

# Proactive Intervention and Multidimensional Collaboration: Prevention and Comprehensive Management of Osteoporosis in Perimenopausal and Postmenopausal Women

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**Abstract.** The clinical burden of osteoporosis in perimenopausal and postmenopausal women is becoming increasingly prominent. The disease has a well-defined onset stage: perimenopause is a critical window for accelerated bone loss, while the five to ten years after menopause are a peak period for fractures. Epidemiological surveys show that the prevalence in Chinese women over 50 years old is nearly half, and the disease continues to rise with age. Its core mechanism is enhanced bone resorption and insufficient bone formation caused by a sudden drop in estrogen levels. Combined with calcium and vitamin D deficiency and genetic susceptibility, this ultimately leads to a sharp increase in the risk of vertebral and hip fractures. Clinical treatment primarily involves drugs such as bisphosphonates and denosumab, which can reduce fracture incidence, but poor adherence to treatment and long-term adverse effects limit their widespread use. Lifestyle interventions such as resistance training and calcium and vitamin D supplementation, while effective adjunctively, are rarely effective alone in high-risk populations. Emerging therapies, such as drugs targeting the RANKL pathway and stem cell therapy, are being explored, but the evidence remains insufficient to support routine use. This review aims to clarify the epidemiology, molecular mechanisms, and progress in prevention and treatment of this disease, and to propose possible approaches for individualized and multidisciplinary management in the future.

## 1. Introduction

Perimenopausal and postmenopausal osteoporosis has emerged as a major public health concern amid global population aging. The perimenopausal stage, extending from the onset of menopausal transition to one year after menopause, represents a critical period of accelerated bone loss. Postmenopausal osteoporosis, typically occurring five to ten years after menopause, is classified as Type I primary osteoporosis and is characterized by low bone mass and deterioration of bone microarchitecture, which together increase bone fragility and fracture risk. The prevalence of this condition among women over fifty in China continues to rise with age, posing substantial medical and socioeconomic burdens.

Estrogen deficiency plays a central role in disease pathogenesis by disrupting the equilibrium between bone resorption and bone formation. Reduced estrogen levels accelerate bone turnover, while inadequate calcium and vitamin D intake and genetic susceptibility further exacerbate bone deterioration. Clinically, patients often present with low back pain, loss of height, and vertebral or hip fractures. Hip fractures are particularly devastating, with a high one-year mortality rate and long-term disability in many survivors. These outcomes highlight the need to redefine osteoporosis management as a process of early risk identification and continuous

prevention rather than delayed pharmacological intervention.

Current treatments rely primarily on pharmacological and lifestyle approaches. Bisphosphonates, denosumab, selective estrogen receptor modulators, hormone replacement therapy, and teriparatide remain the mainstays of therapy, though adherence and safety issues limit their long-term utility. Lifestyle interventions such as resistance and balance training, adequate calcium and vitamin D intake, and smoking and alcohol reduction provide additional benefits but show variable efficacy across individuals. New strategies, including stem cell therapy, agents targeting the RANKL pathway, and combination regimens, show promise yet remain constrained by technical, cost, and safety challenges. This review aims to synthesize current evidence on the epidemiology, pathogenesis, and management of perimenopausal and postmenopausal osteoporosis and to explore the development of individualized and multidisciplinary approaches for long-term bone health.

## 2. Critical Window and Molecular Mechanism of Bone Loss

Beginning at approximately 35 years of age, women experience a gradual decline in bone mass. During the period of menopause, the rate of bone loss accelerates

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due to increased bone resorption and decreased bone formation. Existing studies have found that age and menopausal status are closely associated with the bone resorption activity of invasive osteoclasts *in vitro*. This is mainly manifested in two aspects: the level of mature cathepsin K protein in osteoclasts *in vitro* is increased in menopausal women and the degree of promoter methylation of the dendritic cell-specific transmembrane protein gene decreases with age. These two findings indicate a close link between enhanced bone resorption capacity and age as well as menopausal status [1]. Proteomic studies have further revealed the key regulatory factors at the molecular level. It has been found that progranulin (PGRN) is a key regulator of bone mineral density (BMD) for postmenopausal women. Mechanistic studies show that there is a positive feedback regulatory loop between PGRN and estrogen signaling. In addition, the loss of PGRN leads to a reduction in the level of estrogen receptor  $\alpha$  (ER $\alpha$ ) by enhancing K48-linked ubiquitin-dependent degradation. Since ER $\alpha$  is a crucial receptor for estrogen to regulate osteoporosis, which suggests that estrogen-mediated inhibition of osteoclastogenesis and bone resorption, as well as the protective effect against ovariectomy-induced bone loss, mainly depend on the level of PGRN. Epidemiological surveys provide strong support for this pathophysiological evidence. A study measured the BMD of the femoral neck (FN), lumbar spine (LS), and the whole body in 1062 women aged 40 to 59 years using Dual-energy X-ray Absorptiometry (DXA). Each woman underwent two BMD measurements with an interval of approximately two years. After excluding the correlation between changes in BMD and changes in body weight and fat mass, the results showed that the changes in FN BMD of all perimenopausal and postmenopausal women in the study could be divided into three phases: a mean annual decline of 0.51% in the 45-49 age group; a significant acceleration compared to the previous phase, with a mean annual decline of 1.39% in the 49-54 age group; and a slowdown to a mean annual decline of 0.31% after the age of 55 [2]. Combining molecular mechanisms and clinical observations, it can be seen that the perimenopausal period is a critical window for profound changes in women's bone metabolism. Therefore, in this critical period of perimenopause, the prevention and intervention of osteoporosis in middle-aged and elderly women are of great significance. It can not only delay the process of bone loss but also significantly reduce the risk of postmenopausal osteoporosis and fractures.

### 3. Risk Assessment and Early Identification of Osteoporosis

Conventional methods generally involve the use of medications to treat osteoporosis in menopausal and perimenopausal patients. Systematic reviews and network meta-analyses have shown that bisphosphonates and denosumab could effectively reduce hip fractures, clinical and radiological vertebral fractures, and other clinical fracture symptoms in perimenopausal and postmenopausal women with osteoporosis. However,

long-term use of bisphosphonates for 36 months or longer may conversely increase the risk of atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ), although the incidence rate is relatively low. While abaloparatide and teriparatide alleviate clinical and radiological vertebral fracture symptoms, they significantly increase the risk of fractures caused by adverse events (WAEs). The use of raloxifene and bazedoxifene for 36 months or longer can reduce radiological vertebral fracture symptoms, but has little effect on alleviating clinical fracture symptoms. In addition, sequential administration of alendronate following treatment with abaloparatide, teriparatide, or romosozumab has been reported to further reduce the incidence of clinical fractures in postmenopausal women at high fracture risk within 17 to 24 months compared with bisphosphonate monotherapy. However, the efficacy is not significant, and it is accompanied by the drawback of complex treatment methods [3]. Estrogen replacement therapy (ERT) can inhibit osteoclast activity, reduce bone loss, and lower the risk of fractures. Studies have found that transdermal estrogen therapy can increase or maintain the BMD of the lumbar spine, femoral greater trochanter, and mid-radius in women with osteoporosis, and effectively reduce the incidence of vertebral fractures [4]. However, long-term use of estrogen replacements after menopause may increase the risk of breast cancer, which limits their widespread application [5].

Due to issues such as poor compliance, insufficient long-term safety, and limited efficacy in conventional medication therapy, the prevention and treatment of osteoporosis need to shift toward earlier intervention, with emphasis on risk assessment and early identification. In recent years, molecular markers have gradually gained attention in bone metabolism research. Studies have shown that the miR-424/503 cluster inhibits the Wnt/ $\beta$ -catenin signaling pathway by targeting two binding sites in the 3'UTR region of the LRP6 co-receptor [6]. The Wnt signaling pathway is a key pathway involved in osteoporosis. It participates in bone development and metabolism, and is also involved in the differentiation and proliferation of chondrocytes, mesenchymal stem cells, osteoclasts, and osteoblasts. Inhibiting the activation of the canonical Wnt signaling pathway can prevent the proliferation and differentiation of osteoblasts [7]. Therefore, clinically, the detection of the level of the miR-424/503 cluster in patients can, to a certain extent, help infer the risk of osteoporosis in patients and enable intervention. In addition, miRNAs have been proven to be essential post-transcriptional regulators of bone development and homeostasis. The detection of miRNAs released into the blood using highly sensitive methods such as quantitative PCR provides a potential tool for the prediction and screening of osteoporosis [8]. Another group of studies has focused on pre-osteoblasts. Research has found that there is a positive correlation between the number of human circulating osteoprogenitor cells (cOCPs) and osteoclast activity, and the sorted cOCPs have a higher potential to differentiate into osteoclasts compared with other myeloid cells. Among untreated postmenopausal women,

circulating levels of cOCs vary considerably, showing a negative correlation with lumbar spine BMD and a positive correlation with serum C-terminal telopeptide of type I collagen (CTX), a biochemical marker of bone resorption. This indicates that the level of cOCs is closely related to the occurrence and development of osteoporosis, and it is expected to serve as an auxiliary indicator for early identification and risk stratification in the future [9]. In summary, the management of osteoporosis should not rely solely on post-diagnosis medication therapy. Instead, risk assessment and early identification should be conducted through the detection of molecular markers and cytological indicators during the perimenopausal period and even earlier stages. Through this strategy of shifting intervention to an earlier stage, it is expected to achieve a transformation in the disease prevention and control model, extending from single treatment to prevention and individualized management.

## **4. Multidimensional Strategies for Comprehensive Management of Osteoporosis**

### **4.1 Nutritional Interventions and Dietary Optimization**

The combined supplementation of calcium and vitamin D is regarded as the most fundamental intervention measure. A meta-analysis showed that dairy products rich in calcium and vitamin D can improve BMD in postmenopausal women, and the combined supplementation of calcium and vitamin D can effectively prevent hip fractures in postmenopausal women [10]. A large-scale study involving 48,584 postmenopausal women found no significant association between magnesium intake and fracture risk. However, among women with a calcium-to-magnesium intake ratio of 1.7 or higher, a calcium intake exceeding 400 mg per day was associated with an approximately 40%–50% reduction in fracture risk. As a macronutrient, protein is an important component of bones and plays a crucial role in the prevention and treatment of osteoporosis [11]. Adequate vitamin K intake is necessary to obtain sufficient carboxylated vitamin K-dependent proteins, such as osteocalcin and matrix Gla protein (MGP), which are of great significance for preventing bone health problems. Meanwhile, studies have found that increasing the intake of soy isoflavones can also reduce the risk of osteoporotic fractures (OF), and this negative correlation is more pronounced in women who have been menopausal for nearly 10 years.

### **4.2 Exercise-Based Bone Health Enhancement**

Exercise training has been consistently demonstrated to enhance BMD and improve skeletal microarchitecture. Among various modalities, resistance training, particularly programs involving low loads with high repetitions, has shown notable efficacy in increasing BMD in both the extremities and the lumbar spine. A

controlled study involving twenty sedentary but otherwise healthy adults demonstrated that participants performing full-body, high-intensity, low-load exercises achieved significant increases in BMD compared with baseline values, with improvements observed in the arms (+4%,  $p < 0.001$ ), legs (+8%,  $p < 0.01$ ), pelvis (+6%,  $p < 0.01$ ), and lumbar spine (+4%,  $p < 0.05$ ). These results suggest that low-load, high-repetition resistance training is an effective and practical approach to enhance bone density in adults [12]. Another study used meta-analysis to evaluate 666 participants from 18 experiments, and the results showed that the BMD at the femoral neck in the group that performed jump training was significantly higher than that in the group that did not perform jump training. At the same time, compared with no exercise, all types of exercise interventions, including combined exercise, resistance exercise, aerobic exercise, and mind-body exercise, can significantly increase BMD, among which mind-body exercise has the best effect [13].

### **4.3 Pharmacological Approaches in Menopausal Osteoporosis**

Pharmacological intervention still plays an important role in the management of perimenopausal and postmenopausal osteoporosis. A study found that the combined use of estrogen (0.3-0.625 mg/day) and progesterone can effectively increase the BMD level of perimenopausal and postmenopausal women and alleviate symptoms. However, this therapy poses potential risks to patients with breast cancer and those at high risk of venous thrombosis [14]. Transdermal ultra-low-dose estradiol monotherapy can also increase the BMD level in postmenopausal women, but the long-term safety of this therapy is controversial, and its effectiveness in perimenopausal women has not been confirmed. Currently, common osteoporosis drugs on the market, such as alendronate sodium, zoledronic acid, denosumab, and raloxifene, have been proven effective, but the data on their use in perimenopausal women is still insufficient.

### **4.4 Psychological and Behavioral Interventions for Long-Term Adherence**

Osteoporosis is not only a metabolic disease but also closely associated with mental health. Large-scale studies have shown that the presence of fear of falling, previous vertebral fractures, and comorbidities can significantly reduce quality of life, and this depressive mood is independently correlated with the decline in health-related quality of life (HRQOL). Meanwhile, the decrease in estrogen after menopause can affect both BMD and neurotransmitters. Patients with high health literacy can significantly improve treatment compliance, cooperate with BMD testing, and achieve better health behavior. Therefore, improving patients' health literacy, enhancing social support, and alleviating patients' depressive mood all have significant effects on the treatment and prevention of osteoporosis. Thus, psychological and behavioral intervention has become an

indispensable part of the comprehensive management strategy.

## 5. Challenges and Future Prospects in Osteoporosis Management

### 5.1 Integration of Digital Health Technologies for Long-Term Monitoring

In recent years, with the rapid growth of the wearable device market and the popularization of wearable devices, it has become possible to use wearable devices for the prevention and management of osteoporosis in perimenopausal and postmenopausal women. Current wearable devices already have the function of collecting multi-modal data such as heart rate, electrocardiogram (ECG), and blood oxygen. However, most devices are used for short-term prediction, and most of them are single-device and single-point prediction. If technical limitations can be overcome, and sensors can be used for long-term dynamic monitoring of BMD and bone quality in multiple parts of the human body, it will surely provide continuous data support for risk assessment and early intervention of osteoporosis in perimenopausal and postmenopausal women, and may reshape the future management model.

### 5.2 Toward Personalized and Molecularly Guided Prevention

Molecular markers and emerging technologies have provided new possibilities for the precise prevention and treatment of osteoporosis. Small biological molecules such as miRNAs have been proven to be closely related to bone metabolism. By screening the molecular levels in blood samples of perimenopausal and postmenopausal women at high risk of osteoporosis, and tracking the personalized changes in molecular levels based on individual differences of each patient, it is expected to achieve personalized risk stratification and intervention. This model can not only improve the effectiveness of prevention but also avoid the risks of over-treatment or under-treatment in traditional methods.

### 5.3 Establishing an Integrated Care Network Linking Hospitals, Communities, and Families

The treatment of osteoporosis should not be limited to medication therapy in hospitals; instead, it should involve communities and families for multi-dimensional prevention and management. For the prevention and management of osteoporosis in perimenopausal and postmenopausal women, communities can organize educational activities on osteoporosis prevention to help elderly women recognize the harms of unhealthy lifestyles. Family members should also promptly correct the unhealthy living habits of elderly women. For patients who have already been diagnosed, family members should encourage them to stay away from negative emotions such as depression and anxiety, and actively follow doctors' advice for treatment.

## 6. Conclusion

This study reviewed the epidemiological characteristics and molecular basis of osteoporosis in perimenopausal and postmenopausal women, emphasizing that perimenopause is a critical period of rapid bone mass loss. Targeting this time window, a combination of bone density monitoring, nutritional interventions, personalized exercise prescriptions, medications, and psychological support can significantly slow bone loss before fractures occur, thereby altering the trajectory of disease progression. This approach avoids the previous limitation of passive treatment only after fractures or severe osteopenia. However, several practical challenges remain in its implementation. Existing assessment tools lack predictive accuracy across diverse populations, patient compliance with long-term calcium supplementation, regular exercise, and medication interventions is poor, and the coordination mechanisms between hospitals, communities, and families are not well-established. These issues limit the widespread implementation of comprehensive strategies. Future research should focus on developing high-precision risk prediction tools that integrate multi-omics and clinical indicators, exploring the application of wearable devices and digital platforms for long-term follow-up and adherence management, and validating the sustained benefits of multidimensional interventions through large-scale clinical trials. Gradually establishing a continuous care system covering hospitals, communities and families will enable perimenopausal and postmenopausal women to obtain stable and continuous bone health management at different stages of care.

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