Review Article

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# Potential application of anti-osteoporotic therapy to relieve sarcopenia in the elderly

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**Abstract**

Sarcopenia is a progressive and systemic skeletal muscle disorder associated with aging that usually occurs with age in the elderly. Sarcopenia currently lacks effective pharmacological treatment modalities. Multiple pharmacological intervention modalities are available for osteoporosis, a comprehensive disease characterized by decreased systemic bone mass, degradation of bone microarchitecture, and increased bone fragility. Several recent studies have shown an extremely strong correlation between sarcopenia and osteoporosis, leading to the concept of "osteosarcopenia". Therefore, it is possible to alleviate sarcopenia simultaneously by improving osteoporosis.

**Keywords:** bone, interaction, muscle, osteoporosis, sarcopenia

## Introduction

Population aging has become a major trend in population development[1]. Medical health issues associated with aging are also becoming increasingly prominent, including the significant loss of skeletal muscle strength and/or function called sarcopenia. Sarcopenia is widely distributed in the elderly population, and in a study with 4866 participants included in the baseline prevalence analysis (50.3% men, 49.7% women; mean age: 67.7±6.4 years). A total of 2238 subjects were likely to have sarcopenia at baseline, with an overall prevalence of 46.0% (95% CI: 44.6–47.4%)[2] There was a strong correlation between falls, fractures, functional decline, functional capacity, death, and multisystem disorders, and therefore a significant medical and economic burden[3]. Patients with comorbid osteoporosis are more likely to experience falls, fractures, and death[4]. The biological mechanisms underlying the interaction between sarcopenia and osteoporosis are not fully understood. It is difficult to identify pathophysiological mechanisms and, thus, targets for the prevention and treatment of sarcopenia. As sarcopenia is closely related to osteoporosis, it would be beneficial to understand the aetiology of sarcopenia and explore potential therapeutic approaches for its prevention and treatment. This review aimed to explore anti-osteoporosis therapy as a possible opportunity for the prevention and treatment of sarcopenia.

### HIGHLIGHTS

- Sarcopenia is a skeletal muscle disease associated with aging.
- Sarcopenia currently lacks effective pharmacological treatment modalities.
- There is an extremely strong correlation between "sarcopenia" and "osteoporosis".
- Is there a possibility of improving sarcopenia by treating osteoporosis?

## Potential mechanisms for the development of sarcopenia

Myosin plays an important role in muscle contraction and is classified into type I, type IIA, and type IIB, according to the type of myosin heavy chain. Changes in myofibers include changes in cell size, number, and percentage of myosin heavy chain subtypes[5]. Unlike myasthenic diseases secondary to other diseases, sarcopenia is an age-related skeletal muscle disease that can be considered as the aging of muscle at the cellular and organelle levels (e.g. reduced mitochondrial function, reduced number of myosin heavy chains[6], caused mainly by the loss of its intrinsic functions, such as a decrease in the number of myoblasts, a decrease in muscle protein synthesis,an increase in catabolism, and an imbalance in hormone secretion[7]. There is an interactive relationship between sarcopenia and osteoporosis, and the mechanisms of action will be discussed below.

## Sarcopenia and osteoporosis

In recent years, several studies have shown a strong correlation between sarcopenia and osteoporosis[4], which led to the concept

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of "osteosarcopenia". In a study involving 17 891 African American, Caucasian, and Chinese subjects, sarcopenia was reported to be associated with low bone mineral density and osteoporosis[8]. It has also been reported that patients with osteoporosis, in combination with sarcopenia, have an increased risk of fracture. In addition, it was mentioned that the cases in this study were predominantly type II muscle fibre atrophy[9]. Thus, sarcopenia and osteoporosis are closely related, and extensive studies have been conducted in recent years regarding their interrelationship. However, the mode of the interaction between the two requires further clarification.

## Current treatments for sarcopenia

### Exercise

Exercise is an essential non-pharmacological treatment for sarcopenia, and several recent guidelines and studies have emphasized its importance[10]. A meta-analysis of 17 studies (985 patients with sarcopenia, aged 67.6–86 years) showed that exercise training significantly improved muscle strength[11]. Both whole-body vibration training and resistance training improved muscle strength and speed of movement, with no significant difference in the degree of improvement between the two exercise training modalities[12]. Aerobic exercise training improves the loss of skeletal muscle mitochondria and thus has the potential to prevent sarcopenia[13]. Exercise programs including strength training, home training, and combination training have shown improvements in muscle strength. However, there was still no significant difference in the extent to which various exercise programs improved muscle strength[14]. However, we should also note that there are limitations and that some older adults have difficulty adhering to exercise prescriptions[15]. In patients with trauma or other disorders.

### Nutrition interventions

Nutritional interventions are important in the non-pharmacological treatment and prevention of sarcopenia, and protein and amino acid supplementation currently the main nutritional interventions for sarcopenia[9]. Studies have reported that essential amino acid supplements, including leucine and β-hydroxy β-methylbutyrate, are effective in improving muscle strength. In contrast, protein supplementation had no significant effect on the muscle strength[15]. Also, some studies have reported that increased protein intake can maintain or increase the body weight[16]. Increased protein intake has also been reported to improve the skeletal muscle mass in patients with sarcopenia[17,18]. Therefore, the improvement in muscle strength with increased protein supplementation require further investigation.

### Hormone replacement therapy

The more popular form of pharmacological treatment for declining levels of multiple hormones in older adults is hormone replacement therapy, which includes growth hormone, oestrogen, cortisol, dehydroepiandrosterone, and related analogues, and hormone replacement therapy has been shown to improve muscle mass. A Meta-analysis of 11 studies showed that testosterone supplementation increased muscle mass and strength in older men[19]. The use of growth hormone therapy in older adults has demonstrated positive effects on muscles, such as increased muscle mass[20]. However, sarcopenia requires long-term treatment, meaning that the medication needs to be applied over a long period of time, and too many growth hormones will have numerous side effects, including fluid retention, gynaecomastia, and upright hypotension[21]. Low doses of androgens have no practical effect on muscle mass[22]. Supraphysiological doses of androgens can increase muscle size and strength[23]. However, there is an increased risk of prostate enlargement and prostate cancer[24]. In summary, hormone replacement therapy is associated with significant side effects and its use in sarcopenia is limited.

### Vitamin D

Chronic vitamin D deficiency leads to muscle atrophy and impaired muscle mass and strength. In patients with vitamin D deficiency, vitamin D supplementation will maintain muscle fibres at normal functional levels[25]. In healthy individuals with normal vitamin D, supplementation will not result in improvements in indices associated with sarcopenia[26]. Excessive vitamin D supplementation can increase the risk of fall[27].

### Angiotensin-converting enzyme inhibitors

In an observational study, patients with hypertension showed a slower rate of muscle strength loss with ACEI than with other hypertensive drugs[28]. However, a placebo-controlled, parallel-group, double-blind, randomized two-by-two analysis of causes showed no improvement in walking speed, muscle strength, or muscle mass after 12 months of perindopril in patients greater than or equal to 70 years of age with sarcopenia[29]. A randomized controlled study and meta-analysis showed the same results[30,31].

In summary, although dietary and exercise interventions are effective for sarcopenia, new therapeutic measures must be explored. It is important to note that the purpose of this review was to highlight the possibility and importance of the impact of osteoporosis treatment on sarcopenia.

### Treatment of osteoporosis to improve the mechanism of sarcopenia

The bone is one of the eight systems of the human body. It was previously thought to be a structural organ that supports body movement and protects internal organs, and the interaction between bone and muscle is carried out by mechanical transduction, however, in 2006, it was first proposed that bone is an endocrine organ that[32] Bone consists of osteoblasts, osteocytes, and osteoclasts, with osteoblasts accounting for about 5% of all bone cells, osteocytes for about 90–95%, and osteoclasts for about 1%. Growth factor-1 (IGF-1), prostaglandin E2 (PGE2), transforming growth factor β (TGF-β), receptor activator of nuclear factor kappa-B ligand (RANKL), fibroblast growth factor-23 (FGF-23), and other factors have been found to affect muscle anabolism. fibroblast growth factor-23 (FGF-23), sclerostin (SOST), and Dickkopf-1 (Dkk-1). Recent evidence suggests that patients with osteoporotic fractures have a higher prevalence of sarcopenia[4,8]. The bone-muscle crosstalk provides a theoretical basis for the treatment of osteoporosis to alleviate sarcopenia[33]. Possible mechanisms for this are as follows.

Osteocalcin (OCN) is produced and released into the circulatory system by the osteoblasts and osteocytes[34]. It binds to G protein coupled receptor C family 6 group A (GPRC6A) and regulates muscle anabolism via the GPRC6A/AMPK/mTOR/S6 kinase pathway. Serum osteocalcin levels are elevated in the exercise state compared to resting serum osteocalcin levels[35]. An animal study found that osteocalcin maintain muscle mass[36]. And a population-based study also showed low serum osteocalcin levels in older adults[37].

Insulin-like growth factor-1 (IGF-1) circulating IGF-1 is mainly produced by the liver, while bone tissue is mainly secreted by osteoblasts and has little effect on circulating IGF-1 levels[38]. IGF-1 can act in muscles by paracrine secretion that[39] promotes the proliferation and differentiation of satellite cells and acts on muscle cell proliferation, repair, and hypertrophy[40].

PGE2 is mainly secreted by osteoblasts and is further enhanced in the presence of load, acting in skeletal muscle in a paracrine manner.PGE2 promotes myoblast proliferation through signalling at the EP4 receptor, while blocking this receptor leads to an increase in intracellular reactive oxygen species levels[41].

TGF-β is mainly produced by osteoblasts and acts on skeletal muscle through paracrine secretion, negatively affecting skeletal muscle protein homoeostasis, and leading to muscle atrophy. It showed high expression with increasing age[42–44].

RANKL is mainly derived from osteoblasts[45]. In an animal experiment, it was found that the corresponding receptor exists on myocytes and that RANKL binds to the receptor via paracrine secretion. It was also found that muscle-specific RANK deficiency prevents denervated muscle weakness[46].

FGF-23 is secreted by osteoblasts and osteoclasts[32]. FGF-23 does not act directly on skeletal muscle, but enters the circulation to regulate phosphate and vitamin D metabolism in distant organs such as the kidney, leading to disorders of calcium and phosphorus metabolism and low levels of 1,25-dihydroxyvitamin D, resulting in reduced muscle strength and mass[47–49]. An animal study corroborates the negative regulation of muscle by FGF-23[50]. However, the exact underlying mechanism requires further investigated.

SOST and Dkk-1 are expressed by osteoblasts and are secreted by osteoclasts, both of which are negative regulators of the Wnt/β-catenin signalling pathway[51]. In contrast, several studies have shown that the Wnt/β-catenin signalling pathway has a positive regulatory effect on skeletal muscles[52,53] (Table 1).

**Table 1**

**Factors secreted by osteoblasts that can have an effect on muscle mass/strength.**

| | Muscle mass / strength↑ | Muscle mass / strength↓ |
|---|---|---|
| Factors secreted by osteoblasts, osteoclasts, and osteoclasts that have been found to affect muscle | OCN, IGF-1, PGE2, Wnt3a | TGF-β, RANKL, FGF-23, SOST, Dkk-1 |

Dkk-1, Dickkopf-1; FGF-23, fibroblast growth factor-23; IGF-1, insulin-like growth factor-1; OCN, osteocalcin; PGE2, prostaglandin E2; RANKL, receptor activator of nuclear factor kappa-B ligand; SOST, sclerostin; TGF-β, transforming growth factor β.

### *Possible effects of anti-osteoporosis drugs on muscle*

At present, drugs for osteoporosis treatment can be divided into two main categories: inhibition of bone resorption and promotion of bone synthesis, and drugs to inhibit bone resorption, including bisphosphonates (Alendronate, Risedronate, Ibandronate, Zoledronate), selective oestrogen receptor modulators (Raloxifene (Raloxifene), mixed steroid receptor agonist (Tibolone), anti-RANKL monoclonal antibody (denosumab), and osteosynthesis-promoting drugs including parathyroid hormone analogues (teriparatide), parathyroid hormone receptor analogues (Abaloparatide Abaloparatide), and an anti-osteosclerotic protein monoclonal antibody (Romosozumab)[54].

Drugs that inhibit bone resorption inhibit osteoblast and osteoclast apoptosis and osteoclast production. Bisphosphonates inhibit bone resorption by inhibiting osteoclast apoptosis through the inhibition of FPPS, an essential enzyme in the mevalonate pathway[55]. Selective oestrogen receptor modulator raloxifene decreases serum IL-6 and TGF-β1 levels, and serum levels of inflammatory markers such as IL-6 are associated with decreased muscle mass and strength[56]. TGF-β1 skeletal muscle protein homoeostasis has a negative effect, leading to muscle atrophy, and[44] It also induces 25-OH vitamin D production. Mixed steroid receptor agonist is an oestrogen receptor present in skeletal muscle that binds to tibolone to produce a direct effect on the skeletal muscle. A randomized double-blind controlled trial showed that tibolone enhanced grip strength[57]. Monoclonal antibody against RANKL (monoclonal antibody against RANKL) The corresponding RANKL receptor is present on myocytes and the antibody binds to RANKL and antagonizes the negative regulatory effect of RANKL on myocytes. Increased osteoblasts and osteocytes that constitute the skeleton, and high expression of secreted bone factors such as OCN, IGF-1, RANKL, FGF-23, SOST, and Dkk-1 have possible effects on muscle and promote osteosynthesis drugs for osteoclastogenesis. Parathyroid hormones affect blood calcium concentrations by regulating bone metabolism. Low doses of parathyroid hormone promote bone synthesis and lower blood calcium, while high doses of parathyroid hormone promote bone breakdown and elevate blood calcium[58] The presence of parathyroid hormones receptor in myocytes and the direct action of parathyroid hormone or its analogue, parathyroid hormone analogue, on muscles enhances muscle contraction and promotes muscle synthesis[59]. Parathyroid hormones also promote the synthesis of 1,25-dihydroxyvitamin D, thereby improving muscle strength[60]. PTHR1 is mainly found in osteoblasts, the kidneys, and tumours. The parathyroid receptor analogue PTHrP binds to PTHR1 and promotes osteoblast and osteoclast synthesis[61]. Monoclonal antibody against sclerostin are secreted by osteoblasts and negatively regulate bone synthesis and muscle strength through the Wnt/β-catenin signalling pathway[51,62]. Romosozumab binds to osteosclerostin and reduces negative feedback to the Wnt/β-catenin signalling pathway[63].

Current studies have shown conflicting results between anti-osteoporosis treatment and improvement of sarcopenia, with some drugs relying on a common pathway between the bone and muscle to improve sarcopenia alongside anti-osteoporosis treatment, such as denosumab and tibolone[64,65]. It is still unknown whether altering the ratio of cells in the skeleton without the common pathway can have an effect on muscle output, while studies on the effect of denosumab on muscle through the common pathway are very scarce, lacking control groups and considering the effect of protein intake and exercise interventions[66].

## Conclusion

There are still no drugs for sarcopenia that can be effectively treated, and as the aging society progresses, it is crucial to find a treatment for sarcopenia. Multiple mechanisms could explain the improvement in sarcopenia after anti-osteoporosis treatment. Current evidence suggests that denosumab binds to RANKL and antagonizes the negative regulatory effect of RANKL on myocytes, Tibolone binds to oestrogen receptors in muscle and directly increases muscle anabolism. Furthermore, in addition to the common pathway, it does not mean that bone is negligible through the light effect of the paracrine bone factor on skeletal muscle; In conclusion, the current study suggests that anti-osteoporotic therapy offers a lasting and easy to use program for patients with sarcopenia in general.

## Ethical approval

Ethics approval was not required for this review.

## Consent

Informed consent was not required for this review.

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## Author contribution

Conceptualization: L.Y.G., L.X.B., K.S.R., Y.B.F., L.Z.L. and L.H.J.; Funding acquisition: L.H.J.; Investigation: L.Y.G., L.X.B., K.S.R., Y.B.F., L.Z.L. and L.H.J.; Methodology: L.Y.G., L.X.B., K.S.R., Y.B.F., L.Z.L. and L.H.J.; Writing—original dra ft: L.Y.G., L.X.B.; Writing—review and editing: L.Y.G., L.X.B., K.S.R., Y.B.F., L.Z.L. and L.H.J. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest disclosure

The authors declare no conflict of interest.

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## References

[1] Gietel-Basten S, Sobotka T. Trends in population health and demography. Lancet 2021;398:580–1.
[2] Chen Z, Ho M, Chau PH. Prevalence, incidence, and associated factors of possible sarcopenia in community-dwelling chinese older adults: a population-based longitudinal study. Front Med 2022;8:769708.
[3] Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16–31.
[4] Kirk B, Zanker J, Duque G. Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers. J Cachexia Sarcopenia Muscle 2020;11:609–18.
[5] Essén-Gustavsson B, Borges O. Histochemical and metabolic characteristics of human skeletal muscle in relation to age. Acta Physiol Scand 1986;126:107–14.
[6] Wiedmer P, Jung T, Castro JP, *et al*. Sarcopenia—molecular mechanisms and open questions. Ageing Res Rev 2021;65:101200.
[7] Argilés JM, Busquets S, Stemmler B, *et al*. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol 2015;22:100–6.
[8] He H, Liu Y, Tian Q, *et al*. Relationship of sarcopenia and body composition with osteoporosis. Osteoporos Int 2016;27:473–82.
[9] Tarantino U, Baldi J, Scimeca M, *et al*. The role of sarcopenia with and without fracture. Injury 2016;47:S3–10.
[10] Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet 2019;393:2636–46.
[11] Zhang Y, Zou L, Chen S-T, *et al*. Effects and moderators of exercise on sarcopenic components in sarcopenic elderly: a systematic review and meta-analysis. Front Med 2021;8:649748.
[12] Roelants M, Delecluse C, Verschueren SM. Whole-body-vibration training increases knee-extension strength and speed of movement in older women: strength gain following whole-body vibration. J Am Geriatr Soc 2004;52:901–8.
[13] Broskey NT, Greggio C, Boss A, *et al*. Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training. J Clin Endocrinol Metab 2014;99:1852–61.
[14] Bao W, Sun Y, Zhang T, *et al*. Exercise programs for muscle mass, muscle strength and physical performance in older adults with sarcopenia: a systematic review and meta-analysis. Aging Dis 2020;11:863–73.
[15] Baker MK, Kennedy DJ, Bohle PL, *et al*. Efficacy and feasibility of a novel tri-modal robust exercise prescription in a retirement community: a randomized, controlled trial: exercise in a retirement community. J Am Geriatr Soc 2007;55:1–10.
[16] Deer RR, Volpi E. Protein intake and muscle function in older adults. Curr Opin Clin Nutr Metab Care 2015;18:248–53.
[17] Naseeb MA, Volpe SL. Protein and exercise in the prevention of sarcopenia and aging. Nutr Res 2017;40:1–20.
[18] Wang Z, Xu X, Gao S, *et al*. Effects of internet-based nutrition and exercise interventions on the prevention and treatment of sarcopenia in the elderly. Nutrients 2022;14:2458.
[19] Parahiba SM, Ribeiro ÉCT, Corrêa C, *et al*. Effect of testosterone supplementation on sarcopenic components in middle-aged and elderly men: a systematic review and meta-analysis. Exp Gerontol 2020;142:111106.
[20] Franco C, Brandberg J, Lönn L, *et al*. Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. J Clin Endocrinol Metab 2005;90:1466–74.
[21] Sullivan DH, Carter WJ, Warr WR, *et al*. Side effects resulting from the use of growth hormone and insulin-like growth factor-i as combined therapy to frail elderly patients. J Gerontol A Biol Sci Med Sci 1998;53A:M183–7.
[22] Nair KS, Short KR, Basu R, *et al*. DHEA in elderly women and DHEA or testosterone in elderly men. N Engl J Med 2006;13:1647–59.
[23] Bhasin S, Storer TW, Berman N, *et al*. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335:1–7.
[24] Welén K, Damber J-E. Androgens, aging, and prostate health. Rev Endocr Metab Disord 2022;23:1221–31.
[25] Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. Mol Aspects Med 2005;26:203–19.
[26] Cheng S-H, Chen K-H, Chen C, *et al*. The optimal strategy of vitamin D for sarcopenia: a network meta-analysis of randomized controlled trials. Nutrients 2021;13:3589.
[27] Sanders KM, Stuart AL, Williamson EJ, *et al*. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815.

[28] Onder G, Penninx BW, Balkrishnan R, *et al*. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet 2002;359: 926–30.
[29] Achison M, Adamson S, Akpan A, *et al*. Effect of perindopril or leucine on physical performance in older people with sarcopenia: the LACE randomized controlled trial. J Cachexia Sarcopenia Muscle 2022;13:858–71.
[30] Sumukadas D, Band M, Miller S, *et al*. Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? a randomized controlled trial. J Gerontol A Biol Sci Med Sci 2014;69: 736–43.
[31] Caulfield L, Heslop P, Walesby KE, *et al*. Effect of angiotensin system inhibitors on physical performance in older people—a systematic review and meta-analysis. J Am Med Dir Assoc 2021;22:1215–221.e2.
[32] Feng JQ, Ward LM, Liu S, *et al*. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet 2006;38:1310–5.
[33] Picca A, Calvani R, Manes-Gravina E, *et al*. Bone-muscle crosstalk: unraveling new therapeutic targets for osteoporosis. Curr Pharm Des 2018;23:6256–63.
[34] Hauschka PV, Lian JB, Cole DE, *et al*. Osteocalcin and matrix Gla protein: vitamin K-dependent proteins in bone. Physiol Rev 1989;69: 990–1047.
[35] Mera P, Laue K, Ferron M, *et al*. Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. Cell Metab 2016;23:1078–92.
[36] Mera P, Laue K, Wei J, *et al*. Osteocalcin is necessary and sufficient to maintain muscle mass in older mice. Mol Metab 2016;5:1042–7.
[37] Oosterwerff MM, van Schoor NM, Lips P, *et al*. Osteocalcin as a predictor of the metabolic syndrome in older persons: a population-based study. Clin Endocrinol (Oxf) 2013;78:242–7.
[38] Sheng MH-C, Zhou X-D, Bonewald LF, *et al*. Disruption of the insulin-like growth factor-1 gene in osteocytes impairs developmental bone growth in mice. Bone 2013;52:133–44.
[39] Derek LR. Insulin-like growth factors. N Engl J Med 1997;8:633–40.
[40] Velloso CP, Harridge SDR. Insulin-like growth factor-I E peptides: implications for ageing skeletal muscle. Scand J Med Sci Sports 2010;20:20–7.
[41] Mo C, Zhao R, Vallejo J, *et al*. Prostaglandin E2 promotes proliferation of skeletal muscle myoblasts via EP4 receptor activation. Cell Cycle 2015; 14:1507–16.
[42] Waning DL, Mohammad KS, Reiken S, *et al*. Excess TGF-β mediates muscle weakness associated with bone metastases in mice. Nat Med 2015;21:1262–71.
[43] Klein GL. Transforming growth factor-beta in skeletal muscle wasting. Int J Mol Sci 2022;23:1167.
[44] Zhao H, Patra A, Tanaka Y, *et al*. Transforming growth factor-bs and their receptors in aging rat prostate. Biochem Biophys Res Commun 2002;6:464–9.
[45] Nakashima T, Hayashi M, Fukunaga T, *et al*. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. Nat Med 2011;17:1231–4.
[46] Dufresne SS, Dumont NA, Boulanger-Piette A, *et al*. Muscle RANK is a key regulator of Ca2 + storage, SERCA activity, and function of fast-twitch skeletal muscles. Am J Physiol Cell Physiol 2016;310:C663–72.
[47] Avin KG, Vallejo JA, Chen NX, *et al*. Fibroblast growth factor 23 does not directly influence skeletal muscle cell proliferation and differentiation or ex vivo muscle contractility. Am J Physiol Endocrinol Metab 2018; 315:E594–604.
[48] Czaya B, Heitman K, Campos I, *et al*. Hyperphosphatemia increases inflammation to exacerbate anemia and skeletal muscle wasting independently of FGF23-FGFR4 signaling. eLife, 11:e74782.
[49] Quarles LD. Skeletal secretion of FGF-23 regulates phosphate and vitamin D metabolism. Nat Rev Endocrinol 2012;8:276–86.
[50] Aono Y, Hasegawa H, Yamazaki Y, *et al*. Anti-FGF-23 neutralizing antibodies ameliorate muscle weakness and decreased spontaneous movement of Hyp mice. J Bone Miner Res 2011;26:803–10.
[51] Ke HZ, Richards WG, Li X, *et al*. Sclerostin and Dickkopf-1 as therapeutic targets in bone diseases. Endocr Rev 2012;33:747–83.
[52] Han S, Cui C, He H, *et al*. Myoferlin regulates Wnt/β-catenin signaling-mediated skeletal muscle development by stabilizing dishevelled-2 against autophagy. Int J Mol Sci 2019;20:5130.
[53] Zhang D-H, Yin H-D, Li J-J, *et al*. KLF5 regulates chicken skeletal muscle atrophy via the canonical Wnt/β-catenin signaling pathway. Exp Anim 2020;69:430–40.
[54] Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. Lancet 2022;399:1080–92.
[55] Cremers S, Drake MT, Ebetino FH, *et al*. Pharmacology of bisphosphonates. Br J Clin Pharmacol 2019;85:1052–62.
[56] Schaap LA, Pluijm SMF, Deeg DJH, *et al*. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. J Gerontol A Biol Sci Med Sci 2009;64A:1183–9.
[57] Meeuwsen IBAE, Samson MM, Duursma SA, *et al*. Muscle strength and tibolone: a randomised, double-blind, placebo-controlled trial. BJOG Int J Obstet Gynaecol 2002;109:77–84.
[58] Rendina-Ruedy E, Rosen CJ. Parathyroid hormone (PTH) regulation of metabolic homeostasis: An old dog teaches us new tricks. Mol Metab 2022;60:101480.
[59] Fujimaki T, Ando T, Hata T, *et al*. Exogenous parathyroid hormone attenuates ovariectomy-induced skeletal muscle weakness in vivo. Bone 2021;151:116029.
[60] Leung EKY. Parathyroid hormone. Adv Clin Chem. 2021;101:41–93.
[61] Ansari N, Ho PW, Crimeen-Irwin B, *et al*. Autocrine and Paracrine Regulation of the Murine Skeleton by Osteocyte-Derived Parathyroid Hormone-Related Protein. J Bone Miner Res 2018;33:137–53.
[62] Iwamoto R, Koide M, Udagawa N, *et al*. Positive and negative regulators of sclerostin expression. Int J Mol Sci 2022;23:4895.
[63] Prather C, Adams E, Zentgraf W. Romosozumab: a first-in-class sclerostin inhibitor for osteoporosis. Am J Health Syst Pharm 2020;77: 1949–56.
[64] Bonnet N, Bourgoin L, Biver E, *et al*. RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass. J Clin Invest, 129: 3214–23.
[65] Jacobsen DE, Samson MM, Kezic S, *et al*. Postmenopausal HRT and tibolone in relation to muscle strength and body composition. Maturitas 2007;58:7–18.
[66] Rupp T, von Vopelius E, Strahl A, *et al*. Beneficial effects of denosumab on muscle performance in patients with low BMD: a retrospective, propensity score-matched study. Osteoporos Int 2022;33:2177–84.