

## Perspective

## Primary osteoporosis in postmenopausal women

Meng-Xia Ji, Qi Yu\*

*Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Peking Union Medical College,  
Chinese Academy of Medical Sciences, Beijing 100730, China*

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**Introduction**

World Health Organization (WHO) defines natural menopause as at least 12 consecutive months of amenorrhea not due to physiologic and pathologic causes. Statistics show that the mean age of natural menopause is 51 years in industrialized nations, compared to 48 years in poor and non-industrialized nations.<sup>1</sup> With the average life span extended to 70 years, most women will spend more than one third of their life time beyond the menopausal transition. Besides, the proportion of menopausal women is rising since the aging population is expanding rapidly. Thus, the health of menopausal women becomes a prime concern worldwide.

Menopause is a natural physiological phenomenon resulting from primary ovarian failure secondary to apoptosis or programmed cell death. Ovarian function declines with age. The onset of menopause features the decreasing production of estradiol, as well as increasing levels of follicle-stimulating hormone

(FSH). During the menopausal transition period, women will experience a number of bothersome symptoms, such as hot flashes, night sweats, vaginal atrophy and dryness, dyspareunia, sleep disturbance, and mood swings. Besides these, osteoporosis is the most prevalent disease in menopausal women, and is strongly associated with low quality of life and we concentrate on postmenopausal osteoporosis in this review.

**Primary osteoporosis**

Osteoporosis, a multifactorial systemic skeletal disease, is characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue resulting in bone fragility.<sup>2</sup> BMD measured by dual X-ray absorptiometry is the gold standard to diagnose osteoporosis. According to WHO criteria, osteoporosis is defined as the T-score of less or equal to -2.5 and osteopenia as the T-score between -1.0 and -2.5. The femoral neck and lumbar spine are recommended as the anatomic region of interest.<sup>3</sup> BMD decreases with age, thus primary osteoporosis mainly occurs in women 10–15 years after menopause and elderly men around 75–80 years old. With an expanding aging population, osteoporosis and osteoporosis-related fractures are fast becoming important public health issues that are a considerable economic burden on health service resources.

\* Corresponding author.

E-mail address: [yuqimd@163.com](mailto:yuqimd@163.com) (Q. Yu).

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## The pathogenesis of postmenopausal osteoporosis

The achievement of peak bone mass is important to bone health, and plays a vital part in preventing osteoporosis and subsequent fractures in later years. It is reported that hip fractures could be reduced by 30% with an increase in peak bone mass of 10%.<sup>2</sup> Bone mass accretion starts from childhood and continues into adulthood, and peak bone mass can be achieved in the mid-twenties for spine and hip while other bones, such as the radius, reach a peak at age of 40 years. After that, bone mass normally declines. By the age 70 years, bone mass has decreased by 30–40%.<sup>4</sup> The main determinant of the peak bone mass is genetic factors. Studies found several genetic variants which are related to bone mass, including low-density lipoprotein receptor related protein 5 (LRP5), osteoprotegerin (OPG), sclerostin (SOST), oestrogen receptor 1, and the receptor activator of NF- $\kappa$ B (RANK) pathway genes.<sup>5</sup> It has been found that hormone status regulates bone mass accretion, especially that of estrogen. Other factors including nutrition, smoking and exercise may also play a role in the process of the peak bone mass accumulation.<sup>6,7</sup>

Healthy bone requires continuous remodeling which is pivotal for bone density maintenance. It is estimated that nearly 10% of the bone is updated by this process every year.<sup>8</sup> Osteoclasts (bone resorbing cells) and osteoblasts (bone forming cells) are two kinds of cells that essentially form the bone multi-cellular unit, coordinating well to regular the balance of bone resorption and bone formation. The normal bone remodeling process consists of five phases: the resting phase, the activation phase, the resorption phase, the reversal phase, and the formation phase. Firstly, osteoclasts are recruited to the surface of the bone where they generate an acidic micro-environment between the cell and the surface of the bone, dissolving and resorbing the mineral content of the bone. After that, the osteoclasts undergo apoptosis and osteoblasts are recruited to the bone surface and then deposit collagen which is mineralized afterwards to form new bone.<sup>9</sup> This process is regulated by several hormones, including parathyroid hormone, calcitonin, 1,25(OH)<sub>2</sub>-vitamin D<sub>3</sub>, and estrogen. Estrogen affects bone through the following mechanisms: 1) lowering the sensitivity of bone mass to PTH (parathyroid hormone), thus reducing bone resorption, 2) increasing the production of calcitonin, thus inhibiting bone resorption, 3) accelerating calcium resorption by the intestine, 4) reducing the calcium excretion from the kidney, and 5) estrogen can also have direct effects in the bone since there are estrogen receptors.<sup>10</sup>

At menopause the normal bone turnover cycle is impaired by estrogen deficiency. This may be due to the presence of estrogen receptors in osteoclast progenitor cells and multi-nucleated osteoclasts. The osteoclastic resorption activity increases while the osteoblastic activity decreases. As a result, the amount of bone resorbed exceeds the amount deposited, which leads to a net loss of bone. The increase of overall bone resorption is due to a weakened inhibition effect due to the reduction of available estrogen on both osteoclastogenesis and osteoclast activity. The enhanced expression of cytokines known to stimulate osteoclastogenesis, such as IL-1, IL-6, and TNF, or enhanced expression of M-CSF (macrophage colony-stimulating factor) and RANKL in osteoblasts/stromal cells may also play an important role. The stimulatory effect of estrogen on bone formation is less-well-understood, but may be mediated by estrogen-receptor-responsive elements on promoters for genes involved in bone matrix biosynthesis, including type I collagen, or cytokines believed to be important for coupling of bone resorption and bone formation.<sup>8</sup>

There are two phases of bone loss in women: The first occurs predominantly in trabecular bone and starting at menopause. It results from estrogen deficiency, and leads to a disproportionate increase in bone resorption as compared with formation. This phase could be defined as menopause related bone loss. After 4–8 years, the second phase exhibits a persistent, slower loss of both trabecular and cortical bone, and is mainly attributed to reduced bone formation.<sup>11</sup> This is age related bone loss, which is the only phase that also happens in men.

During the menopausal transition period, the average reduction in BMD is about 10%. Approximately half of women are losing bone even more rapidly, perhaps as much as 10%–20% in those 5–6 years around menopause. About 25% of postmenopausal women can be classified as fast bone losers, and they could be discovered by the measurement of bone loss and bone resorption markers.<sup>12</sup>

## The epidemics of osteoporosis

The aging population is expanding at an unprecedented rate. This explosion in population will lead to a greater number of individuals with osteoporosis. It is estimated that the prevalence of osteoporosis rises from 1/3 in people at age 50–60 to more than 50% of people aged over 80 years. By 2050, the global osteoporosis sufferers will reach 6 million (including both males and females), 3/4 of who will reside in developing countries.<sup>13,14</sup>

The major health threat of osteoporosis is osteoporotic fractures, which occur at a site associated with

low BMD (most commonly in the spine, the hip, or the wrist, sometimes the humerus or ribs are also involved), and it increases in incidence after the age of 50 years. Osteoporotic fractures take place in temporal sequence, with the first sign being fractures of the lower end of radius starting at age 50 years, followed by vertebral fractures at age 60–75 years and hip fractures beginning in the late 70s.<sup>9</sup> Osteoporotic fracture may lead to loss of mobility and autonomy, a reduction of the quality of life and development of serious complications such as pneumonia or thromboembolic disease which poses a considerable health and economic burden to public health. For example, during the 1st year after hip fracture 20–30% of patients died, with the cost amounting to about \$21,000 in USD.<sup>15</sup>

The prevalence of osteoporosis and related fractures are higher in postmenopausal women than in older men since estrogen plays a key role in maintaining bone health. The National Osteoporosis Foundation (NOF) estimates there are 9.1 million women with osteoporosis and an additional 26 million with low bone mass. This far exceeds the estimated number of men with osteoporosis, 2.8 million, and with low bone mass, 14.4 million.<sup>16</sup> The fracture risk is also higher in women than in men. The lifetime risk of fracture for a 60-year-old woman is close to 44%, nearly double the risk for a man of the same age, which is 25%. In 2005, there were nearly 1.45 million fractures in women older than 50 years in the United States, compared with 594,000 fractures in men of the same age.<sup>17</sup>

Worldwide, the frequency of osteoporosis and osteoporotic fractures is also influenced by race and ethnicity. Generally speaking, Caucasian and Asian women are more susceptible to osteoporosis than black women. In the United States, among women who suffered from osteoporotic fractures, white women account for the majority of all fractures, which is as high as 89%, followed by blacks and Hispanics, both are 4%, and other women 3%.<sup>18</sup> Meantime, the lifetime risk of hip fracture in the United States at age 50 years is 15.8% and 6.0% in women and men, respectively, whereas in Chinese women and men it is 2.4% and 1.9%, and in Hispanic women and men 8.5% and 3.8%. Additionally, it seems that hip fractures occur at an earlier age in developing countries compared with western countries since the peak age for hip fractures in India is in the 60s compared to 80s in western countries.<sup>19</sup> In a meta-analysis evaluating the data on the epidemiology of Chinese elderly people, the author found that the total prevalence of osteoporosis at an age above 40 years in China was 13.2%, and it is significantly higher among females than males, 14.2% vs. 11.8% ( $P < 0.05$ ). The

prevalence of osteoporosis increases in both men and women with aging, while it increases gradually in males it increases significantly in females over 50 years old.<sup>20</sup>

### **The management of postmenopausal osteoporosis**

As early as 1940s, Albright and Reifstein found that estrogen could prevent osteoporosis. In the 1960s, the association between menopause and osteoporosis was first identified and then estrogen treatment was adopted to prevent bone loss. Nowadays, a large number of studies have proven that estrogen is effective in the prevention of osteoporosis and hormone therapy can still be considered a first line choice for postmenopausal women.

Menopause Hormone Therapy (MHT) has long been known to significantly increase BMD. In a meta-analysis of 57 trials (both prevention and treatment trials) which included about 10,000 women, the combined results imply that on average the change in bone density is significantly higher in the MHT group (both opposed and unopposed estrogen) at all measurement sites. After one year the MHT group showed an average increase of bone mineral density at the lumbar spine of 5.4%, and the forearm and femoral neck were also increased by 3.0% and 2.5% respectively. After two years of treatment, the percentage change in favor of MHT increased by about 1.5% at all sites with an increase by 6.8%, 4.5%, and 4.1% at the lumbar spine, forearm, and femoral neck, respectively.<sup>9,21</sup>

The HOPE trial recruited 822 healthy postmenopausal women 40–65 years old who were randomized to either daily conjugated equine estrogen treatment with 0.3 mg, 0.45 mg or 0.625 mg with or without continuous daily medroxy progesterone acetate at 1.5 mg or 2.5 mg. A calcium supplement of 600 mg was given to all of the participants including the placebo group. After two years of treatment, compared to the placebo group, women assigned to all of the active treatment groups had significant gains from baseline ( $P < 0.001$ ) in spine and hip BMD, the difference being about 3–5% for spine BMD and 1–3% for total hip BMD.<sup>22</sup>

MHT is also effective in preventing osteoporotic fractures. In a meta-analysis of 22 randomized trials, there was an overall 27% reduction favoring MHT groups in non-vertebral fractures in a pooled analysis ( $RR = 0.73$ , 95%  $CI$ , 0.56–0.94,  $P = 0.02$ ). For hip and wrist fractures alone, the effectiveness of MHT appeared more striking ( $RR = 0.60$ , 95%  $CI$ , 0.40–0.91,  $P = 0.02$ ).<sup>23</sup>

In the Women's Health Initiative (WHI) study, 16,608 women were randomized to estrogen plus

progesterin (HT) or placebo. Meanwhile, 10,600 women were randomized to estrogen (ET) or placebo. After three years on ET and after two years on HT, the fracture risk started to decrease. In the HT arm after 5.6 years, the risk of hip fractures was lowered by 33% and the risk of all fractures was lowered by 24%. In the ET trial of 10,739 women that were followed up for 7.1 years, there was a similar reduction in hip fractures of 35% and 29% in all fractures. In all, HT/ET results showed reduced hip fractures by 35%.<sup>24</sup> This trial provides a strong support that hormone therapy is effective in preventing osteoporotic fractures.

In a randomized trial investigating the effects of tibolone on fractures,<sup>25</sup> 4538 women who are at risk for fractures were assigned to a tibolone or placebo group. During a median of 34 months of treatment, compared with the placebo group, vertebral fractures in the tibolone group were lower by 45%, ( $RR = 0.55$ , 95%  $CI$ , 0.41 to 0.74,  $P < 0.001$ ), and nonvertebral fracture decreased by 26% ( $RR = 0.74$ , 95%  $CI$  0.58 to 0.93,  $P = 0.01$ ).

It is worth mentioning that withdrawal of estrogen results in rapid bone loss and within one year most of the previous increased BMD accumulated over 3–4 years has disappeared. In a randomized study, which included early post-menopausal women who age 55 years, MHT increased BMD by 5%–6%. However, four years after treatment was stopped there was a rapid decrease in spine BMD by 7% in the MHT group. Another similar analysis showed that within two years hip fractures increased by 50% and after five years by 77%.<sup>26</sup> It is recommended therefore that women who discontinue MHT should select other therapies to prevent osteoporosis.

### The window of opportunity hypothesis

There is ceaseless debate about MHT since it may relate to breast cancer, coronary heart disease (CHD), strokes and thromboembolism.<sup>27,28</sup> To prevent postmenopausal osteoporosis, how can we weigh the risk/benefit and when should we start menopause hormone therapy? The window of opportunity hypothesis emerges as an answer and has become accepted among specialists from various countries today.

Cumulated data from studies concerning MHT demonstrate two populations of postmenopausal women who respond differently to MHT. The diversified response to MHT is based on age or years postmenopausal. Specifically, when MHT is started in women less than 60 years old and/or less than 10 years postmenopausal, the CHD events and overall mortality are decreased, and the overall benefits outweigh risks.

Contrarily, when MHT is started in women older than 60 years old and/or longer than 10 years after menopause, there is a null effect and sometimes even an adverse effect.<sup>27</sup> That is the window of opportunity hypothesis. The hypothesis is further validated by data published recently from the DOPS study,<sup>28</sup> which suggests that MHT can reduce cardiovascular endpoints in women if started shortly after menopause, which happens to be the period of fast bone loss. Thus, the timing hypothesis should be kept in mind when we are prescribing hormones to prevent postmenopausal osteoporosis. As we discussed in previous paragraphs, bone resorption has been proven to be fastest in the first 3–4 years after menopause, and it is reasonable to start hormone therapy early after menopause. During this period of time, the response to treatment can be the highest since stopping resorption leads to instant filling in of the resorption or remodeling space and increases bone formation and results in a greater increase in BMD.

The North American Menopause Society guidelines suggest that as long as the lowest effective dose of MHT is used, extending treatment for an individual woman's treatment goals are acceptable when the benefits of menopause symptom relief outweigh potential risks and for further prevention of osteoporotic fracture or preservation of bone mass in women with an established reduction in bone mass other therapies are not suitable.<sup>9</sup> Determination of the lowest effective dose of MHT should be based on vasomotor symptom relief.<sup>9</sup>

The Chinese menopause guidelines suggest that menopause hormone therapy is recommended for women who are at risk of osteoporotic fractures and who are younger than 60 years old; while for those who are older than 60 years, menopause hormone therapy is not recommended if it is intended only for the prevention of osteoporotic fractures.<sup>29</sup> MHT should be individualized in administration and dose, and benefits/risks should be carefully weighed during the treatment. To prevent osteoporosis, the lowest effective dose of MHT should be used and there are fewer side effects in transdermal preparations than with oral medicines. Bone loss will recur after stopping hormone therapy. For those who are at risk of osteoporotic fractures, other protective drugs should be taken.<sup>29</sup>

What can we do for women greater than 60 years old and/or greater than 10 years postmenopausal if they wish to prevent osteoporosis? Other pharmacological interventions including bisphosphonates, selected estrogen receptor modulators (SERM), recombinant human parathyroid hormone, and denosumab are also effective. Calcium and vitamin D should be taken as basic nutritional supplements. Adjustment of lifestyle such as

regular exercise, quitting smoking and alcohol, and strategies for prevention of falls can also play a vital role.<sup>30</sup>

## Summary

Being a systemic skeletal disease, osteoporosis becomes an important public health and financial issue that is associated with increased mortality and morbidity. Postmenopausal women are susceptible to primary osteoporosis since osteoporosis is closely related to estrogen deficiency. During the menopausal transition period, the drop of estrogen leads to more bone resorption than formation, resulting in osteoporosis. The major health threat of osteoporosis is osteoporotic fractures. The prevalence of osteoporosis and related fractures are higher in postmenopausal women than in older men and is influenced by ethnicity. Since low estrogen levels are the main cause of postmenopausal osteoporosis, menopause hormone therapy is considered as the first line choice for prevention of osteoporosis and its effectiveness has been demonstrated by various studies. However, hormone therapy is recommended for women who are less than 60 years old and/or less than 10 years postmenopausal. For those who are greater than 60 years old and/or greater than 10 years postmenopausal, menopause hormone therapy is not appropriate and other medicines should be considered.

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