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Advances in the Study of Denosumab Treatment for Osteoporosis and Sarcopenia in the Chinese Middle-Aged and Elderly Population

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Abstract: Osteosarcopenia (OS) is a geriatric syndrome characterized by the concurrent presence of osteoporosis and sarcopenia, predominantly affecting the elderly population. Osteoporosis (OP) is a systemic skeletal disorder characterized by decreased bone mass, compromised bone microarchitecture, and heightened bone fragility, substantially elevating fracture risk. Sarcopenia (SP) is defined by decreased muscle mass, strength, and/or functional capacity. Both conditions are age-related degenerative diseases with overlapping pathophysiological mechanisms, commonly co-occurring in elderly individuals and substantially increasing fracture risk. Denosumab, a targeted anti-osteoporotic agent, mediates therapeutic effects by inhibiting bone resorption through the RANK-RANKL-OPG (RRO) pathway, consequently enhancing bone mineral density. International studies indicate that Denosumab not only treats osteoporosis but also improves sarcopenia-related metrics, suggesting its potential as a sarcopenia treatment. However, research focusing on the Chinese population remains limited. Additionally, the pathophysiological mechanisms of sarcopenia and the pathways through which Denosumab ameliorates sarcopenia are not yet fully understood, warranting further experimental investigation. In summary, Denosumab's therapeutic efficacy in osteoporosis treatment and its potential impact on sarcopenia are of substantial research interest. However, research and literature on these topics in China remain notably scarce. This article aims to offer a systematic review and critical analysis of these topics.

Keywords: osteoporosis, sarcopenia, denosumab, RANK-RANKL-OPG pathway, comorbidity

Introduction

According to the 2020 national census by the National Bureau of Statistics of China, nearly 270 million people in China are aged 60 and above, comprising 18.7% of the total population, while those aged 65 and above number over 190 million, or 13.5% of the total population.[1] As China transitions into an aging society, degenerative conditions like osteoporosis and sarcopenia have emerged as major health concerns for its elderly population. A 2008 report by the International Osteoporosis Foundation estimates that approximately 200 million people worldwide suffer from osteoporosis,[2] with a considerable proportion of cases occurring in China.[3] Additionally, osteoporosis and sarcopenia share regulatory mechanisms, including common genes, endocrine networks, and signaling pathways within the musculoskeletal system,[4] leading to a close relationship and frequent coexistence that substantially heightens the risk of falls and fractures in affected individuals.[5] A cross-sectional study in Australia reported a prevalence of osteosarcopenia of 14.2% among individuals aged 70 and above.[6] Similarly, a cross-sectional study in China found osteosarcopenia prevalence rates of 10.4% in elderly men and 15.1% in elderly women aged 65 and above,[7] showing comparable findings between the two studies.

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In recent years, Denosumab, a targeted anti-osteoporotic agent, has gained widespread clinical use.[8] However, comprehensive clinical studies and published literature examining Denosumab's effects on sarcopenia in the Chinese population remain scarce, particularly double-blind randomized controlled trials. Additionally, the pathophysiological basis of sarcopenia and the mechanisms through which Denosumab may mitigate sarcopenia remain poorly understood. Thus, examining Denosumab's dual impact on sarcopenia and osteoporosis has become a research priority.

Definition and Diagnostic Criteria of Osteoporosis and Sarcopenia

Osteoporosis (OP) is a systemic skeletal disease characterized by decreased bone mass and compromised bone micro-architecture, which increases bone fragility and fracture risk.[9] Bone mass typically peaks between ages 30 and 40, then gradually declines, decreasing by about 30% by age 70. In postmenopausal women, bone mass decline is especially rapid, with reductions reaching up to 20% within the first 5–7 years post-menopause. Consequently, OP is more prevalent among postmenopausal women and elderly men, though it can occur across all age groups, including adolescents.[10] OP carries significant health implications, as fractures associated with the condition are among the leading causes of disability in elderly patients, markedly decreasing quality of life and imposing substantial burdens on families and society due to treatment and care costs. The World Health Organization (WHO) defines osteoporosis based on bone mineral density (BMD) measurements obtained via dual-energy X-ray absorptiometry (DXA). Osteoporosis is diagnosed when the BMD T-score at the central skeleton (lumbar spine L1-4, femoral neck, or total hip) or the distal one-third of the radius is ≤ -2.5. For T-scores between -2.5 and -1, fracture risk assessment (FRAX) should supplement the diagnosis. If the FRAX score shows a 10-year probability of a major osteoporotic fracture exceeding 30% or hip fracture risk over 4.5%, osteoporosis is diagnosed.[11]

Sarcopenia (SP) is a chronic syndrome defined by a progressive decline in skeletal muscle mass, strength, and physiological function.[12] Along with osteoporosis, it is collectively termed "mobility disability syndrome" and is prevalent in the elderly, frequently coexisting with OP. Muscle mass typically peaks around age 25, declining after age 40 at approximately 1% to 2% per year, amounting to a total loss of about 30% by age 80. Notably, the rate of decline in muscle strength and power exceeds that of muscle mass.[13] Muscle strength decreases by about 1.5% per year between ages 50 and 60, accelerating to approximately 3% per year thereafter[14] (Figure 1). Osteoporosis heightens the risk of falls and fractures, and reductions in muscle mass and function decrease strength and mobility, compounding the risk of falls and fractures.[5]

The European Working Group on Sarcopenia in Older People (EWGSOP)[16] recommends assessing muscle strength through handgrip strength or the chair stand test. Muscle mass is evaluated with dual-energy X-ray absorptiometry (DXA) or bioimpedance analysis (BIA). Muscle function is evaluated by gait speed, the Short Physical Performance Battery (SPPB), the timed-up and go (TUG) test, or the 400-meter walk test. The Asian Working Group for Sarcopenia (AWGS) recommends diagnostic criteria and assessment methods largely similar to those of EWGSOP, with only minor differences in reference values.[17]

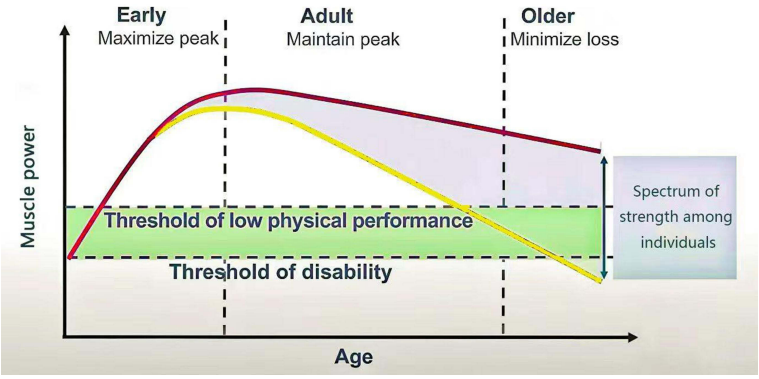

Figure 1 Muscle strength and the life course.
Notes: Data from Cruz-Jentoft et al.[15]

At present, a unified diagnostic standard for sarcopenia does not exist in China. Based on international standards,[15,18,19] the following screening and assessment steps are recommended: first, measure gait speed. If gait speed is ≤ 0.8 m/s, proceed to assess muscle mass. If gait speed exceeds 0.8 m/s, evaluate muscle strength (dominant handgrip strength). If dominant handgrip strength is within normal range (men > 25 kg, women > 18 kg), sarcopenia is excluded. If dominant handgrip strength falls below this threshold, assess muscle mass. If muscle mass is within normal range (not below −2 standard deviations from the peak value of healthy young adults), sarcopenia is excluded. If muscle mass is reduced (below −2 standard deviations from the peak value of healthy young adults), sarcopenia is diagnosed.

Denosumab

Denosumab is a fully human IgG2 monoclonal antibody that binds with high specificity and affinity to the receptor activator of nuclear factor-kappa B ligand (RANKL), preventing RANKL from binding to its receptor, receptor activator of nuclear factor-kappa B (RANK). This inhibition prevents the formation and activation of osteoclasts.[20] Primarily used in treating both primary and secondary osteoporosis,[21] Denosumab is administered at 60 mg every six months. Denosumab is also indicated for bone-related malignancies, including solid tumor bone metastases, giant cell tumor, and multiple myeloma,[22,23] at a dose of 120 mg every four weeks. Administered subcutaneously (in the upper arm, upper thigh, or abdomen), Denosumab's infrequent dosing schedule supports high patient compliance. Denosumab is considered relatively safe, with adverse reactions and complications being infrequent.[24] The most common adverse reactions (occurring in >1/10 of patients) include musculoskeletal and limb pain. Common adverse reactions (in ≥1/100 to <1/10 of patients) include urinary tract and upper respiratory infections, while less common reactions (in ≥1/1000 to <1/100 of patients) include diverticulitis, cellulitis, and ear infections. Rare adverse reactions (in ≥1/10000 to <1/1000 of patients) include drug hypersensitivity and anaphylactic reactions.[25]

Mechanism of Action of Denosumab in Treating Osteoporosis

Under normal physiological conditions, bone formation and resorption are maintained in dynamic balance through a process known as bone remodeling, ensuring proper bone metabolism. The pathogenesis of osteoporosis (OP) involves an imbalance in bone remodeling, characterized by bone resorption exceeding bone formation. The RANK/RANKL/OPG signaling pathway is a key regulator of osteoclast differentiation and maturation, thereby influencing bone metabolism.[26] RANK is a type I transmembrane protein highly expressed in osteoclast precursors and mature osteoclasts. RANKL, the ligand for RANK, is primarily expressed by osteoblasts and activated T lymphocytes and exists in both membrane-bound and soluble forms. RANKL binds to RANK on the surface of osteoclast precursors, inducing NF-κB activation through intracellular signaling pathways associated with RANK, which regulates gene expression involved in osteoclast differentiation and maturation. Research indicates that elevated RANKL expression in postmenopausal women plays a central role in the development of osteoporosis.[27] The interaction between RANKL and its receptor RANK triggers a cascade of signaling events leading to osteoclast differentiation and maturation.[28] Osteoprotegerin (OPG), secreted by osteoblasts, functions as a decoy receptor for soluble RANKL, competitively binding to RANKL and thereby inhibiting osteoclastogenesis and activation.[29] Denosumab, the most potent RANKL inhibitor available for human use, binds strongly to RANKL, thereby blocking the RANK-RANKL pathway, reducing osteoclast formation, and inhibiting its functional activity. This mechanism results in increased bone mineral density and effective treatment of osteoporosis (Figure 2).

Potential Mechanisms by Which Denosumab May Improve Sarcopenia

The mechanisms by which Denosumab might improve sarcopenia are not yet fully understood, but several potential mechanisms have been proposed.

Inhibition of Inflammatory Responses and Cytokine Regulation

As individuals age, immune system activity gradually declines, while chronic inflammatory responses persistently increase, resulting in elevated levels of pro-inflammatory cytokines, such as TNF and IL-6, in the serum, thereby placing the elderly in a state of chronic inflammation.[30,31] This inflammatory state can impact muscle protein metabolism, resulting in reduced muscle protein synthesis or increased muscle protein breakdown, thereby exacerbating muscle tissue

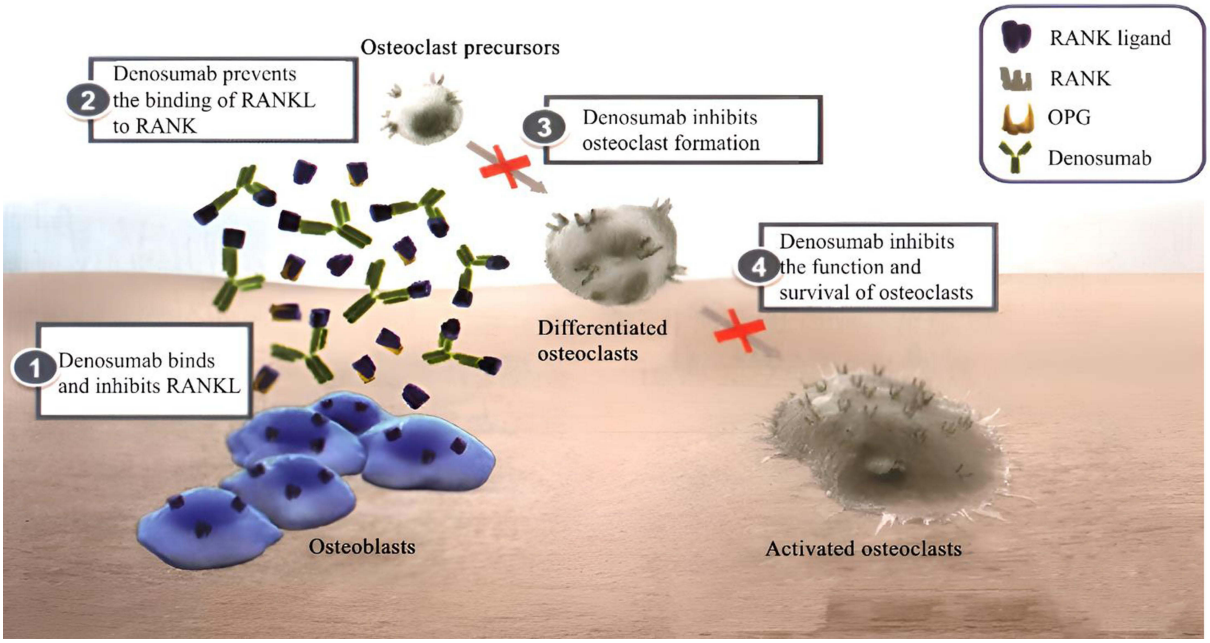

Figure 2 Mechanism of the action of denosumab.
Notes: Modified from Chinese Society of Osteoporosis and Bone Mineral Diseases.[25]

degradation and increasing the prevalence of sarcopenia.[32] Additionally, with aging, the basal metabolic rate declines by approximately 5% to 25%, and physical capacity decreases, contributing to increased body mass and body fat content. Subcutaneous fat infiltrates bone and muscle tissues, while visceral fat functions as an endocrine organ, secreting inflammatory factors that negatively regulate muscle synthesis and metabolism.[33] Interestingly, activation of the RANK-RANKL pathway, which mediates osteoporosis, also activates NF-κB, leading to the release of various inflammatory factors and cytokines, such as IL-1, IL-6, and TNF-α.[34] The release of these inflammatory factors may promote muscle breakdown. Denosumab, by antagonizing the RANK-RANKL pathway, inhibits NF-κB activation and the production of inflammatory factors, potentially mitigating sarcopenia.

Improvement of Insulin Resistance

An additional key function of the RANK/RANKL/OPG pathway is the regulation of glucose homeostasis. Inhibition of RANK activity in the liver of mice can prevent diet-induced glucose intolerance. Conversely, exposure to RANKL in primary hepatocytes directly stimulates the NF-κB pathway, resulting in the upregulation of pro-inflammatory genes and activation of Kupffer cells. Both effects contribute to hepatic insulin resistance and adversely affect overall glucose homeostasis.[35,36] Insulin resistance is closely associated with sarcopenia, as changes in glucose uptake by muscle tissue can indicate muscle contraction and other physiological functions.[37] The RANKL inhibitor Denosumab may enhance muscle function by inhibiting the RANK-RANKL pathway, thereby modulating insulin signaling in muscle cells, improving insulin sensitivity, and increasing glucose uptake.

Interaction Between Muscle and Bone

Current research indicates that the occurrence of sarcopenia may be associated with the systemic atrophy of both type I and type II muscle fibers, with atrophy of type II fibers being prevalent among elderly individuals with osteoporosis.[38] Furthermore, sarcopenia and osteoporosis exhibit several shared pathophysiological pathways (Figure 3), including decreased sensitivity to anabolic hormones, heightened activity of inflammatory cytokines, and diminished release of anabolic or catabolic molecules (muscle and bone growth factors) from skeletal muscle or bone cells.[39] Additionally, from a genetic perspective, osteoporosis and sarcopenia have shared genetic etiologies, as both osteoblasts and myoblasts differentiate from identical mesenchymal precursors.[40] Denosumab, while primarily used in the treatment of

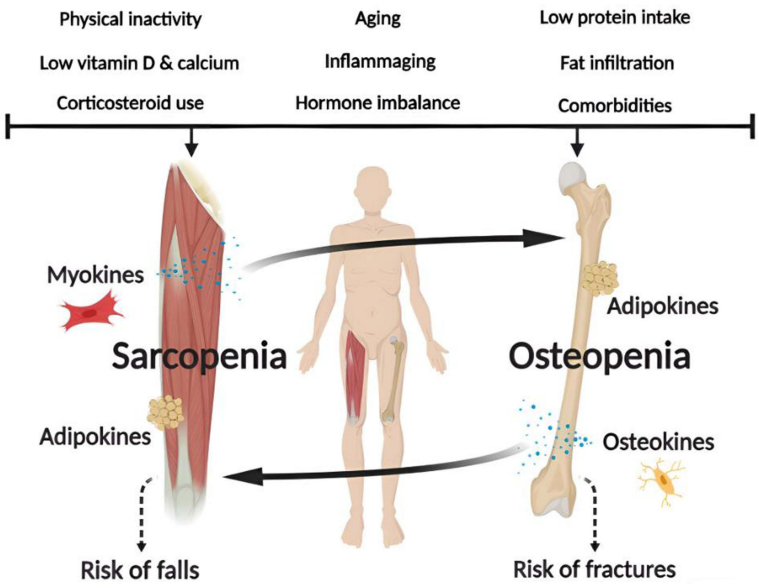

Figure 3 Muscle-bone crosstalk.
Notes: Reproduced from Kirk B, Zanker J, Duq G. Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers. Journal of Cachexia, Sarcopenia and Muscle. 2020;11(3)609-618.[41]

osteoporosis, may also enhance the production and release of specific muscle and bone growth factors, thereby potentially improving muscle function.

Thus, it is reasonable to hypothesize that Denosumab may beneficially influence skeletal muscle damage and functional recovery by inhibiting the RANK-RANKL-OPG (RRO) signaling pathway and blocking downstream pathways, such as NF-κB. This pathophysiological overlap provides a theoretical basis for Denosumab's potential to simultaneously address both osteoporosis and sarcopenia. However, whether the RRO pathway is directly involved in the development of sarcopenia and whether Denosumab can ameliorate or manage sarcopenia through this pathway requires further investigation through extensive molecular, cellular, and clinical research.

Efficacy of Denosumab in the Treatment of Osteoporosis

Denosumab, a novel therapeutic agent for osteoporosis, has been widely utilized internationally and has demonstrated clear efficacy. Numerous clinical trials have shown that Denosumab effectively increases bone mineral density (BMD) and reduces fracture incidence associated with osteoporotic conditions. In the multicenter, randomized, double-blind, placebo-controlled Phase 3 FREEDOM trial,[42] postmenopausal women aged 60 to 90 years with osteoporosis were recruited from 214 centers across North America, Europe, Latin America, and Australasia. Participants were randomly assigned to receive either a 60 mg subcutaneous injection of Denosumab or a placebo every 6 months for 3 years. Participants who completed the FREEDOM trial and did not discontinue treatment or miss more than one dose were eligible for an open-label 7-year extension trial, during which all participants received Denosumab. Women in the long-term group, who received Denosumab for 3 years and continued into the extension study, received Denosumab treatment for up to 10 years. Those in the crossover group, who initially received placebo for 3 years before transitioning to Denosumab, received Denosumab for up to 7 years. Primary outcomes included safety monitoring, such as the incidence of adverse and serious adverse events, changes in laboratory analyses (eg, serum chemistry and hematology), and the formation of antibodies against Denosumab. Secondary outcomes included the incidence of new vertebral, hip, and nonvertebral fractures and changes in BMD across the lumbar spine, total hip, femoral neck, and one-third radius. A total of 7808 women participated in the FREEDOM trial. After 3 years of Denosumab or placebo treatment, 5928 women (76%) were eligible for the extension study, with 4550 (77%) enrolling (2343 in the long-term group and 2207 in the crossover group). The incidence of serious adverse events remained stable, with rates per 100 participant-years ranging from 11.5% to 14.4%. During the extension period, the annual incidence of new vertebral fractures (0.90% to 1.86%) and

nonvertebral fractures (0.84% to 2.55%) remained low, comparable to the rates in the Denosumab group during the initial 3 years and lower than predicted in a virtual long-term placebo cohort. In the long-term group, BMD increased by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, and 2.7% at the one-third radius from the FREEDOM baseline. In the crossover group, BMD increased by 16.5% at the lumbar spine, 7.4% at the total hip, 7.1% at the femoral neck, and 2.3% at the one-third radius from the extension baseline.

A meta-analysis comparing Denosumab (study group) with Zoledronic Acid (control group), another first-line anti-osteoporosis drug, demonstrated significant findings.[43] In three studies assessing changes in lumbar spine BMD,[44–46] involving a total sample of 1163 patients (590 in the study group and 573 in the control group), the percentage change in lumbar spine BMD was substantially greater in the Denosumab group than in the control group, with a statistically significant difference (MD = 1.07, 95% CI = 0.23–1.91, P = 0.01). Additionally, two studies examined improvements in hip BMD, with a total sample of 1099 patients (556 in the study group and 543 in the control group). Similar to the lumbar spine BMD findings, the percentage change in hip BMD was substantially greater in the Denosumab group, with a statistically significant difference (MD = 0.89, 95% CI = 0.13–1.65, P = 0.02).

In summary, long-term use of Denosumab for the treatment of osteoporosis is characterized by a low incidence of adverse events and fractures, while consistently increasing bone mineral density (BMD). These findings emphasize the safety and efficacy of Denosumab in managing osteoporosis.

In China, the use of Denosumab for osteoporosis treatment has been introduced more recently than in other countries, and there is a relative scarcity of relevant clinical studies and reports. Gao[47] conducted a randomized controlled trial involving 40 postmenopausal patients with osteoporosis in China, assigned to an observation group (subcutaneous Denosumab) and a control group (oral Calcium D and Vitamin D tablets), with 20 patients in each group. The treatment lasted one year, and the primary outcomes included changes in bone mineral density, bone metabolism markers, bone pain, activities of daily living, and the incidence of adverse reactions before and after the intervention. The results indicated that the overall clinical efficacy rate in the observation group (90.0%, 18/20) was greater than that in the control group (70.0%, 14/20), with a statistically significant difference ($P < 0.05$). After one year of treatment, bone mineral density at the lumbar spine and hip increased in both groups compared to baseline, with the observation group showing significantly higher BMD compared to the control group ($P < 0.01$). These findings suggest that Denosumab is safe and effective for treating osteoporosis in Chinese patients. However, existing studies in China exhibit limitations, including small sample sizes, short observation periods, and single-center designs. Further large-scale, multicenter, long-term randomized controlled trials are needed to confirm the reliability of this medication.

Impact of Denosumab on Sarcopenia

Currently, research on the effects of Denosumab on sarcopenia in China is limited. However, several international studies have explored Denosumab's potential in improving sarcopenia. Miedany et al,[48] conducted a follow-up study to investigate whether Denosumab, compared to other anti-resorptive agents (such as bisphosphonates), exerts a unique dual effect on both bone and muscle, particularly regarding its potential to alleviate symptoms of sarcopenia. The study involved 135 patients with postmenopausal or age-related osteoporosis treated with Denosumab, compared to a control group of 272 patients divided into two subgroups: 136 receiving Alendronate and 136 receiving Zoledronic Acid. All patients were assessed for bone mineral density, fall risk (FRAS), fracture risk (FRAX), and sarcopenia-related indicators, including grip strength, physical performance, timed-up-and-go test, and 4-meter gait speed. Follow-up assessments were conducted after 5 years of Denosumab treatment, 3 years of bisphosphonate treatment, and 1 year following the cessation of osteoporosis treatment. After 5 years of Denosumab treatment, fall risk was significantly reduced ($P = 0.001$), and all sarcopenia indicators showed marked improvement ($P = 0.01$). However, one year after discontinuing Denosumab, both fall risk and sarcopenia indicators significantly deteriorated ($P = 0.01$). These findings suggest that Denosumab has a beneficial impact, significantly improving both osteoporosis and sarcopenia.

Bonnet et al,[49] along with colleagues, investigated the effects of RANKL inhibitors (Denosumab) on osteoporosis in women and muscle in mice. The study involved women and mice that either overexpressed RANKL (HuRANKLTg+) or lacked Pparb, leading to sarcopenia (Pparb-/-). The results indicated that, in women with osteoporosis, Denosumab treatment for over 3 years resulted in improved appendicular muscle mass and grip strength, while bisphosphonates

showed no such effect. Similarly, in a Denosumab-treated muscle atrophy mouse model, the Denosumab-treated mice exhibited a significant increase in trabecular and cortical bone volume, reduced bone turnover, and greater muscle mass in both the gastrocnemius (16%) and soleus muscles (10%), alongside enhanced limb strength (18%) and maximum speed (33%) when compared to control mice, with all P-values <0.05. The impact of Denosumab on maximum speed remained statistically significant even after controlling for gastrocnemius muscle mass. Additionally, spontaneous motor activity, including fine motor skills, in the Denosumab-treated mice also exhibited a notable increase. In summary, Denosumab, while effectively treating osteoporosis, may also provide a viable strategy for improving or managing sarcopenia.

Evaluation and Current Status of Denosumab

Denosumab, a novel biological agent for the management of osteoporosis, has undergone extensive study and demonstrated efficacy. It is characterized by its low incidence of adverse reactions and minimal side effects,[50] demonstrating a favorable safety profile. Additionally, Denosumab provides convenient administration with infrequent dosing, thereby enhancing patient compliance and adherence. Notably, in comparison with other first-line osteoporosis treatments, Denosumab has a lower "effect-cost", signifying a lower cost per unit of effect, thus indicating superior cost-effectiveness.

Despite the significant efficacy of Denosumab in treating osteoporosis, its long-term safety warrants careful consideration. Recent studies indicate that prolonged use of Denosumab can increase bone mineral density; however, discontinuation can result in significant bone loss, causing BMD to revert to baseline levels and increasing the risk of multiple vertebral fractures, particularly in patients with a history of such fractures.[51,52] Some studies suggest that sequential treatment with alendronate or zoledronic acid following the discontinuation of Denosumab may partially alleviate this decline in BMD.[53,54] Further research is required to explore optimal sequential treatment strategies focused on addressing the decline in BMD and the heightened fracture risk after Denosumab cessation. Patients receiving Denosumab should not discontinue treatment without proper guidance. When considering long-term Denosumab use, clinicians should carefully evaluate the risk-benefit profile for each patient and discuss potential safety considerations. This includes individualized adjustments to the treatment regimen, regular monitoring of bone density, and consideration of additional therapeutic measures, such as calcium and vitamin D supplementation and moderate physical activity, to optimize treatment efficacy and mitigate potential risks.

However, in China, the utilization of Denosumab for osteoporosis management has not kept pace with other countries, resulting in many patients being either unfamiliar with or resistant to the drug and frequently opting for alternative first-line treatments or conservative management strategies. This highlights the need for healthcare professionals to actively advocate for the clinical benefits of Denosumab, considering its demonstrated safety and efficacy, and to position it as a preferred treatment option for eligible patients.

Influence of Other Factors on the Bone-Muscle System

In addition to its effectiveness in inhibiting osteoclast activity, increasing BMD, and reducing fracture incidence by suppressing RANKL, Denosumab has been shown in recent studies to interact with various endocrine and inflammation-related factors that are critical in the pathogenesis of osteoporosis, particularly in elderly patients with hypertension. Research indicates that corticosteroid aldosterone may exert a dual role in bone health, particularly in hypertensive individuals. Elevated plasma aldosterone levels correlate with decreased bone mineral density and an elevated risk of developing osteoporosis. Aldosterone may exacerbate bone resorption by promoting inflammation and oxidative stress, thereby weakening the bone matrix and contributing to osteoporosis.

The study conducted by Song et al[55] demonstrated that spironolactone significantly reduces the risk of osteoporosis and fractures in middle-aged and elderly hypertensive patients. This study underscored the role of antihypertensive medications, including spironolactone, in alleviating the adverse effects of aldosterone on bone metabolism, thereby contributing to reduced bone loss. Furthermore, additional studies have indicated that elevated aldosterone levels exert a dual impact on hyperuricemia and gout, thereby further complicating the clinical manifestations of osteoporosis in hypertensive patients.[56]

Inflammation represents another critical link between hypertension, osteoporosis, and sarcopenia. Chronic systemic inflammation, frequently observed in hypertensive patients, enhances osteoclast activity by upregulating pro-inflammatory cytokines, including IL-6 and TNF-α, thereby contributing to the progression of bone loss. Ma et al[57] reported that systemic inflammatory markers are significantly correlated with reduced bone mineral density (BMD) in elderly hypertensive patients, indicating a direct involvement of inflammation in the pathogenesis of osteoporosis. This inflammatory burden not only adversely affects bone health but also contributes to muscle wasting, thereby further emphasizing the need for comprehensive management strategies for these interconnected conditions.

Furthermore, antihypertensive agents that target the renin-angiotensin-aldosterone system (RAAS), including aldosterone antagonists and angiotensin-converting enzyme (ACE) inhibitors, have demonstrated potential to enhance bone health outcomes. The study conducted by Song et al[57] found that managing aldosterone levels in hypertensive patients positively influences bone mineral density (BMD) while reducing the risk of subsequent fractures. These findings suggest that commonly prescribed antihypertensive medications may concurrently serve a dual purpose in mitigating risks associated with both cardiovascular and bone health, thereby emphasizing the importance of incorporating bone health monitoring and interventions into the management of hypertensive patients.

The aforementioned perspectives may facilitate the development of innovative therapeutic strategies designed to concurrently address osteoporosis, sarcopenia, and their common risk factors, including hypertension and inflammation. The interrelationship among these conditions necessitates further investigation into the roles of aldosterone and inflammation in the pathophysiology of bone and muscle, particularly in the development of personalized treatment regimens for hypertensive patients that target the reduction of osteoporosis and fracture risk.

Summary and Future Directions

This study systematically evaluates the effects of Denosumab in treating osteoporosis and its potential impact on sarcopenia, particularly among the Chinese elderly population. The findings indicate that Denosumab, as a novel anti-osteoporotic agent, demonstrates substantial clinical efficacy. Results from multicenter randomized controlled trials conducted abroad suggest that Denosumab effectively increases bone mineral density while significantly reducing the risk of fractures associated with osteoporosis, thereby reinforcing its status as a first-line treatment for osteoporosis in elderly patients. Regarding its effects on sarcopenia, although relevant studies remain limited, preliminary evidence indicates that Denosumab may have a beneficial effect on muscle function, particularly in terms of improving muscle quality and functional parameters among elderly patients. This finding offers novel insights regarding the application of Denosumab in treating sarcopenia. However, this potential effect remains hypothetical and requires validation through further clinical trial data to substantiate its applicability and efficacy within the Chinese elderly population. Furthermore, the underlying mechanisms through which Denosumab may improve sarcopenia remain poorly understood. The RANK-RANKL-OPG pathway is likely to play a significant role in this process, as it is widely acknowledged for its critical interaction between bone metabolism and muscle function. Nonetheless, there remains a lack of substantial experimental data to verify this hypothesis, leaving the specific effects of Denosumab on muscle quality and function yet to be determined.

Finally, although Denosumab demonstrates robust efficacy and safety in enhancing bone density and reducing fracture risk, potential long-term side effects must be addressed. Among these, rebound bone loss represents a significant clinical concern. Studies have shown that upon discontinuation of Denosumab, bone mineral density may rapidly decline and potentially fall below baseline levels, subsequently increasing the risk of fractures. Moreover, long-term use may be associated with further side effects, including hypocalcemia, increased infection risk, and renal impairment.

In summary, future research regarding the application of Denosumab for the treatment of osteoporosis and sarcopenia within the Chinese population should focus on the following key aspects:

1. Clinical Trials. Undertake large-scale, multicenter, long-term, prospective randomized controlled trials to confirm Denosumab's effectiveness in treating osteoporosis, particularly regarding its potential positive effects on sarcopenia among the Chinese population, including improvements in muscle function and quality. This may include: 1) Investigating the efficacy differences of Denosumab among patients of varying ages, genders, and underlying

conditions to elucidate the response profiles of different subpopulations. 2) Evaluating the combined effects of Denosumab with other medications (such as calcium supplements, vitamin D, and antihypertensive agents) on the comprehensive management of osteoporosis and sarcopenia to identify optimal strategies for combination therapy. 3) Assessing quality of life by incorporating assessment tools and regularly evaluating Denosumab's impact on overall health status and quality of life, particularly regarding functional activities and mental health.

2. Basic Research. Although sarcopenia and osteoporosis share several pathogenic pathways and genetic factors, no clearly defined molecular or signaling pathway clearly elucidates the pathogenesis of sarcopenia. Future research should therefore focus on basic research on sarcopenia to identify more effective therapeutic strategies. Additionally, active exploration of shared molecular pathways in both osteoporosis and sarcopenia is essential for establishing a theoretical foundation to address this comorbidity.
3. Denosumab typically requires long-term administration. As the duration of treatment extends, a more thorough investigation into its long-term safety is critical. This includes monitoring adverse reactions, side effects, patient compliance, and rebound bone loss post-discontinuation. To capture these adverse events, a robust long-term follow-up mechanism must be implemented to regularly evaluate patients' physiological parameters and laboratory data, thereby ensuring timely identification and management of potential issues. Additionally, this approach will aid in determining the optimal treatment duration and sequential therapy regimens after discontinuation.
4. Personalized and Comprehensive Treatment. If clinical trials confirm that Denosumab is effective in treating osteoporosis and sarcopenia in the Chinese population, personalized and comprehensive treatment approaches should be adopted to maximize therapeutic outcomes. Since the clinical manifestations of osteoporosis and sarcopenia can vary among individuals, further research and observation are necessary to determine which patients are the most suitable candidates for Denosumab therapy. Personalized treatment plans are likely to enhance therapeutic efficacy. Furthermore, Denosumab should be combined with other treatment strategies, including nutritional support (a balanced diet, calcium and vitamin D supplementation), physical exercise, and lifestyle modifications, to ensure a more comprehensive and optimal therapeutic effect.
5. Treatment Duration and Discontinuation Management. Given that long-term use of Denosumab may result in a rapid decline in bone mineral density upon discontinuation, it is essential to closely monitor patients when contemplating treatment discontinuation. A well-structured discontinuation plan should be established, and if necessary, transitioning to alternative medications should be considered to mitigate the heightened fracture risk associated with discontinuation.
6. Multidisciplinary Collaboration. In clinical practice in China, adopting a multidisciplinary approach for managing patients receiving Denosumab is recommended, especially for elderly patients with multiple complex comorbidities. Osteoporosis and its associated conditions frequently involve multiple physiological systems; thus, experts from various fields—such as orthopedics, endocrinology, and geriatrics—should collaborate actively in the patient care process. Through the collaboration of a multidisciplinary team, a comprehensive assessment of the patient's bone health, muscle quality, endocrine function, and other factors can be achieved, enhancing the scientific rigor and adaptability of the treatment plan. Moreover, effective communication among clinical teams facilitates the early identification and management of potential complications or safety issues that may arise during the long-term use of Denosumab, such as rebound bone loss or drug interactions, ultimately minimizing risks while optimizing treatment outcomes.

Denosumab, as a promising treatment for osteoporosis and sarcopenia, holds significant promise for patients in China. With further research and investigation, we can gain a more comprehensive and detailed understanding of this drug's efficacy and safety, thereby providing improved treatment options for domestic patients, alleviating their disease burden, and enhancing their overall quality of life.

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Disclosure

The authors report no conflicts of interest in this work.

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