**CHAPTER TITLE**

**Primary Postmenopausal Osteoporosis**

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**The Review of a Female Postmenopausal with Primary Osteoporosis.**

 **Abstract**

According to the World Health Organisation (WHO), natural menopause is defined as at least 12 months of amenorrhoea that are not brought on by pathological or physiological factors. According to statistics, the average age for natural menopause is fifty-one in developed countries. At the same time, it is 48 years in developing and underdeveloped countries.1. The majority of women will live longer compared to one-third of their adult lives after going through the menopausal transition, with an average lifespan of 70 years. In addition, as the ageing population grows faster than ever, the percentage of menopausal women is increasing. As a result, menopausal women's health has gained international attention. Apoptosis, or programmed cell death, is the cause of primary ovarian failure, which leads to the natural physiological phenomenon known as menopause. As we age, our ovarian function decreases. Follicle-stimulating hormone levels rise along with a decrease in oestradiol production when menopause begins (FSH). Women will go through several uncomfortable symptoms through their menstrual period, including dyspareunia, atrophy of the vagina and dryness, mood swings, hot flashes, and night sweats. In addition to these, bone loss is the most common condition affecting women going through menopause and is closely linked to a lower quality of life; in this review, we focus on osteoporosis that occurs after menopause.

**Keywords**: Menopause, mineral density, primary osteoporosis, osteoporotic fracture, and menopause hormone therapy

**1. Introduction**

Micro-architectural deterioration of the bone tissue leading to bone fragility and low bone mineral density (BMD) are the hallmarks of osteoporosis, a multifactorial systemic skeletal disease. The gold standard for identifying osteoporosis is dual X-ray absorptiometry-measured bone mineral density (BMD). The WHO defines osteoporosis as having a T-score of less than or equal to 2.5, while osteopenia is defined as having a T-score between 1.0 and 2.5. The suggested anatomic continent of interest is the lumbar spine and femoral neck.3 Because BMD declines with age, primary osteoporosis primarily affects women 10–15 years postmenopausal and older men 75–80 years of age. Osteoporosis and fractures caused by it are rapidly becoming significant public health concerns that place a significant financial strain on healthcare resources due to the ageing population**.**

**2. The postmenopausal osteoporosis pathogenesis**

Reaching peak bone mass is crucial for maintaining bone health and for averting osteoporosis and the fractures that follow in later life. It has been reported that a ten per cent rise in the maximum amount of bone could reduce hip fractures by 30%.2. The accretion of bone mass begins during childhood and goes on into adulthood. The hip and spine can reach their maximum bone mass in the mid-20s, while other bones, like the radius, peak at 40 years of age. The mass of bone usually decreases after that. The bone mass has reduced by 30–40% by the time one reaches the age of 70.4 Genetic factors are the primary factor that determines the peak bone mass. Numerous genetic variants, including those involving the receptor activator of NF-kB (RANK) route genes, bone marrow protein (OPG), sclerostin (SOST), low-density lipoprotein receptor-related amino acids 5 (LRP5), and oestrogen receptor 1 have been linked in studies to bone mass.5. It has been discovered that hormone status, particularly level of oestrogen, controls the accretion of bone mass. Other variables, such as exercise, smoking, and nutrition may also influence the development of maximum bone mass accumulation.

 Maintaining bone density necessitates ongoing remodelling of healthy bone. It has been estimated that this process updates approximately 10% of the bones annually.8 The two types of cells that make up the multicellular unit that is the bone are osteoclasts, which resorb bone, and osteoblasts, which form new bone. These cells work together well to maintain the proper balance between the formation and resorption of bone. The resting phase, activation phase, resorption phase, reversal phase, and formation phase are the five stages of normal bone remodelling. First, osteoclasts are drawn to the outer layer of the bone, where they dissolve and resorb the mineral makeup of the bone by creating an acidic microenvironment between the cell and the bone's outer layer. Following this, the osteoclasts die, and osteoblasts are drawn to the surface of the bone to deposit collagen, which subsequently mineralises to form new bone.9. Several hormones, including the hormone parathyroid, calcitonin, 1,25(OH)2-vitamin D3, and oestrogen, control this process.

Bone is impacted by oestrogen through the following processes:

1. reducing the amount of calcium excreted from the kidney,
2. increasing the generation of calcitonin, which inhibits bone loss,
3. accelerating resorption of calcium by the intestine,
4. decreasing the importance of bone density to The hormone PTH (parathyroid hormone).
5. oestrogen can also have immediate impacts on the bone because there are oestrogen receptors.

In women, there are two stages to bone loss: The first begins at menopause and mostly affects the trabecular bone. A lack of oestrogen causes it and causes an unwarranted rise in bone resorption relative to formation. One could characterise this stage as bone loss associated with menopause. The second phase, which lasts for 48 years, is primarily caused by a decrease in bone formation and shows a persistent, slower decrease of both the trabecular and cortical bone.11 This is the only stage for men; it's age-related bone loss.

The average BMD decrease throughout the menopause period is 10%. Even more quickly, approximately fifty per cent of women have lost bone, possibly by as many as 10% to 20% in the five to six years leading up to menopause. Fast bone losers, who make up approximately twenty-five per cent of postmenopausal women, can be identified by measuring markers associated with bone resorption and loss.

**3. The osteoporosis epidemic**

The number of elderly people is growing at a never-before-seen rate. There will be more people with osteoporosis as a result of this population explosion. According to estimates, the incidence of osteoporosis increases from one-third in individuals over 50 to over 50% in those over 80. Six million people worldwide—both males and females—will have osteoporosis by the year 2050, with three-quarters of them living in developing nations.

Osteoporotic fractures, which mostly affect the wrist, hip, or spine but can also occasionally affect the humerus or ribs, are the main health risks associated with osteoporosis. Their frequency rises beyond the age of 50. Osteoporotic fractures occur in chronological order, with hip fractures starting in the late 70s and vertebral fractures occurring between 60 and 75 years of age being the first indications, which start at age 50.9. Osteoporotic fractures may result in decreased quality of life, loss of mobility and autonomy, and the emergence of major complications like pneumonia or thromboembolic disease, which have a significant negative impact on both health and the economy. For instance, 20–30% of patients died within the first year following a hip fracture, and the associated costs came to roughly USD 21,000.

Because oestrogen is essential for maintaining bone health, postmenopausal women are more likely than older men to experience osteoporosis and the fractures that result from it. 9.1 million women are estimated to have osteoporosis by the National Bone Loss Foundation (NOF), and more than 26 million are estimated to have low bone mass. This is far more than the estimated 14.4 million men with low bone mass and 2.8 million men with osteoporosis.16 Women are also more likely than men to fracture. A 60-year-old woman's lifetime probability of a fracture is almost 44%, which is almost twice as high as a man's risk of 25% for the same age group. In the US, there were 594,000 broken bones in men over 50 in 2005, compared to approximately 1.45 million broken bones in women over 50.

Race and ethnicity also have an impact on the prevalence of bone loss and osteoporotic fractures globally. Osteoporosis is generally more common in Asian and Caucasian women than in Black women. White women make up the majority of women who suffer osteoporotic fractures in the United States—up to 89% of all fractures—followed by Black and Hispanic women (4% each) and other women (3%).18 In the meantime, the average lifetime chance of a hip fracture in Americans at age 50 is 5.8% for men and 6.0% for women, while it is 2.4% and 1.9% for Chinese and 8.5% and 3.8% for Hispanic women and men. Furthermore, given that the average age for fractures of the hip in the nation of India is in the 60s, contrasted to the 80s in the West, it appears that hip fractures happen earlier in developing nations than in Western nations.19 The overall prevalence of osteoporosis in China among those over 40 was found to be 13.2% in a meta-analysis analysing data on the health status of the country's senior population. Notably, the prevalence is significantly higher in females than in males, at 14.2 11.8% (P < 0.05). As people age, osteoporosis becomes more common among men and women. Although it increases more slowly in men, it becomes more noticeable in women over 50.

**4. Handling osteoporosis after menopause**

Albright and Reifenstein discovered that oestrogen could stop osteoporosis as early as the 1940s. When the link between osteoporosis and menopause was first discovered in the 1960s, oestrogen therapy was used to stop bone loss. These days, a plethora of research has demonstrated the effectiveness of oestrogen in preventing osteoporosis, and hormone therapy remains a viable first-line treatment option for postmenopausal women.

 It has long been established that menopause Hormone Therapy (MHT) considerably raises BMD. The combined results of a systematic review of 57 trials (both treatment and prevention trials) involving approximately 10,000 women suggest that, on average, the MHT connecting (both compared and unopposed oestrogen) had a significantly higher reduction in bone density at all evaluation sites. Following a year, the MHT group exhibited an average 5.4% increase in lumbar spine bone mineral density and 2.5% and 3.0% increases in femoral neck and forearm bone mineral density, respectively. Following two years of therapy, the rate of change in favour of MHT rose by roughly 1.5% across the board, with increases of 6.8%, which is 4.5%, and 4.1% that the femoral neck, forearm, and lumbar spine, respectively.

 In the HOPE trial, 822 healthy postmenopausal women between the ages of 40 and 65 were enrolled. They were then randomly assigned to receive constant daily medroxyprogesterone acetate, at 1.5 mg or 2.5 mg, or daily conjugated equine oestrogen treatment at 0.3 mg, 0.45 mg, or 0.625 mg. A 600 mg calcium supplement was administered to every subject, such as the placebo group. Women assigned to all active treatment groups showed significant increases in spine and hip bone mineral density (BMD) after a year of treatment, with the difference being approximately 3e5% for the spine BMD as well as 1e3% for total hip BMD, when compared to the group receiving the placebo (P < 0.001).

It is important to note that stopping oestrogen causes quick bone loss; most of the higher BMD that had been built up over the previous three to four years vanishes in just a single year. In a randomised trial, MHT increased BMD by 5%–6% in early postmenopausal women 55 years of age. Nevertheless, the MHT group experienced a sharp 7% decline in spine BMD a decade after treatment was discontinued. Hip fractures rose by 50% in two years and 77% in five years, according to a similar analysis.26 For this reason, it is advised that women who stop taking MHT choose alternative forms of osteoporosis prevention.

**5. The opportunity window theory**

Since MHT may be linked to thromboembolism, strokes, breast cancer, and coronary heart disease (CHD), there is a never-ending discussion regarding it.27, 28 How can we balance the risks and benefits of postmenopausal osteoporosis prevention, and when should we begin menopause hormone therapy? The notion of a window of possibilities hypothesis appears as a solution and is now acknowledged by experts from different nations. Research on MHT shows that two groups of postmenopausal women react to MHT in different ways. The age and years postmenopausal determine the varied reactions to MHT. In particular, CHD events and general mortality are reduced when MHT is initiated in women under 60 years of age and within 10 years of postmenopausal age, and the overall advantages outweigh the risks.

On the other hand, there is an insignificant impact and occasionally even a negative effect, if MHT begins in women who are older than 60 and/or who, have gone past menopause by more than 10 years.27 This is the theory of the window of opportunity. Data from the recently released DOPS study28, which indicates that MHT can lower cardiovascular devices in women if begins soon after menopause—also known as the time of rapid bone loss—further supports the hypothesis. Thus, when prescribing hormones to avoid osteoporosis in postmenopausal women, we should consider the timing hypothesis. It makes sense to begin hormone therapy soon after menopause because, as we have already covered, the breakdown of bones has been shown to occur most quickly in the first three to four years following menopause. Since stopping resorption causes the resorption space to instantly fill in or remodel, increasing bone formation and ultimately leading to a greater increase in BMD, this is the time when the response to therapy may be at its highest.

 In cases where the advantages of menopause relief from symptoms outweigh potential risks, the guidelines of the North American Menopause Society suggest that extending treatment for a woman's specific treatment goals is acceptable, provided that the smallest possible dose of MHT is used. Other therapies are not recommended to further prevent osteoporotic fractures or for preserving bone mass in women who have already experienced a reduction in bone mass.9. Based on the reduction of vasomotor symptoms, the smallest effective amount of MHT must be chosen.

According to Chinese menopause guidelines, women under 60 who are at risk for osteoporotic fractures should consider menopause hormone therapy; however, women over 60 should not consider menopause hormone therapy if the primary goal is to prevent osteoporotic fractures.29 MHT ought to be administered and dosed according to individual needs, and treatment-related benefits and risks ought to be carefully considered. The smallest possible dose of MHT ought to be used to prevent osteoporosis, and transdermal preparations have fewer side effects than oral medications. Once hormone therapy is stopped, bone loss will return. If a person is susceptible to osteoporotic fractures, they should take additional preventive medication.

 If women want to prevent osteoporosis, what can we do for them if they are over 60 and/or over 10 years postmenopausal? Additional pharmacological treatments that show promise include denosumab, regenerated human parathyroid hormone, bisphosphonates, and selective oestrogen receptor modulators (SERM). As fundamental nutritional supplements, vitamin D and calcium should be consumed. Lifestyle changes like consistent exercise, giving up alcohol and tobacco, and learning fall prevention techniques can all be extremely important.

**6. Treatment of osteoporosis**

The purpose of pharmacological treatment is to lower the fracture risk.2–4 Drugs for osteoporosis are divided into two groups: anabolic (teriparatide) and antiresorptive **(**bisphosphonates, oestrogen agonist/antagonists, oestrogens, calcitonin, and denosumab). Anabolic drugs promote bone growth more than bone resorption, whereas antiresorptive drugs mainly slow down the process of bone resorption. The Food and Drug Administration (FDA) has not approved all osteoporosis medications to treat GIO, PMO, or osteoporosis in men, even though many of them have overlapping indications (Table 1). Alendronate, risedronate, zoledronic acid, or denosumab are the first-line treatments for the majority of PMO patients who are at high risk of fracture, according to AACE/ACE guidelines. If a patient is in greater danger of fracture and is unable to receive oral therapy zoledronic acid, denosumab, or teriparatide use is advised.

**Table 1. Guidelines for Bisphosphonate Doses**

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| **Bisphosphonate** | **Prophylactic Dose** | **treatment Dose** |
| Alendronate | 5 mg PO once a day or 35 mg PO once every seven days. | 10 mg PO once every day or 70 mg PO once every week |
| Risedronate | 5 mg PO once daily or 35 mg once weekly | 5 mg PO once daily, 35 mg PO once every seven days, or 150 mg PO once every month |
| Zoledronic acid | 5 mg IV every two years | 5 mg IV once a year |
| Ibandronate | 150 mg PO once a month or 2.5 mg PO once a day | 3 mg IV every three months, 2.5 mg PO once daily or 150 mg PO once a month |

Treatment recommendations are determined by some factors, including fracture risk level, gender, and extra risk factors, like concurrent illnesses or drug use.3–6 The AACE/ACE advises starting pharmacological treatment for the following conditions: 1) Individuals suffering from osteopenia either low bone mass and a history of fragility fractures at the hip or spine;2) patients in which there is no fracture but a T-score of –2.5 or less in the lumbar spine, femoral neck, hip, or 33% radius; or3) patients in which a T-score falls between –1.0 and –2.5 if the FRAX 10-year probability is higher than 20% for a major osteoporotic fracture or higher than 3% for a hip fracture. Similar recommendations are made by the Endocrine Society and the NOF for the diagnosis and start of treatment.

**7. Summary**

Osteoporosis, an underlying skeletal disease linked to higher mortality and morbidity, has emerged as a significant public health and economic concern. Given the strong correlation between osteoporosis and oestrogen deficiency, postmenopausal women are particularly vulnerable to primary osteoporosis. Osteoporosis results from the decrease in oestrogen throughout the menopausal transition time frame, which causes a greater loss of bone than formation. Osteoporotic fractures are the main health risk associated with osteoporosis. Postmenopausal women are more likely than older men to experience osteoporosis and related fractures, and this tendency is influenced by ethnicity. Menopause hormonal therapy is thought to be the first line of treatment for the prevention of bone loss because low oestrogen levels are the primary cause of osteoporosis after menopause, and numerous studies have shown its efficacy. However, women who are under sixty years aged and/or less than ten years postmenopausal should consider hormone therapy. The menopause treatment with hormones is not recommended for people over 60 or who have been postmenopausal for more than ten years; instead, alternative medications should be taken into consideration.

**8. Conclusion**

Osteoporosis is a global health concern that results in over 8.9 million fractures annually. The anticipated rise in medical visits, hospital stays, and placements in nursing homes associated with osteoporotic fractures will place a significant financial strain on healthcare systems. In light of age, gender, and other risk factors, screening is crucial. Although bisphosphonates are still the most economical and first-line treatment for osteoporosis, questions are growing regarding their long-term safety. Soon, new medications to treat osteoporosis should be available.3–6 Osteoporosis can be avoided with appropriate diet, lifestyle, and fall prevention measures, in addition to appropriate BMD screening and medication treatment.

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