Research Progress in Sequential Treatment for Osteoporosis (Postprint)

Authors: Wang Yanye, Li Mei, Li Mei

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Abstract

As the population enters a stage of deep aging, osteoporosis and its series of complications, such as fractures, have become serious public health issues. According to the mechanism of action, currently potent drugs for treating osteoporosis primarily include bone resorption inhibitors, bone formation promoters, and dual-action drugs; however, monotherapy often struggles to achieve long-term therapeutic effects for osteoporosis. Sequential therapy, through the strategic switching of drugs with different mechanisms of action, aims to achieve sustainable protective effects and reduce the risk of rapid bone loss following the discontinuation of short-acting drugs, making it an inevitable choice for long-term management. Nevertheless, this strategy currently faces challenges such as insufficient evidence-based medical data for optimal sequential regimens, a lack of standardization regarding the timing of transitions, and the need for verification of long-term safety. This article systematically reviews the latest research progress in sequential therapy for osteoporosis, with the aim of providing a reference for the clinical formulation of precise and effective long-term treatment strategies.

Full Text

Preamble

Progress in Research on Sequential Treatment for Osteoporosis

Wang Yanye, Li Mei. Peking Union Medical College Hospital, CAMS & PUMC, Beijing 100730, China.

With the acceleration of population aging and changes in lifestyle, the prevalence of osteoporosis in China has risen rapidly, making it the most common

metabolic bone disease threatening the health of middle-aged and elderly populations. Osteoporosis is characterized by reduced bone mass and the destruction of bone tissue microstructure, which leads to an increased risk of fractures and severely impacts the quality of life for patients. Large-scale epidemiological studies indicate that among people over 40 years old in China, the prevalence of osteoporosis is 5.0% for men and as high as 20.6% for women. According to a 2023 report by the International Osteoporosis Foundation (IOF), approximately 37 million fragility fractures occur annually worldwide among people over 55 years of age; furthermore, one-third of women and one-fifth of men over the age of 50 suffer from osteoporotic fractures. Therefore, preventing and treating osteoporosis to reduce the risk of primary and secondary fractures is of great clinical significance.

The primary pathogenesis of osteoporosis and osteoporotic fractures lies in the imbalance between osteoclast activity and osteoblast function during the bone remodeling process. This imbalance leads to enhanced bone resorption and a relative deficiency in bone formation; persistent disruption of bone homeostasis ultimately triggers the onset of osteoporosis. Targeting this pathogenic mechanism, current pharmacological treatments for osteoporosis primarily include: bone resorption inhibitors (such as bisphosphonates), bone-forming agents (such as parathyroid hormone analogues), and drugs with dual regulatory effects (such as romosozumab). In recent years, treatment strategies for osteoporosis have progressively shifted from generalized pharmacological interventions toward individualized treatment models based on fracture risk stratification [**?**, **?**].

100730 北京市，中国医学科学院

Peking Union Medical College Hospital, Department of Endocrinology, Key Laboratory of Endocrinology of the National Health Commission, Doctoral Supervisor; As the population enters a stage of deep aging, osteoporosis and its associated complications, such as fractures, have emerged as critical public health concerns.

Based on their mechanisms of action, current potent pharmacological treatments for osteoporosis primarily include bone resorption inhibitors, bone formation promoters, and dual-action agents. However, monotherapy often fails to achieve the desired long-term therapeutic outcomes for osteoporosis management. Sequential therapy, which involves the strategic transition between drugs with different mechanisms of action, aims to provide sustainable skeletal protection and mitigate the risk of rapid bone loss following the discontinuation of short-acting medications. Consequently, sequential therapy has become an essential choice for long-term disease management. Nevertheless, this strategy currently faces several challenges, including a lack of sufficient evidence-based medical data for optimal sequential regimens, a lack of standardized timing for drug transitions, and the need for further validation of long-term safety. This article systematically reviews the latest research progress in sequential treatment strategies for osteoporosis, aiming to provide a reference for the development of

precise and effective long-term clinical management strategies.

Keywords: Osteoporosis; Sequential therapy; Bone formation promoters; Bone resorption inhibitors; Review

Abstract

As the population is deeply ageing, osteoporosis and its complications such as fractures have become a serious public health problem. According to the mechanism of action, currently available potent osteoporosis treatments primarily include bone resorption inhibitors, bone formation promoters, and dual-action agents. However, monotherapy often fails to achieve long-term therapeutic effects for osteoporosis. Consequently, sequential therapy with multiple drugs has emerged as an inevitable trend in osteoporosis treatment strategies. This review systematically synthesizes research advances in sequential therapy for osteoporosis, aiming to provide reference for the rational treatment of the disease.

Key words Osteoporosis; Sequential therapy; Bone formation promoter; Bone resorption inhibitor; Review Wang Y Y, Li M. Advances in sequential treatment strategies for osteoporosis[J]. Chinese General Practice，2026. [Epub ahead of print]Editorial Office of Chinese General Practice.

Authoritative guidelines from organizations such as the International Osteoporosis Foundation (IOF), the American Association of Clinical Endocrinologists (AACE), and the Osteoporosis and Bone Mineral Disease Branch of the Chinese Medical Association emphasize the importance of precision treatment based on a patient' s fracture risk. These guidelines recommend adopting sequential therapy strategies for the long-term management of the disease [**?**, **?**]. Currently, drugs such as bisphosphonates, denosumab, teriparatide, abaloparatide, and romosozumab have been widely utilized in clinical research, leading to the gradual development of relatively mature sequential treatment regimens.

However, existing sequential therapies still face significant challenges and limitations. These include a lack of long-term efficacy and safety data, as well as insufficient evidence-based support for specific sequential protocols. Furthermore, determining how to formulate precise sequential treatment strategies based on individual differences and fracture risk stratification remains a primary focus of current research. Therefore, this article aims to review the progress of clinical research related to sequential therapy for osteoporosis and to explore its application value in long-term disease management, with the goal of providing assistance in improving clinical treatment standards.

1 抗骨质疏松症药物的种类与作用机制

Currently, pharmacological treatments for osteoporosis are primarily classified into three categories:

Bone Resorption Inhibitors: These include agents such as bisphosphonates and denosumab. They function by inhibiting osteoclast activity, thereby reducing bone loss, increasing bone mineral density (BMD), and lowering the risk of fractures [**?**].

Bone Formation Stimulators: Agents such as teriparatide and abaloparatide fall into this category. These medications enhance osteoblast activity and promote bone formation, leading to improved bone density [**?**].

Dual-Action Agents: Romosozumab is a representative drug in this class. It functions by inhibiting sclerostin to activate the Wnt signaling pathway, which promotes bone formation. Simultaneously, it acts on the receptor activator of nuclear factor kappa B (RANK) - receptor activator of nuclear factor-kappa B ligand (RANKL) - osteoprotegerin (OPG) (OPG-RANK-RANKL) pathway to inhibit osteoclast activity, reduce bone resorption, and increase bone mineral density.

2.1 药物作用机制与疗程限制

The mechanism of action of osteoporosis medications dictates inherent limitations on their duration of use, making it difficult for a single drug to meet long-term treatment requirements. Bisphosphonates reduce bone resorption by inhibiting osteoclast function; however, long-term use may lead to excessive suppression of bone turnover, accumulation of bone microstructural damage, and an increased risk of atypical fractures and osteonecrosis of the jaw. Furthermore, bone mineral density (BMD) improvement typically reaches a plateau after five years of oral administration or three years of intravenous administration. Clinical guidelines recommend using these drugs for 3 to 5 years; if the fracture risk transitions to low or moderate, a "drug holiday" is advised. Nevertheless, patients experience bone loss and an increased risk of fracture after long-term discontinuation of bisphosphonates. If a new fracture occurs or the femoral neck T-score drops below -2.5 during a drug holiday, anti-osteoporosis treatment must be restarted [**?**]. Denosumab inhibits bone resorption by blocking RANKL, but its discontinuation triggers a RANKL rebound effect, leading to elevated bone turnover markers, a rapid decline in BMD, and a rebound increase in fracture risk. Its longest evidence-based treatment duration is 10 years. Teriparatide is approved for a 24-month course, while sclerostin monoclonal antibodies are approved for only 12 months. Consequently, the discontinuation of short-acting anti-osteoporosis drugs must be followed by sequential treatment with other anti-osteoporosis agents [**?**, **?**]. Since osteoporosis is a chronic metabolic disease that is difficult to arrest with monotherapy, long-term sequential therapy has become an inevitable strategy for its management.

Sequential Therapy Based on Fracture Risk Stratification

Treatment recommendations for osteoporosis advocate for precision therapy strategies based on fracture risk, and sequential treatment regimens should

adhere to this principle. Authoritative Chinese guidelines suggest that for patients at very high risk of fracture, injectable anti-osteoporosis drugs such as zoledronate, denosumab, teriparatide, or romosozumab are recommended as first-line options. For patients at high risk of fracture, denosumab, teriparatide, or oral/intravenous bisphosphonates are preferred. Patients at high risk of fracture should undergo long-term sequential therapy [**?**, **?**].

3.1 骨形成促进剂序贯骨吸收抑制剂

Sequential therapy involving bone-forming agents followed by bone resorption inhibitors has emerged as a critical strategy in the treatment of osteoporosis. By leveraging the synergistic effects of initially promoting bone formation and subsequently inhibiting bone resorption, this approach significantly increases bone mineral density and reduces fracture risk. It is particularly indicated for patients at high risk of fractures.

3.1.1 特立帕肽序贯骨吸收抑制剂

Teriparatide, a recombinant human parathyroid hormone fragment (1-34), significantly stimulates osteoblast activity and promotes bone formation when administered in intermittent low doses. This treatment effectively increases bone mineral density (BMD) in the lumbar spine and femoral neck, thereby significantly reducing the risk of both vertebral and non-vertebral fractures. The approved course of treatment is 24 months; however, patients experience a rapid decline in BMD upon discontinuation. Consequently, sequential therapy with other anti-osteoporosis medications is required to consolidate the therapeutic effects. Clinical studies have demonstrated that following teriparatide with bone resorption inhibitors, such as denosumab or bisphosphonates, results in significant BMD gains and a sustained reduction in fracture risk.

Retrospective studies have shown that initiating denosumab for two years after three months of teriparatide treatment leads to a significantly greater increase in lumbar spine BMD and a lower fracture incidence compared to denosumab monotherapy. Furthermore, the DATA-Switch randomized controlled trial demonstrated that a sequence of two years of teriparatide followed by two years of denosumab results in a continuous increase in BMD at the lumbar spine and hip (lumbar spine +18.3%, total hip +6.6%, and femoral neck +8.3%).

Low fracture incidence ($P < 0.001$)

Similarly, administering alendronate for 12 months following 18 months of teriparatide treatment reduces the risk of vertebral fractures more significantly than 30 months of alendronate monotherapy ($P < 0.05$) [**?**]. Additionally, retrospective studies comparing the efficacy of sequential therapy using zoledronic acid versus denosumab after teriparatide found that both groups showed significant increases in lumbar spine and hip BMD, along with reduced fracture rates (13% vs. 15%). No significant difference in efficacy was observed between the

two groups, suggesting that both bisphosphonates and denosumab are viable options for sequential therapy following teriparatide.

3.1.2 阿巴洛肽序贯骨吸收抑制剂

Abaloparatide is an analog of parathyroid hormone-related peptide (PTHrP). It exerts its effects by binding to the parathyroid hormone type 1 receptor (PTH1R).

Chinese General Practice. Bone mineral density (BMD) changes. Bone-forming agents → Bone resorption inhibitors: Postmenopausal osteoporosis (PMOP). Teriparatide → Alendronate: Female patients with primary osteoporosis at high risk of fracture. Abaloparatide → Alendronate: PMOP. Bone resorption inhibitors → Bone-forming agents: PMOP. Bisphosphonates → Teriparatide: PMOP. Denosumab → Teriparatide: PMOP. Sequential bone resorption inhibitor therapy: PMOP. Bisphosphonates → Denosumab: PMOP. Primary osteoporosis.

Denosumab (treatment duration $>$ 2 years) → single dose of zoledronic acid at baseline.

Denosumab → Romosozumab sequential regimen for PMOP. Romosozumab (12 months) → Denosumab (12 months) for PMOP. Romosozumab → Denosumab (12 months) vs. continuous Denosumab for 10 years in PMOP. Romosozumab (24 months) → Denosumab (12 months) for PMOP. Romosozumab (12 months) → Alendronate (12 months) vs. continuous Alendronate for PMOP. Romosozumab → Ibandronate (12 months) for primary and secondary osteoporosis. Romosozumab → Teriparatide (12 months) vs. Teriparatide → Romosozumab (12 months). Romosozumab (12 months) → Bisphosphonates/Denosumab vs. Teriparatide → Romosozumab (12 months). Romosozumab retreatment in patients with osteoporosis at very high risk of fracture. BMD of the lumbar spine and hip in both groups.

The risk of vertebral fracture was significantly reduced (0.9% vs. 5.6%, $P <$ 0.001).

The increases in BMD at the lumbar spine, femoral neck, and total hip were significantly higher (all $P < 0.001$).

Lumbar spine BMD increased significantly (+1.3%, $P < 0.05$), while BMD at the total hip and femoral neck did not increase (-2.2% and -1.1%, respectively, $P < 0.05$).

BMD increased at the lumbar spine (+14%), femoral neck (+4.9%), and total hip (+2.8%), while radial BMD decreased (-1.8%).

The increases in BMD at the total hip, femoral neck, and lumbar spine were all significantly higher than those in the control group ($P < 0.001$) in this randomized controlled trial.

No new vertebral or non-vertebral fractures were observed. Lumbar spine BMD decreased (-0.68%), and the decrease in BMD became more pronounced as the duration of prior denosumab treatment increased.

The incidence of vertebral fractures was reduced by 75% (0.6% vs. 2.5%; $P < 0.001$).

BMD at the lumbar spine, total hip, and femoral neck continued to increase ($P < 0.001$).

The increase in BMD at the lumbar spine and hip was similar to that observed with 7 years of continuous denosumab treatment.

分析

Bone mineral density (BMD) increased in the lumbar spine and total hip by 19.4% and 7.1%, respectively.

The risk of new vertebral fractures was reduced by 48% (6.2% vs. 11.9%; $P < 0.001$), and the risk of hip fractures was reduced by 38% (2.0% vs. 3.2%; $P < 0.05$).

The increases in BMD at the lumbar spine and total hip were significantly higher than those in the control group (14.9% vs. 8.5% and 7.0% vs. 3.6%, respectively; $P < 0.001$).

Sequential treatment with denosumab for 12 months resulted in a significantly greater increase in lumbar spine BMD compared to sequential treatment with ibandronate ($P < 0.05$).

The increases in BMD at the lumbar spine, total hip, and femoral neck were lower than those observed in the control group.

In a regimen of teriparatide for 18 months followed by alendronate for 12 months, compared to 30 months of continuous alendronate, the incidence of vertebral fractures was significantly reduced ($P < 0.01$).

Switching from bisphosphonates to denosumab for 12 months, compared to continuous bisphosphonate therapy, led to a significant increase in lumbar spine BMD; however, changes in BMD at the femoral neck and total hip exhibited heterogeneity.

分析

In patients with osteoporosis, transitioning from denosumab (treatment duration <3 years) to a single dose of zoledronic acid resulted in a significant increase in bone mineral density (BMD) at the lumbar spine and femoral neck (+9.1% and +6.1%, respectively; $P < 0.05$).

For patients receiving denosumab for an average of 3 years, transitioning to a single dose of zoledronic acid led to BMD increases in the lumbar spine, total hip,

and femoral neck (+6.4%, +2.4%, and +2.0%, respectively), with no occurrences of multiple vertebral fractures. However, in patients treated with denosumab for >3 years, a single dose of zoledronic acid was associated with a decrease in lumbar spine and hip BMD ($P < 0.05$). Conversely, when patients treated with denosumab for >3 years received two doses of zoledronic acid, BMD at the lumbar spine and hip remained stable during the second year of zoledronic acid treatment. In cases of primary osteoporosis, transitioning from denosumab to two doses of zoledronic acid generally resulted in a significant decrease in lumbar spine BMD; however, lumbar spine BMD remained stable in patients with C-terminal telopeptide of type I collagen (CTX) levels <280 ng/L. Other sequential regimens studied include 12 months of placebo followed by 12 months of denosumab, and 24 months of romosozumab followed by 12 months of placebo, as well as 12 months of romosozumab followed by 12 months of denosumab.

Retrospective analysis demonstrated that the proportion of patients with T-scores >-2.5 at the lumbar spine, total hip, and femoral neck increased significantly from baseline ($P < 0.001$).

The ACTIVE trial and its extension study demonstrated that 18 months of abaloparatide followed by 24 months of alendronate significantly increased BMD and reduced the risk of vertebral fractures in postmenopausal women with osteoporosis compared to a placebo-to-alendronate sequence. Abaloparatide acts on the parathyroid hormone 1 receptor (PTH1R) to exert pro-osteogenic effects [**?**]. Consequently, sequential therapy using bone-forming agents (such as teriparatide and abaloparatide) followed by antiresorptive agents can effectively and continuously improve BMD and reduce fracture risk. This approach is particularly suitable for patients at high or very high risk of fracture. Regarding the transition from antiresorptive agents to bone-forming agents, long-term antiresorptive therapy has certain limitations. Bisphosphonates significantly inhibit bone turnover, potentially increasing the risk of atypical fractures and osteonecrosis of the jaw. Although patients may enter a "drug holiday," the risk of fracture may rise again as the holiday extends, necessitating the resumption of anti-osteoporosis treatment. Furthermore, the discontinuation of denosumab is associated with accelerated bone loss and an increased risk of fracture; therefore, an effective sequential osteoporosis medication is required following the cessation of antiresorptive therapy.

Research indicates that in postmenopausal women with osteoporosis previously treated with bisphosphonates (alendronate, risedronate, or etidronate), sequential treatment with teriparatide for two years significantly increases BMD in the lumbar spine and hip. In patients with long-term bisphosphonate exposure (median duration of 7 years), sequential teriparatide significantly increased lumbar spine BMD; however, total hip BMD experienced a transient decline during the initial phase of treatment, and no significant increases were observed in total hip or femoral neck BMD over the two-year period. The DATA-Switch study found that transitioning from denosumab to teriparatide resulted in a decline in BMD during the first 6 to 12 months, followed by a continuous increase in

lumbar spine, total hip, and femoral neck BMD. Notably, radial BMD continued to decline throughout the entire treatment period. These findings suggest that the efficacy of transitioning from antiresorptive agents to bone-forming agents is complex. Potent antiresorptive agents require a longer duration of subsequent bone-forming therapy to achieve sustained benefits. Furthermore, the development of more potent bone-forming agents remains a priority.

Sequential Treatment Between Different Antiresorptive Agents

Sequential therapy using different classes of antiresorptive agents is a strategy worth exploring for the long-term management of osteoporosis. Studies have shown that the efficacy of different sequential regimens varies significantly and is influenced by the duration of previous treatment, the timing of the drug switch, and the patient' s bone turnover status.

3.3.1 双膦酸盐序贯地舒单抗

Clinical studies have demonstrated that switching from bisphosphonates to denosumab can further increase bone mineral density (BMD). A randomized, open-label study showed that in postmenopausal women with osteoporosis, transitioning from bisphosphonate to denosumab treatment for 12 months resulted in significantly higher BMD gains in the lumbar spine, total hip, and femoral neck compared to continuing bisphosphonate therapy. Furthermore, a meta-analysis of four randomized controlled trials involving 3,290 patients confirmed that sequential treatment with denosumab following bisphosphonates significantly improves lumbar spine BMD in postmenopausal osteoporotic patients. However, the study noted heterogeneity in the BMD changes observed at the femoral neck and total hip.

3.3.2 地舒单抗序贯唑来膦酸

Numerous studies have demonstrated that short-term ($\leq$ 3 years) denosumab treatment followed by a single dose of zoledronic acid can effectively maintain bone mineral density (BMD) without a significant increase in fracture risk [**?**]. However, following long-term ($>$ 3 years) denosumab treatment, a single sequential dose of zoledronic acid is insufficient to inhibit bone loss. In such cases, lumbar spine BMD may decrease significantly, with the magnitude of the decline correlating positively with the duration of prior denosumab therapy. A randomized open-label study initiated sequential single-dose zoledronic acid at 6 months, 9 months, or other time points (such as when bone turnover markers increased) after denosumab discontinuation. The results showed that BMD in the lumbar spine and hip continued to trend downward during the first year of sequential zoledronic acid treatment, only stabilizing during the second year. Retrospective studies have further shown that in patients with osteoporosis who received zoledronic acid 6–7 months after their last denosumab dose, 75% required a second dose of zoledronic acid when serum C-terminal telopeptide of type I col-

lagen (CTX, a bone resorption marker) levels reached $\geq$ 280 ng/L six months later. In this group, lumbar spine BMD still significantly decreased, whereas BMD remained stable in patients with lower CTX levels. Research indicates that patients with significantly elevated bone markers after denosumab discontinuation experience more pronounced BMD loss and require a longer duration of sequential zoledronic acid therapy. Consequently, sequential bisphosphonate therapy after denosumab provides clear benefits: short-term denosumab users can maintain BMD with a single dose of zoledronic acid, while long-term users require multiple sequential doses to sustain the gains in BMD.

Sequential Therapy with the Dual-Action Agent Romosozumab

Romosozumab, which possesses the dual effect of promoting bone formation and inhibiting bone resorption, has become an important treatment option for postmenopausal osteoporosis patients at high risk of fracture. However, the currently approved course for romosozumab is limited to 12 months, making the exploration of subsequent treatment strategies a matter of urgency.

Sequential treatment with romosozumab followed by denosumab can significantly increase BMD and reduce the risk of vertebral fractures. The FRAME study and its extension demonstrated that 12 months of romosozumab followed by 12 months of denosumab significantly reduced the risk of vertebral fractures compared to a placebo-to-denosumab sequence [**?**]. A randomized controlled trial showed that 24 months of romosozumab followed by 12 months of denosumab led to a continuous increase in BMD; conversely, switching to a placebo resulted in a rapid return of BMD to baseline levels. Research also indicates that romosozumab followed by bisphosphonates can reduce fracture risk. The ARCH study showed that 12 months of romosozumab followed by 12 months of alendronate reduced the risk of vertebral and hip fractures. However, the VICTOR study found that the increase in lumbar spine BMD after 12 months of romosozumab followed by 12 months of denosumab was significantly higher than that achieved with sequential ibandronate. Retrospective studies suggest that a history of bisphosphonate treatment may weaken the efficacy of romosozumab followed by zoledronic acid. Therefore, sequential therapy with potent antiresorptive agents (such as denosumab) after romosozumab may provide sustained benefits, while the efficacy of sequential bisphosphonates may be influenced by the specific drug choice and the patient' s prior treatment history.

A retrospective cohort study compared different administration sequences of romosozumab and teriparatide. The results indicated that, compared to the "romosozumab followed by teriparatide" sequence, the "teriparatide followed by romosozumab" regimen showed more significant gains in BMD at the lumbar spine, total hip, and femoral neck. However, these findings require further validation through prospective randomized controlled trials.

For patients at very high risk of fracture, it is recommended to use bone-forming agents first, followed by sequential antiresorptive agents, to better reduce frac-

ture risk; if necessary, long-term multiple sequential treatments may be required. Some studies have shown that even after completing 12 months of initial romosozumab treatment followed by sequential antiresorptive or bone-forming therapy, some patients may still remain at high risk for fractures and require further sequential treatment. A study of 72 patients at very high fracture risk showed that after completing initial romosozumab treatment and receiving sequential therapy with bisphosphonates, denosumab, or teriparatide, a subsequent 12-month course of romosozumab significantly increased bone formation markers and BMD at the lumbar spine and femoral neck, allowing more patients to achieve a BMD T-score > -2.5. This suggests that romosozumab retreatment has positive clinical value for patients at very high fracture risk. Prospective cohort studies have found that, regardless of prior bisphosphonate exposure, 12 months of romosozumab treatment significantly increases BMD in the lumbar spine and femoral neck, with efficacy superior to that of denosumab, although no significant difference was observed between the two groups in total hip BMD. Another study found that in postmenopausal women with osteoporosis previously treated with bisphosphonates, the increase in hip BMD after 12 months of sequential romosozumab was superior to that achieved with teriparatide. This indicates that for patients previously treated with bisphosphonates, sequential romosozumab is more effective at increasing BMD than other anti-osteoporosis medications.

4 总结与展望

Osteoporosis is a chronic metabolic bone disease requiring long-term treatment and scientific management. Sequential therapy, which involves the strategic transition between medications with different mechanisms of action, has become the core strategy for achieving long-term control of fracture risk. This article systematically reviews the sequential treatment pathways for osteoporosis: for patients at very high risk of fracture, it is recommended to initiate treatment with bone-forming agents (teriparatide, abaloparatide) or dual-action drugs (romosozumab). Following the completion of these courses, treatment should transition to potent bone resorption inhibitors (denosumab or bisphosphonates) to consolidate therapeutic efficacy. For patients at high risk of fracture, potent bone resorption inhibitors may be used as first-line options. Short-acting drugs, such as denosumab, carry a risk of rapid bone loss upon discontinuation; therefore, they must be followed by other medications (e.g., transitioning to zoledronic acid after stopping denosumab) to maintain skeletal benefits. During a "drug holiday" from long-acting anti-osteoporosis medications like bisphosphonates, if there is a significant increase in bone turnover markers, a substantial decrease in bone mineral density, or an increased risk of fracture, the drug holiday should be terminated and sequential anti-osteoporosis therapy should be resumed. All patients receiving sequential therapy require continuous monitoring to allow for real-time adjustments of treatment strategies through dynamic assessment, thereby forming a closed-loop long-term management system centered on fracture risk prevention and control.

Despite significant progress in the clinical practice of sequential therapy for osteoporosis, several limitations remain. Currently, the vast majority of clinical studies focus on postmenopausal women, resulting in a lack of evidence-based sequential treatment protocols for male osteoporosis and secondary osteoporosis patients. Regarding safety, long-term use of bone resorption inhibitors (particularly bisphosphonates) may increase the risk of atypical femoral fractures and osteonecrosis of the jaw; however, it remains unclear whether sequential therapy can mitigate these risks. Furthermore, long-term safety data for newer drugs, such as romosozumab, still require further refinement. Clinical practice also faces a lack of standardized timing for sequential transitions; existing protocols are largely based on fixed treatment durations rather than individualized indicators (such as bone turnover marker thresholds). Additionally, no consensus has been reached on the frequency of monitoring bone loss following the discontinuation of denosumab. In summary, the construction of a precise and individualized sequential therapy system will be a key direction for the long-term management of osteoporosis in the future.

Author Contributions: Wang Yanye was responsible for the conception and design of the article, the collection and organization of research materials, and the writing and revision of the manuscript. Li Mei was responsible for the revision of the manuscript, quality control, and peer review, as well as overall responsibility for the article and supervisory management.

The authors declare no conflicts of interest.

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1 Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fracture. As a "silent killer," osteoporosis often remains asymptomatic until a fracture occurs. With the rapid aging of the global population, osteoporosis and its associated fragility fractures have become a major public health challenge, imposing a significant socioeconomic burden.

Primary osteoporosis is the most common form of the disease, encompassing postmenopausal osteoporosis (Type I), senile osteoporosis (Type II), and idiopathic osteoporosis. To standardize the clinical management of primary osteoporosis in China, the Osteoporosis and Bone Mineral Disease Branch of the Chinese Medical Association has updated the clinical practice guidelines based on the latest international and domestic evidence-based medical data.

2 Epidemiology

The prevalence of osteoporosis increases significantly with age. According to the first large-scale epidemiological survey of osteoporosis in China conducted by the National Health Commission, the prevalence of osteoporosis among people over 50 years old is 19.2%, with 32.1% in women and 6.0% in men. Among those over 65 years old, the prevalence reaches 32.0%, with 51.6% in women and 10.7% in men.

Fragility fractures are the most serious consequence of osteoporosis. Common sites include the vertebrae, hip, distal forearm, and proximal humerus. Hip fractures are particularly devastating, associated with high rates of disability and mortality within the first year following the injury.

3 Pathogenesis

The maintenance of bone health depends on the dynamic balance between bone resorption by osteoclasts and bone formation by osteoblasts, a process known as bone remodeling. In primary osteoporosis, this balance is disrupted.

In postmenopausal osteoporosis, estrogen deficiency leads to an increase in the lifespan and activity of osteoclasts, resulting in bone resorption that exceeds bone formation. In senile osteoporosis, the primary factors include a decline in osteoblast function, secondary hyperparathyroidism due to vitamin D deficiency, and age-related changes in the bone marrow microenvironment.

4 Diagnosis and Differential Diagnosis

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Issues Requiring Attention in the Clinical Treatment of Primary Osteoporosis

Authors: Deng Siqi, Yue Hua **Source:** *Chinese Journal of General Practitioners*, 2024, 23(4): 425-428. **DOI:** 10.3760/cma.j.cn114798-20231114-00247

Abstract

Primary osteoporosis is a chronic systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fracture. With the aging of the global population, the prevalence of osteoporosis is rising significantly. Effective clinical management requires not only pharmacological intervention but also a comprehensive approach involving risk assessment, long-term monitoring, and patient education. This article discusses critical issues in the clinical treatment of primary osteoporosis, emphasizing the importance of standardized diagnosis, individualized treatment strategies, and the management of long-term medication adherence.

Introduction

Primary osteoporosis is a major public health concern, particularly among postmenopausal women and the elderly. It is often referred to as a "silent disease" because bone loss occurs without symptoms until a fracture happens. The primary goal of treatment is to prevent fractures, especially fragility fractures, which are associated with high morbidity, mortality, and significant healthcare costs. Despite the availability of effective therapies, several challenges remain in clinical practice, including low diagnosis rates, inadequate treatment initiation, and poor long-term adherence to therapy.

Standardized Diagnosis and Risk Assessment

The foundation of effective treatment lies in accurate diagnosis and comprehensive risk assessment. While Dual-energy X-ray Absorptiometry (DXA) remains the gold standard for measuring Bone Mineral Density (BMD), clinicians must also integrate clinical risk factors into their decision-making process. The Fracture Risk Assessment Tool (FRAX) is a valuable instrument for identifying patients at high risk of fracture who may benefit from pharmacological intervention even if their BMD T-scores do not meet the traditional threshold for osteoporosis (T-score ≤ -2.5).

Furthermore, it is essential to differentiate primary osteoporosis from secondary causes. Laboratory investigations should be conducted to rule out conditions such as hyperparathyroidism, vitamin D deficiency, and multiple myeloma, which may require specific management strategies alongside or instead of standard anti-osteoporotic therapy.

Individualized Pharmacological Treatment

The selection of anti-osteoporotic medications should be

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Developing Population Medicine to Realize the "People' s Health-Centered" Philosophy

The core philosophy of "centering on people's health"represents a significant shift in the paradigm of medical practice and public health strategy. To effectively implement this vision, the development of Population Medicine has emerged as a critical disciplinary necessity. Population Medicine integrates clinical medicine, public health, and rehabilitative medicine to address health issues at a collective level, moving beyond the traditional focus on individual patient care to encompass the well-being of entire populations.

The advancement of this field requires a multi-dimensional approach. First, it necessitates the restructuring of medical education to foster a comprehensive understanding of health determinants, including social, environmental, and biological factors. By equipping future medical professionals with the tools of Population Medicine, the healthcare system can transition from a reactive "disease-centered" model to a proactive "health-centered" model. This transition is essential for managing chronic diseases and addressing the health disparities that persist across different demographic groups.

Furthermore, the integration of information technology and big data plays a pivotal role in the evolution of Population Medicine. The ability to collect, analyze, and utilize large-scale health data allows for more precise interventions and informed policy-making. By leveraging these technological advancements, healthcare providers can identify high-risk populations more accurately and implement preventive measures that are both cost-effective and impactful.

Ultimately, realizing the "people' s health-centered" philosophy through Population Medicine requires a collaborative effort across various sectors of society. It is not merely a clinical challenge but a social imperative that demands the alignment of healthcare delivery, public policy, and community engagement. Through the systematic development of Population Medicine, we can build a more resilient and equitable healthcare system that prioritizes the long-term health and vitality of all citizens.

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Abstract

Background: The prevalence of chronic kidney disease (CKD) is increasing globally, and it is frequently associated with cognitive impairment, which significantly impacts the quality of life and prognosis of patients. While physical exercise is generally considered beneficial for cognitive function, its specific effects and the optimal exercise modalities for patients with CKD remain a subject of ongoing investigation.

Objective: This study aims to systematically evaluate the effects of different exercise interventions on cognitive function in patients with CKD through a meta-analysis of randomized controlled trials (RCTs).

Methods: A comprehensive search was conducted across major electronic databases, including PubMed, Embase, the Cochrane Library, and Web of Science, to identify RCTs investigating exercise interventions in CKD patients. The

primary outcome measure was the change in cognitive function scores. Data extraction and quality assessment were performed independently by two reviewers. Statistical analysis was conducted using RevMan software, with effect sizes expressed as standardized mean differences (SMD) and 95% confidence intervals (CI).

Results: A total of [N] studies involving [N] participants were included in the final analysis. The results indicated that exercise interventions significantly improved overall cognitive function in patients with CKD compared to control groups (SMD = [Value], 95% CI [[Lower], [Upper]], $P < 0.05$). Subgroup analyses suggested that aerobic exercise and combined aerobic and resistance training were particularly effective. Furthermore, the duration and frequency of the exercise programs influenced the magnitude of the cognitive benefits.

Conclusion: Exercise interventions, particularly aerobic and combined training, are effective in improving cognitive function in patients with chronic kidney disease. Clinicians should consider incorporating structured exercise programs into the comprehensive management of CKD to mitigate cognitive decline. Further high-quality RCTs are needed to determine the most effective exercise prescriptions regarding intensity and long-term sustainability.

Keywords: Chronic kidney disease; Cognitive impairment; Exercise intervention; Meta-analysis; Randomized controlled trials.

Introduction

Chronic kidney disease (CKD) has emerged as a major global public health challenge, characterized by a progressive loss of renal function over time. Beyond the traditional complications of cardiovascular disease and metabolic bone disorders, cognitive impairment is increasingly recognized as a significant comorbidity in this population. Patients with CKD often experience deficits in executive function, memory, and attention, which can lead to decreased treatment adherence, increased hospitalization rates, and higher mortality.

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Note: Figure translations are in progress. See original paper for figures.