory factors can inhibit the expression of ADPN and influence the promotion effect of ADPN on muscle and bone metabolism, thus increasing the risk of osteoporosis (127).

Disease association. A number of diseases can cause a reduction in bone and muscle mass (128). Patients with neoplastic or inflammatory diseases, both of which are chronic diseases of wasting, can experience decreased muscle function in the middle or late course of the disease (129,130). This mechanism may be associated with the decomposition of muscle fibers induced by the ubiquitin proteasome pathway activated by TNF-α and other inflammatory factors (131). A study has revealed that with the worsening of diabetic nephropathy and the decrease in the BMD of diabetic patients, the incidence of osteoporosis increases gradually; moreover, the severity of osteoporosis is positively correlated with the state of diabetic nephropathy (132). Additionally, in the late course of diabetes, the accumulation of advanced glycation end-products can inhibit the expression of myogenic genes and osteocalcin in myoblasts, which increases muscle and bone loss (133).

Age and other factors. The PBM is reached at ~30 years of age, and after 30 years, BMD and muscle mass begin to decrease (134). For this reason, both the incidence of sarcopenia and osteoporosis will increase with age (135). In old age, the immune system is constantly activated at low level and chronic inflammation occurs, leading to pro-inflammatory response (136). For example, increased IL-6 level intensifies muscle decomposition by inhibiting osteogenesis, promoting osteoclastic resorption and inhibiting the proliferation and differentiation of muscle cells, thus increasing the incidence of osteoporosis and sarcopenia (137).

In addition, other factors can influence the metabolism of bones and muscles simultaneously. For example, in the aging process, malnutrition and insufficient protein intake as a result of the decrease in nutrient absorption efficiency will lead to the reduction of muscle and bone mass (138). Other studies have revealed that excessive drinking and smoking can affect not only osteoblast functions but also calcium and protein metabolism, thus reducing BMD (16,139). Furthermore, a study of 608 older aged men, aged 60-85 (mean age, 68) years, in a community in France revealed that high alcohol consumption will reduce muscle mass (140). In addition, according to a meta-analysis that evaluated the relationship between smoking and sarcopenia, smoking increases the risk of sarcopenia to some extent (141).

Overall, these systematic or local factors affect muscles and bones directly or indirectly, leading to reduction in bone and muscle mass and occurrence of osteosarcopenia.

6. Prevention and treatment of osteosarcopenia

Prevention. Exercise and nutrition can help prevent osteosarcopenia by improving the function of bones and muscles (142). Since osteosarcopenia is proposed to be based on the common pathophysiology of both osteoporosis and sarcopenia, it is important to establish an early intervention system for skeletal and muscle aging for the prevention of OS.

Exercise to prevent and treat osteosarcopenia. Different forms of exercise have different effects on muscles and bones, but a number of the current exercises will be beneficial for osteosarcopenia. For example, resistance exercises have a sufficient effect on restoring muscle strength and mass (143). Aerobic exercise, including jogging, climbing stairs and stepping exercises are suitable for individuals with osteoporosis (144). For older individuals, whole-body vibration training is considered to be the safest way to exercise because the subjects are generally in a still sitting or standing position, which is suitable for the majority of individuals with sarcopenia and osteoporosis, while at the same time you can freely adjust the intensity of exercise and the number of repetitions (145). It has been demonstrated that resistance training can increase myostatin synthesis and improve skeletal muscle mass by activating mTORC1 and its downstream signaling pathways, while also maintaining bone mineral density (146). Exercise therapy must require patients to adhere to the principle of individualized treatment for a long time to avoid causing trauma and more serious injuries.

Nutritional support therapy for the prevention of osteosarcopenia. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases recommends taking 800 IU of vitamin D daily to maintain a level of $1,25(OH)_2D_3$>50 nmol/l in postmenopausal women (16). Similarly, the American Institute of Medicine issued a recommendation in 2011 that advised individuals aged >60 years to take at least 800 IU of vitamin D every day to prevent bone and muscle dysfunction (147). Patients with osteosarcopenia should have at least 1.2 g calcium intake per day, and the most efficient dose of calcium supplement alone is 500 mg (148). Furthermore, the average protein intake of older individuals should reach 1.0-1.2 g/(kg•d) (149). However, for older individuals who exercise, the daily protein intake is >1.2 g/kg (149). At the same time, the protein intake for older patients with acute or chronic diseases should reach 1.2-1.5 g/(kg•d) (150).

As a fat-soluble vitamin, vitamin D enters the body to upregulate the level of vitamin D receptors (VDR) in skeletal muscle and increase VDR activity, thereby enhancing muscle strength (151). In addition, vitamin D promotes intestinal calcium absorption, and vitamin D stimulates bone formation and bone mineralization by affecting the Wnt/βcatenin signaling pathway, making vitamin D supplementation important for maintaining muscle mass, muscle function and bone density (106).

Treatment. After the diagnosis of osteosarcopenia, exercise and nutritional support methods will only improve the symptoms of osteosarcopenia, but they cannot completely cure osteosarcopenia (152). The various drugs currently available are only targeted to their therapeutic targets and their upstream and downstream pathways (153). Regarding the correlation between bones and muscles, a number of studies state that bones and muscles can be regarded as a whole and that a drug for accurate treatment of osteosarcopenia can be found based on their common pathogenic factors and regulation pathways (57,154). However, at present, there are few drugs for the common target of sarcopenia and osteoporosis, and the curative effect is uncertain (155).

Anti-myostatin antibody. Myostatin can stimulate the activin receptor, cause a series of cell signal cascade responses, and then inhibit muscle growth and bone mineral production (70). Therefore, the anti-myostatin antibody may be a new drug for the treatment of myoosteoporosis. Fagundes *et al* reports that the anti-myostatin antibody can promote the improvement in body function, lean body weight and bone mass (156).

Anti-RANKL monoclonal antibody. Both RANKL and the NF-κB receptor activator of NF-κB (RANK) are clearly expressed in the skeletons and skeletal muscles, thus forming a signal network upstream of the NF-κB pathway (157). Anti-RANKL monoclonal antibodies affect bone and muscle growth and development by influencing the RANKL receptor ligand and the upstream NF-κB pathway (158). In bone tissues, RANKL/RANK binds and regulates downstream signaling, which in turn induces osteoclastogenesis and osteoclastic resorption (159). Meanwhile, after overexpression of RANKL in the mouse body, there is decline in muscle functions, such as muscle atrophy, fatty infiltration and inflammation (160). Currently, denosumab (AMC-162) has been approved for the treatment of osteoporosis and bone metastasis in adults, and under laboratory conditions, anti-RANKL therapy has been shown to protect musculoskeletal functions while improving mechanical functions of the bones (161).

Recombinant human GH therapy. In the aging process, the levels of GH and IGF-1 show a notable downward trend (162). Recombinant human GH therapy works by affecting systemic GH and IGF-1 levels, which in turn improves physical function, muscle mass and bone density (163). However, a number of studies have also reported adverse reactions, including carpal tunnel syndrome, peripheral edema, joint pain and swelling, enhanced female breast development, impaired glucose tolerance and increased cancer risk (164).

In clinical practice, a number of drugs have been used to treat sarcopenia and osteoporosis alone. The drugs used to treat osteoporosis, including diphosphonate, calcitonin, parathyroid hormone analogs and estrogen, can be broadly classified into two types: Those that inhibit osteoclastic resorption and those that promote osteogenesis, thus increasing bone mass and BMD and reducing fracture risk (165). At present, there is no clinically specific drug that can cure sarcopenia, but it has been shown that some drugs can delay muscle aging and improve muscle functions to some extent, such as active vitamin D, β adrenergic receptor stimulant and angiotensin converting enzyme inhibitor (166-168). Testosterone replacement therapy and selective estrogen receptor modulators (SERMS) also have a positive effect on muscle mass, muscle strength and bone mass simply by affecting the amount of estrogen in the body (169,170). The safety and effectiveness of SERMS still need to be supported by high-quality research (171). Therefore, it is a future direction to develop new drugs by regarding bones and muscles as a whole and identifying their common target according to the common pathogenesis of sarcopenia and osteoporosis.

7. Conclusions

The proposal of the concept of 'osteosarcopenia' facilitates more in-depth and unified studies on sarcopenia and osteoporosis, which are diseases related to aging. The majority of researchers agree that these two common diseases of the motor system have the same pathogenesis and regulatory pathway and that a common target can be found. Therefore, how to diagnose and treat osteosarcopenia rapidly and accurately should be the focus of future research efforts on osteosarcopenia.

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Authors' contributions

SL conceived the study. CY and YD designed the study and drafted, reviewed and edited the manuscript. YL, CM, FC, CZ, RG, XH and JL wrote the manuscript. ZP, JF, LM, and YZ analyzed the relevant literature. All authors have read and approved the final manuscript. Data sharing is not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Ferrari SL and Rizzoli R: Gene variants for osteoporosis and their pleiotropic effects in aging. Mol Aspects Med 26: 145-167, 2005.

2. Li H, Hastings MH, Rhee J, Trager LE, Roh JD and Rosenzweig A: Targeting age-related pathways in heart failure. Circ Res 126: 533-551, 2020.
3. Roberts S, Colombier P, Sowman A, Mennan C, Rölfing JH, Guicheux J and Edwards JR: Ageing in the musculoskeletal system. Acta Orthop 87 (Suppl 363): 15-25, 2016.
4. Heuberger RA: The frailty syndrome: A comprehensive review. J Nutr Gerontol Geriatr 30: 315-368, 2011.
5. Cooper C, Dere W, Evans W, Kanis JA, Rizzoli R, Sayer AA, Sieber CC, Kaufman JM, Abellan van Kan G, Boonen S, *et al*: Frailty and sarcopenia: Definitions and outcome parameters. Osteoporos Int 23: 1839-1848, 2012.
6. Loh KM, Chen A, Koh PW, Deng TZ, Sinha R, Tsai JM, Barkal AA, Shen KY, Jain R, Morganti RM, *et al*: Mapping the pairwise choices leading from pluripotency to human bone, heart, and other mesoderm cell types. Cell 166: 451-467, 2016.
7. Hamrick MW: Increased bone mineral density in the femora of GDF8 knockout mice. Anat Rec A Discov Mol Cell Evol Biol 272: 388-391, 2003.
8. Pedersen BK and Febbraio MA: Muscles, exercise and obesity: Skeletal muscle as a secretory organ. Nat Rev Endocrinol 8: 457-465, 2012.
9. Herrmann M, Engelke K, Ebert R, Müller-Deubert S, Rudert M, Ziouti F, Jundt F, Felsenberg D and Jakob F: Interactions between muscle and bone-where physics meets biology. Biomolecules 10: 432, 2020.
10. Bonewald L: Use it or lose it to age: A review of bone and muscle communication. Bone 120: 212-218, 2019.
11. Kirk B, Al Saedi A and Duque G: Osteosarcopenia: A case of geroscience. Aging Med (Milton) 2: 147-156, 2019.
12. Di Monaco M, Castiglioni C, Bardesono F, Milano E and Massazza G: Sarcopenia, osteoporosis and the burden of prevalent vertebral fractures: A cross-sectional study of 350 women with hip fracture. Eur J Phys Rehabil Med 56: 184-190, 2020.
13. Patel HP, Dawson A, Westbury LD, Hasnaoui G, Syddall HE, Shaw S, Sayer AA, Cooper C and Dennison EM: Muscle mass, muscle morphology and bone health among community-dwelling older men: Findings from the hertfordshire sarcopenia study (HSS). Calcif Tissue Int 103: 35-43, 2018.
14. Sipilä S, Törmäkangas T, Sillanpää E, Aukee P, Kujala UM, Kovanen V and Laakkonen EK: Muscle and bone mass in middle-aged women: Role of menopausal status and physical activity. J Cachexia Sarcopenia Muscle 11: 698-709, 2020.
15. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B and Kanis JA: Osteoporosis in the European Union: Medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8: 136, 2013.
16. Curtis E, Litwic A, Cooper C and Dennison E: Determinants of muscle and bone aging. J Cell Physiol 230: 2618-2625, 2015.
17. Novotny SA, Warren GL and Hamrick MW: Aging and the muscle-bone relationship. Physiology (Bethesda) 30: 8-16, 2015.
18. Paintin J, Cooper C and Dennison E: Osteosarcopenia. Br J Hosp Med (Lond) 79: 253-258, 2018.
19. Rosenberg IH: Sarcopenia: Origins and clinical relevance. J Nutr 127 (5 Suppl): 990S-991S, 1997.
20. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, *et al*: Sarcopenia: European consensus on definition and diagnosis: Report of the European working group on sarcopenia in older people. Age Ageing 39: 412-423, 2010.
21. Anker SD, Morley JE and von Haehling S: Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle 7: 512-514, 2016.
22. Petermann-Rocha F, Balntzi V, Gray SR, Lara J, Ho FK, Pell JP and Celis-Morales C: Global prevalence of sarcopenia and severe sarcopenia: A systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 13: 86-99, 2022.
23. Hong AR and Kim SW: Effects of resistance exercise on bone health. Endocrinol Metab (Seoul) 33: 435-444, 2018.
24. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, *et al*: Sarcopenia in Asia: Consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15: 95-101, 2014.
25. Janssen I, Heymsfield SB and Ross R: Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 50: 889-896, 2002.
26. Morley JE: Sarcopenia: Diagnosis and treatment. J Nutr Health Aging 12: 452-456, 2008.
27. Bouchard DR, Dionne IJ and Brochu M: Sarcopenic/obesity and physical capacity in older men and women: Data from the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec longitudinal Study. Obesity (Silver Spring) 17: 2082-2088, 2009.
28. Sjöblom S, Suuronen J, Rikkonen T, Honkanen R, Kröger H and Sirola J: Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia. Maturitas 75: 175-180, 2013.
29. Kim MK, Baek KH, Song KH, Il Kang M, Park CY, Lee WY and Oh KW: Vitamin D deficiency is associated with sarcopenia in older Koreans, regardless of obesity: The Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) 2009. J Clin Endocrinol Metab 96: 3250-3256, 2011.
30. Cheng Q, Zhu X, Zhang X, Li H, Du Y, Hong W, Xue S and Zhu H: A cross-sectional study of loss of muscle mass corresponding to sarcopenia in healthy Chinese men and women: Reference values, prevalence, and association with bone mass. J Bone Miner Metab 32: 78-88, 2014.
31. Han P, Kang L, Guo Q, Wang J, Zhang W, Shen S, Wang X, Dong R, Ma Y, Shi Y, *et al*: Prevalence and factors associated with sarcopenia in suburb-dwelling older chinese using the asian working group for sarcopenia definition. J Gerontol A Biol Sci Med Sci 71: 529-535, 2016.
32. González Correa CH, Marulanda Mejía F, Castaño González PA, Vidarte Claros JA and Castiblanco Arroyabe HD: Bioelectrical impedance analysis and dual x-ray absorptiometry agreement for skeletal muscle mass index evaluation in sarcopenia diagnosis. Physiol Meas 41: 064005, 2020.
33. van Baar H, Hulshof PJM, Tieland M and de Groot CPGM: Bio-impedance analysis for appendicular skeletal muscle mass assessment in (pre-) frail elderly people. Clin Nutr ESPEN 10: e147-e153, 2015.
34. Frontera WR and Ochala J: Skeletal muscle: A brief review of structure and function. Calcif Tissue Int 96: 183-195, 2015.
35. Vikberg S, Sörlén N, Brandén L, Johansson J, Nordström A, Hult A and Nordström P: Effects of resistance training on functional strength and muscle mass in 70-year-old individuals with pre-sarcopenia: A randomized controlled trial. J Am Med Dir Assoc 20: 28-34, 2019.
36. Liu JC, Dong SS, Shen H, Yang DY, Chen BB, Ma XY, Peng YR, Xiao HM and Deng HW: Multi-omics research in sarcopenia: Current progress and future prospects. Ageing Res Rev 76: 101576, 2022.
37. Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 94: 646-650, 1993.
38. Yin X, Zhou C, Li J, Liu R, Shi B, Yuan Q and Zou S: Autophagy in bone homeostasis and the onset of osteoporosis. Bone Res 7: 28, 2019.
39. Collins FL, Rios-Arce ND, Schepper JD, Parameswaran N and McCabe LR: The potential of probiotics as a therapy for osteoporosis. Microbiol Spectr 5: 10.1128/microbiolspec.BAD-0015-2016, 2017.
40. Das S and Crockett JC: Osteoporosis-a current view of pharmacological prevention and treatment. Drug Des Devel Ther 7: 435-448, 2013.
41. Ensrud KE and Crandall CJ: Osteoporosis. Ann Intern Med 167: ITC17-ITC32, 2017.
42. Anthamatten A and Parish A: Clinical update on osteoporosis. J Midwifery Womens Health 64: 265-275, 2019.
43. Marcucci G and Brandi ML: Rare causes of osteoporosis. Clin Cases Miner Bone Metab 12: 151-156, 2015.
44. Hurley DL and Khosla S: Update on primary osteoporosis. Mayo Clin Proc 72: 943-949, 1997.
45. Stein E and Shane E: Secondary osteoporosis. Endocrinol Metab Clin North Am 32: 115-34, vii, 2003.
46. Armas LAG and Recker RR: Pathophysiology of osteoporosis: New mechanistic insights. Endocrinol Metab Clin North Am 41: 475-486, 2012.
47. Amin S, Achenbach SJ, Atkinson EJ, Khosla S and Melton LJ: Trends in fracture incidence: A population-based study over 20 years. J Bone Miner Res 29: 581-589, 2014.
48. Coughlan T and Dockery F: Osteoporosis and fracture risk in older people. Clin Med (Lond) 14: 187-191, 2014.
49. Gullberg B, Johnell O and Kanis JA: World-wide projections for hip fracture. Osteoporos Int 7: 407-413, 1997.

50. Kanis JA, Cooper C, Rizzoli R and Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF): European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 30: 3-44, 2019.
51. Nishizawa Y, Miura M, Ichimura S, Inaba M, Imanishi Y, Shiraki M, Takada J, Chaki O, Hagino H, Fukunaga M, *et al*: Executive summary of the Japan osteoporosis society guide for the use of bone turnover markers in the diagnosis and treatment of osteoporosis (2018 Edition). Clin Chim Acta 498: 101-107, 2019.
52. Kanis JA and Glüer CC: An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int 11: 192-202, 2000.
53. Lamichhane AP: Osteoporosis-an update. JNMA J Nepal Med Assoc 44: 60-66, 2005.
54. Rossini M, Adami S, Bertoldo F, Diacinti D, Gatti D, Giannini S, Giusti A, Malavolta N, Minisola S, Osella G, *et al*: Guidelines for the diagnosis, prevention and management of osteoporosis. Reumatismo 68: 1-39, 2016.
55. Binkley N and Buehring B: Beyond FRAX: It's time to consider 'sarco-osteopenia'. J Clin Densitom 12: 413-416, 2009.
56. He H, Liu Y, Tian Q, Papasian CJ, Hu T and Deng HW: Relationship of sarcopenia and body composition with osteoporosis. Osteoporos Int 27: 473-482, 2016.
57. Kirk B, Zanker J and Duque G: Osteosarcopenia: Epidemiology, diagnosis, and treatment-facts and numbers. J Cachexia Sarcopenia Muscle 11: 609-618, 2020.
58. Tarantino U, Baldi J, Celi M, Rao C, Liuni FM, Iundusi R and Gasbarra E: Osteoporosis and sarcopenia: The connections. Aging Clin Exp Res 25 (Suppl 1): S93-S95, 2013.
59. Frontera WR, Zayas AR and Rodriguez N: Aging of human muscle: Understanding sarcopenia at the single muscle cell level. Phys Med Rehabil Clin N Am 23: 201-7, xiii, 2012.
60. Sumnik Z, Land C, Coburger S, Neu C, Manz F, Hrach K and Schoenau E: The muscle-bone unit in adulthood: Influence of sex, height, age and gynecological history on the bone mineral content and muscle cross-sectional area. J Musculoskelet Neuronal Interact 6: 195-200, 2006.
61. Frost HM: Why do bone strength and 'mass' in aging adults become unresponsive to vigorous exercise? Insights of the Utah paradigm. J Bone Miner Metab 17: 90-97, 1999.
62. Seeman E: Pathogenesis of bone fragility in women and men. Lancet 359: 1841-1850, 2002.
63. Miyakoshi N, Hongo M, Mizutani Y and Shimada Y: Prevalence of sarcopenia in Japanese women with osteopenia and osteoporosis. J Bone Miner Metab 31: 556-561, 2013.
64. Frost HM and Schönau E: The 'muscle-bone unit' in children and adolescents: A 2000 overview. J Pediatr Endocrinol Metab 13: 571-590, 2000.
65. Žofková I: Hormonal aspects of the muscle-bone unit. Physiol Res 57 (Suppl 1): S159-S169, 2008.
66. Regan JN, Trivedi T, Guise TA and Waning DL: The Role of TGFβ in bone-muscle crosstalk. Curr Osteoporos Rep 15: 18-23, 2017.
67. Lam H and Qin YX: The effects of frequency-dependent dynamic muscle stimulation on inhibition of trabecular bone loss in a disuse model. Bone 43: 1093-1100, 2008.
68. Tagliaferri C, Wittrant Y, Davicco MJ, Walrand S and Coxam V: Muscle and bone, two interconnected tissues. Ageing Res Rev 21: 55-70, 2015.
69. Kawao N and Kaji H: Interactions between muscle tissues and bone metabolism. J Cell Biochem 116: 687-695, 2015.
70. Buehring B and Binkley N: Myostatin-the holy grail for muscle, bone, and fat? Curr Osteoporos Rep 11: 407-414, 2013.
71. Kawatsura R, Hara Y, Akiyama M, Tachikawa N and Nakahama KI: Gap junctional intercellular communication attenuates osteoclastogenesis induced by activated osteoblasts. Biochem Biophys Res Commun 597: 71-76, 2022.
72. Loiselle AE, Paul EM, Lewis GS and Donahue HJ: Osteoblast and osteocyte-specific loss of Connexin43 results in delayed bone formation and healing during murine fracture healing. J Orthop Res 31: 147-154, 2013.
73. Komori T: Functions of osteocalcin in bone, pancreas, testis, and muscle. Int J Mol Sci 21: 7513, 2020.
74. Lai X, Price C, Lu XL and Wang L: Imaging and quantifying solute transport across periosteum: Implications for muscle-bone crosstalk. Bone 66: 82-89, 2014.
75. Laurent MR, Dedeyne L, Dupont J, Mellaerts B, Dejaeger M and Gielen E: Age-related bone loss and sarcopenia in men. Maturitas 122: 51-56, 2019.
76. MacDonald BT and He X: Frizzled and LRP5/6 receptors for Wnt/β-catenin signaling. Cold Spring Harb Perspect Biol 4: a007880, 2012.
77. Maeda K, Kobayashi Y, Udagawa N, Uehara S, Ishihara A, Mizoguchi T, Kikuchi Y, Takada I, Kato S, Kani S, *et al*: Wnt5a-Ror2 signaling between osteoblast-lineage cells and osteoclast precursors enhances osteoclastogenesis. Nat Med 18: 405-412, 2012.
78. Girardi F and Le Grand F: Wnt signaling in skeletal muscle development and regeneration. Prog Mol Biol Transl Sci 153: 157-179, 2018.
79. Tajbakhsh S, Borello U, Vivarelli E, Kelly R, Papkoff J, Duprez D, Buckingham M and Cossu G: Differential activation of Myf5 and MyoD by different Wnts in explants of mouse paraxial mesoderm and the later activation of myogenesis in the absence of Myf5. Development 125: 4155-4162, 1998.
80. Otto A, Schmidt C and Patel K: Pax3 and Pax7 expression and regulation in the avian embryo. Anat Embryol (Berl) 211: 293-310, 2006.
81. Otto A, Schmidt C, Luke G, Allen S, Valasek P, Muntoni F, Lawrence-Watt D and Patel K: Canonical Wnt signalling induces satellite-cell proliferation during adult skeletal muscle regeneration. J Cell Sci 121(Pt 17): 2939-2950, 2008.
82. Ko W, Sohn JH, Jang JH, Ahn JS, Kang DG, Lee HS, Kim JS, Kim YC and Oh H: Inhibitory effects of alternaramide on inflammatory mediator expression through TLR4-MyD88-mediated inhibition of NF-κB and MAPK pathway signaling in lipopolysaccharide-stimulated RAW264.7 and BV2 cells. Chem Biol Interact 244: 16-26, 2016.
83. Brigelius-Flohé R and Flohé L: Basic principles and emerging concepts in the redox control of transcription factors. Antioxid Redox Signal 15: 2335-2381, 2011.
84. Bellezza I, Mierla AL and Minelli A: Nrf2 and NF-κB and their concerted modulation in cancer pathogenesis and progression. Cancers (Basel) 2: 483-497, 2010.
85. Pan H, Wang H, Wang X, Zhu L and Mao L: The absence of Nrf2 enhances NF-κB-dependent inflammation following scratch injury in mouse primary cultured astrocytes. Mediators Inflamm 2012: 217580, 2012.
86. Canning P, Sorrell FJ and Bullock AN: Structural basis of Keap1 interactions with Nrf2. Free Radic Biol Med 88(Pt B): 101-107, 2015.
87. Cuthbertson D, Smith K, Babraj J, Leese G, Waddell T, Atherton P, Wackerhage H, Taylor PM and Rennie MJ: Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. FASEB J 19: 422-424, 2005.
88. Vasilaki A, McArdle F, Iwanejko LM and McArdle A: Adaptive responses of mouse skeletal muscle to contractile activity: The effect of age. Mech Ageing Dev 127: 830-839, 2006.
89. Yang SY, Hoy M, Fuller B, Sales KM, Seifalian AM and Winslet MC: Pretreatment with insulin-like growth factor I protects skeletal muscle cells against oxidative damage via PI3K/Akt and ERK1/2 MAPK pathways. Lab Invest 90: 391-401, 2010.
90. Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimgeour A, Lawrence JC, Glass DJ and Yancopoulos GD: Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol 3: 1014-1019, 2001.
91. Bonetto A, Aydogdu T, Jin X, Zhang Z, Zhan R, Puzis L, Koniaris LG and Zimmers TA: JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. Am J Physiol Endocrinol Metab 303: E410-E421, 2012.
92. Allen DL and Unterman TG: Regulation of myostatin expression and myoblast differentiation by FoxO and SMAD transcription factors. Am J Physiol Cell Physiol 292: C188-C199, 2007.
93. Tarantino U, Piccirilli E, Fantini M, Baldi J, Gasbarra E and Bei R: Sarcopenia and fragility fractures: Molecular and clinical evidence of the bone-muscle interaction. J Bone Joint Surg Am 97: 429-437, 2015.
94. Brotto M, Invernizzi M, Ireland A and Klein GL: Editorial: Osteoporosis and the role of muscle. Front Endocrinol (Lausanne) 13: 951298, 2022.
95. Karsenty G and Mera P: Molecular bases of the crosstalk between bone and muscle. Bone 115: 43-49, 2018.
96. Brotto M and Johnson ML: Endocrine crosstalk between muscle and bone. Curr Osteoporos Rep 12: 135-141, 2014.

97. Binkley N, Krueger D and Buehring B: What's in a name revisited: Should osteoporosis and sarcopenia be considered components of 'dysmobility syndrome?'. Osteoporos Int 24: 2955-2959, 2013.
98. Greenhill C: Unravelling the genetics of osteoporosis. Nat Rev Endocrinol 15: 129, 2019.
99. Tikkanen E, Gustafsson S, Amar D, Shcherbina A, Waggott D, Ashley EA and Ingelsson E: Biological insights into muscular strength: Genetic findings in the UK Biobank. Sci Rep 8: 6451, 2018.
100. Urano T and Inoue S: Recent genetic discoveries in osteoporosis, sarcopenia and obesity. Endocr J 62: 475-484, 2015.
101. Karasik D, Cupples LA, Hannan MT and Kiel DP: Genome screen for a combined bone phenotype using principal component analysis: The Framingham study. Bone 34: 547-556, 2004.
102. Huang J, Hsu YH, Mo C, Abreu E, Kiel DP, Bonewald LF, Brotto M and Karasik D: METTL21C is a potential pleiotropic gene for osteoporosis and sarcopenia acting through the modulation of the NF-κB signaling pathway. J Bone Miner Res 29: 1531-1540, 2014.
103. Hirschfeld HP, Kinsella R and Duque G: Osteosarcopenia: Where bone, muscle, and fat collide. Osteoporos Int 28: 2781-2790, 2017.
104. Gomarasca M, Banfi G and Lombardi G: Myokines: The endocrine coupling of skeletal muscle and bone. Adv Clin Chem 94: 155-218, 2020.
105. Huang J, Romero-Suarez S, Lara N, Mo C, Kaja S, Brotto L, Dallas SL, Johnson ML, Jähn K, Bonewald LF and Brotto M: Crosstalk between MLO-Y4 osteocytes and C2C12 muscle cells is mediated by the Wnt/β-catenin pathway. JBMR Plus 1: 86-100, 2017.
106. Scimeca M, Centofanti F, Celi M, Gasbarra E, Novelli G, Botta A and Tarantino U: Vitamin D receptor in muscle atrophy of elderly patients: A key element of osteoporosis-sarcopenia connection. Aging Dis 9: 952-964, 2018.
107. DiGirolamo DJ, Clemens TL and Kousteni S: The skeleton as an endocrine organ. Nat Rev Rheumatol 8: 674-683, 2012.
108. Lebrasseur NK, Achenbach SJ, Melton LJ III, Amin S and Khosla S: Skeletal muscle mass is associated with bone geometry and microstructure and serum insulin-like growth factor binding protein-2 levels in adult women and men. J Bone Miner Res 27: 2159-2169, 2012.
109. Chen LY, Wu YH, Liu LK, Lee WJ, Hwang AC, Peng LN, Lin MH and Chen LK: Association among serum insulin-like growth factor-1, frailty, muscle mass, bone mineral density, and physical performance among community-dwelling middle-aged and older adults in Taiwan. Rejuvenation Res 21: 270-277, 2018.
110. Messier V, Rabasa-Lhoret R, Barbat-Artigas S, Elisha B, Karelis AD and Aubertin-Leheudre M: Menopause and sarcopenia: A potential role for sex hormones. Maturitas 68: 331-336, 2011.
111. Notelovitz M: Androgen effects on bone and muscle. Fertil Steril 77 (Suppl 4): S34-S41, 2002.
112. Hansen M: Female hormones: Do they influence muscle and tendon protein metabolism? Proc Nutr Soc 77: 32-41, 2018.
113. Colaianni G, Storlino G, Sanesi L, Colucci S and Grano M: Myokines and osteokines in the pathogenesis of muscle and bone diseases. Curr Osteoporos Rep 18: 401-407, 2020.
114. Gonzalez-Gil AM and Elizondo-Montemayor L: The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: A review. Nutrients 12: 1899, 2020.
115. Liu Y, Lehar A, Rydzik R, Chandok H, Lee YS, Youngstrom DW, George J, Matzuk MM, Germain-Lee EL and Lee SJ: Local versus systemic control of bone and skeletal muscle mass by components of the transforming growth factor-β signaling pathway. Proc Natl Acad Sci USA 118: e2111401118, 2021.
116. Omosule CL, Joseph D, Weiler B, Gremminger VL, Silvey S, Jeong Y, Rafique A, Krueger P, Kleiner S and Phillips CL: Combinatorial inhibition of myostatin and activin A improves femoral bone properties in the G610C mouse model of osteogenesis imperfecta. J Bone Miner Res 37: 938-953, 2022.
117. Du Y, Zhang L, Wang Z, Zhao X and Zou J: Endocrine regulation of extra-skeletal organs by bone-derived secreted protein and the effect of mechanical stimulation. Front Cell Dev Biol 9: 778015, 2021.
118. Han Y, You X, Xing W, Zhang Z and Zou W: Paracrine and endocrine actions of bone-the functions of secretory proteins from osteoblasts, osteocytes, and osteoclasts. Bone Res 6: 16, 2018.
119. Sutherland MK, Geoghegan JC, Yu C, Turcott E, Skonier JE, Winkler DG and Latham JA: Sclerostin promotes the apoptosis of human osteoblastic cells: A novel regulation of bone formation. Bone 35: 828-835, 2004.
120. Spatz JM, Fields EE, Yu EW, Divieti Pajevic P, Bouxsein ML, Sibonga JD, Zwart SR and Smith SM: Serum sclerostin increases in healthy adult men during bed rest. J Clin Endocrinol Metab 97: E1736-E1740, 2012.
121. Meex RCR, Blaak EE and van Loon LJC: Lipotoxicity plays a key role in the development of both insulin resistance and muscle atrophy in patients with type 2 diabetes. Obes Rev 20: 1205-1217, 2019.
122. Yu B, Huo L, Liu Y, Deng P, Szymanski J, Li J, Luo X, Hong C, Lin J and Wang CY: PGC-1α controls skeletal stem cell fate and bone-fat balance in osteoporosis and skeletal aging by inducing TAZ. Cell Stem Cell 23: 615-623, 2018.
123. Wong SK, Chin KY, Suhaimi FH, Ahmad F and Ima-Nirwana S: The relationship between metabolic syndrome and osteoporosis: A review. Nutrients 8: 347, 2016.
124. Li W, Xu P, Wang C, Ha X, Gu Y, Wang Y, Zhang J and Xie J: The effects of fat-induced obesity on bone metabolism in rats. Obes Res Clin Pract 11: 454-463, 2017.
125. Ansari MGA, Hussain SD, Wani KA, Yakout SM, Al-Disi D, Alokail MS, Reginster JY and Al-Daghri NM: Influence of bone mineral density in circulating adipokines among postmenopausal Arab women. Saudi J Biol Sci 27: 374-379, 2020.
126. Liu Y and Sweeney G: Adiponectin action in skeletal muscle. Best Pract Res Clin Endocrinol Metab 28: 33-41, 2014.
127. Cervellati C, Bonaccorsi G, Bergamini CM, Fila E, Greco P, Valacchi G, Massari L, Gonelli A and Tisato V: Association between circulatory levels of adipokines and bone mineral density in postmenopausal women. Menopause 23: 984-992, 2016.
128. Gomes MM, da Silva MMR, de Araújo IM and de Paula FJA: Bone, fat, and muscle interactions in health and disease. Arch Endocrinol Metab 66: 611-620, 2022.
129. Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE and Spiegelman BM: Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature 513: 100-104, 2014.
130. Tuttle CSL, Thang LAN and Maier AB: Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis. Ageing Res Rev 64: 101185, 2020.
131. Ali S and Garcia JM: Sarcopenia, cachexia and aging: Diagnosis, mechanisms and therapeutic options-a mini-review. Gerontology 60: 294-305, 2014.
132. Jung YS, Hwang HJ, Yun BH, Chon SJ, Cho S, Choi YS, Kim YT, Lee BS and Seo SK: Renal function is associated with bone mineral density and arterial stiffness in healthy postmenopausal women. Gynecol Obstet Invest 78: 124-129, 2014.
133. Mohsin S, Baniyas MM, AlDarmaki RS, Tekes K, Kalász H and Adeghate EA: An update on therapies for the treatment of diabetes-induced osteoporosis. Expert Opin Biol Ther 19: 937-948, 2019.
134. Fricke O, Beccard R, Semler O and Schoenau E: Analyses of muscular mass and function: The impact on bone mineral density and peak muscle mass. Pediatr Nephrol 25: 2393-2400, 2010.
135. Edwards MH, Dennison EM, Aihie Sayer A, Fielding R and Cooper C: Osteoporosis and sarcopenia in older age. Bone 80: 126-130, 2015.
136. Barbé-Tuana F, Funchal G, Schmitz CRR, Maurmann RM and Bauer ME: The interplay between immunosenescence and age-related diseases. Semin Immunopathol 42: 545-557, 2020.
137. Stefanaki C, Pervanidou P, Boschiero D and Chrousos GP: Chronic stress and body composition disorders: Implications for health and disease. Hormones (Athens) 17: 33-43, 2018.
138. JafariNasabian P, Inglis JE, Reilly W, Kelly OJ and Ilich JZ: Aging human body: Changes in bone, muscle and body fat with consequent changes in nutrient intake. J Endocrinol 234: R37-R51, 2017.
139. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H and Tenenhouse A: Alcohol intake as a risk factor for fracture. Osteoporos Int 16: 737-742, 2005.
140. Renoud A, Ecochard R, Marchand F, Chapurlat R and Szulc P: Predictive parameters of accelerated muscle loss in men-MINOS study. Am J Med 127: 554-561, 2014.

141. Steffl M, Bohannon RW, Petr M, Kohlikova E and Holmerova I: Relation between cigarette smoking and sarcopenia: Meta-analysis. Physiol Res 64: 419-426, 2015.
142. Goljanek-Whysall K, Iwanejko LA, Vasilaki A, Pekovic-Vaughan V and McDonagh B: Ageing in relation to skeletal muscle dysfunction: Redox homoeostasis to regulation of gene expression. Mamm Genome 27: 341-357, 2016.
143. Schoenfeld BJ, Ogborn D and Krieger JW: Effects of resistance training frequency on measures of muscle hypertrophy: A systematic review and meta-analysis. Sports Med 46: 1689-1697, 2016.
144. DiVasta AD and Gordon CM: Exercise and bone: Where do we stand? Metabolism 62: 1714-1717, 2013.
145. Harijanto C, Lim A, Vogrin S and Duque G: Does whole-body vibration training have a concurrent effect on bone and muscle health? A systematic review and meta-analysis. Gerontology 68: 601-611, 2022.
146. Zeng Z, Liang J, Wu L, Zhang H, Lv J and Chen N: Exercise-Induced Autophagy suppresses sarcopenia through Akt/mTOR and Akt/FoxO3a signal pathways and AMPK-mediated mitochondrial quality control. Front Physiol 11: 583478, 2020.
147. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, *et al*: The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab 96: 53-58, 2011.
148. Schnatz PF, Marakovits KA, Dubois M and O'Sullivan DM: Osteoporosis screening and treatment guidelines: Are they being followed? Menopause 18: 1072-1078, 2011.
149. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, Phillips S, Sieber C, Stehle P, Teta D, *et al*: Evidence-based recommendations for optimal dietary protein intake in older people: A position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 14: 542-559, 2013.
150. Shams-White MM, Chung M, Du M, Fu Z, Insogna KL, Karlsen MC, LeBoff MS, Shapses SA, Sackey J, Wallace TC and Weaver CM: Dietary protein and bone health: A systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr 105: 1528-1543, 2017.
151. Tang BM, Eslick GD, Nowson C, Smith C and Bensoussan A: Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet 370: 657-666, 2007.
152. Hassan EB and Duque G: Osteosarcopenia: A new geriatric syndrome. Aust Fam Physician 46: 849-853, 2017.
153. Polito A, Barnaba L, Ciarapica D and Azzini E: Osteosarcopenia: A narrative review on clinical studies. Int J Mol Sci 23: 5591, 2022.
154. Klein GL: Pharmacologic treatments to preserve bone and muscle mass in osteosarcopenia. Curr Osteoporos Rep 18: 228-231, 2020.
155. Inoue T, Maeda K, Nagano A, Shimizu A, Ueshima J, Murotani K, Sato K, Hotta K, Morishita S and Tsubaki A: Related factors and clinical outcomes of osteosarcopenia: A narrative review. Nutrients 13: 291, 2021.
156. Fagundes Belchior G, Kirk B, Pereira da Silva EA and Duque G: Osteosarcopenia: Beyond age-related muscle and bone loss. Eur Geriatr Med 11: 715-724, 2020.
157. Li B, Wang P, Jiao J, Wei H, Xu W and Zhou P: Roles of the RANKL-RANK axis in immunity-implications for pathogenesis and treatment of bone metastasis. Front Immunol 13: 824117, 2022.
158. Ono T, Hayashi M, Sasaki F and Nakashima T: RANKL biology: Bone metabolism, the immune system, and beyond. Inflamm Regen 40: 2, 2020.
159. Boyce BF, Xiu Y, Li J, Xing L and Yao Z: NF-κB-Mediated regulation of osteoclastogenesis. Endocrinol Metab (Seoul) 30: 35-44, 2015.
160. Bonnet N, Bourgoin L, Biver E, Douni E and Ferrari S: RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass. J Clin Invest 130: 3329, 2020.
161. Hamoudi D, Marcadet L, Piette Boulanger A, Yagita H, Bouredji Z, Argaw A and Frenette J: An anti-RANKL treatment reduces muscle inflammation and dysfunction and strengthens bone in dystrophic mice. Hum Mol Genet 28: 3101-3112, 2019.
162. Junnila RK, List EO, Berryman DE, Murrey JW and Kopchick JJ: The GH/IGF-1 axis in ageing and longevity. Nat Rev Endocrinol 9: 366-376, 2013.
163. Altowati MA, Shepherd S, McGrogan P, Russell RK, Ahmed SF and Wong SC: Effects of recombinant human growth hormone in children with crohn's disease on the muscle-bone unit: A preliminary study. Horm Res Paediatr 90: 128-131, 2018.
164. Pawlikowska-Haddal A: Growth hormone therapy with norditropin (somatropin) in growth hormone deficiency. Expert Opin Biol Ther 13: 927-932, 2013.
165. Lane JM, Russell L and Khan SN: Osteoporosis. Clin Orthop Relat Res (372): 139-150, 2000.
166. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, *et al*: Prevalence of and interventions for sarcopenia in ageing adults: A systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43: 748-759, 2014.
167. Kakehi S, Wakabayashi H, Inuma H, Inose T, Shioya M, Aoyama Y, Hara T, Uchimura K, Tomita K, Okamoto M, *et al*: Rehabilitation nutrition and exercise therapy for sarcopenia. World J Mens Health 40: 1-10, 2022.
168. Pana A, Sourtzi P, Kalokairinou A and Velonaki VS: Sarcopenia and polypharmacy among older adults: A scoping review of the literature. Arch Gerontol Geriatr 98: 104520, 2022.
169. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, Ellenberg SS, Cauley JA, Ensrud KE, Lewis CE, Barrett-Connor E, Schwartz AV, Lee DC, *et al*: Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: A controlled clinical trial. JAMA Intern Med 177: 471-479, 2017.
170. Velders M and Diel P: How sex hormones promote skeletal muscle regeneration. Sports Med 43: 1089-1100, 2013.
171. Dieli-Conwright CM, Spektor TM, Rice JC and Todd Schroeder E: Oestradiol and SERM treatments influence oestrogen receptor coregulator gene expression in human skeletal muscle cells. Acta Physiol (Oxf) 197: 187-196, 2009.

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