

Prevention of bone loss beginning in perimenopause: which therapy?

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ABSTRACT

Rapid bone loss and substantial deterioration of bone microarchitecture occur during late perimenopause and early postmenopause, an interval termed transmenopause, contributing significantly to the development of postmenopausal osteoporosis. Low body weight and low bone mineral density at the onset of perimenopause accurately identify women at high risk of developing osteoporosis. Screening women as they enter perimenopause allows identification of those high-risk patients for whom therapy with either estrogen or low-dose bisphosphonates should be considered to prevent menopause-related bone loss. Each of these options has advantages and limitations, and the choice must be individualized. Following therapy to prevent rapid transmenopausal bone loss, a lifelong strategy to preserve bone density and prevent the development of osteoporosis and high fracture risk is necessary.

KEYWORDS

Perimenopause, transmenopause, menopause, osteoporosis, estrogen, bisphosphonates, prevention.

Introduction

Estrogen is an important regulator of bone metabolism^[1] and is required for the large increase in bone mass that occurs at puberty in both sexes^[2]. Estrogen deficiency in women is associated with an upregulation of RANK ligand and a reduction in osteoprotegerin, resulting in increased bone remodeling, dominated by increased osteoclastic bone resorption. An interval of rapid bone loss related to the menopausal decline in estrogen levels occurs across menopause stages, beginning in perimenopause and extending variably in individuals for several years after the final menstrual period (FMP). We will define this general interval of rapid bone loss as transmenopause. It is this transmenopausal bone loss that may ultimately result in osteoporosis and high fracture risk^[3].

Is preventing transmenopausal bone loss important?

During transmenopause, greater bone loss and damage to bone structure occur than at any other time in a woman's life, making this a unique opportunity to decrease the risk of osteoporosis. The effects of natural menopause on skeletal health were characterized by the Study of Women's Health Across the Nation (SWAN) in which 3302 American premenopausal or early perimenopausal women aged 42–52 years were followed before and for several years after the FMP. Bone mineral density (BMD) of the lumbar spine (LS) and proximal femur was measured by dual-energy X-ray absorptiometry (DXA) annually at 5 of the 7 study sites^[3,4]. Bone loss began 2–3 years before the final menstrual period (FMP) and accelerated during the interval from 1 year before until 2 years after the FMP. Over the

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interval of 5 years before until 5 years after the FMP, the average decreases in LS and femoral neck (FN) BMD were 10.8% and 9.1%, respectively, corresponding to T-score decreases of 1.0 at the LS and 0.83 at the FN. Moreover, by the time the diagnosis of menopause was made (12 months after the FMP), half of the bone loss recorded in the LS by 5 years post-FMP, and one-third of that in the FN, had already occurred. These results are consistent with the observed rapid loss of 3.3% and 1.9% in LS and FN BMD, respectively, over 12 months in a cohort of perimenopausal women^[5]. When estrogen deficiency is acute, due to oophorectomy, chemotherapy, disease, or anti-estrogen therapy, bone loss may be even more rapid—as much as 2.6% in 6 months and >6% over 24 months^[6–8].

Rapid deterioration of trabecular bone microarchitecture during transmenopause has been demonstrated by bone biopsy and trabecular bone score (TBS). BMD measurement by DXA and transiliac biopsies were performed at baseline and at 1 year in a placebo group of women (mean age 52 years) at 2.8 years post-FMP^[9]. LS BMD decreased by 3.3% while trabecular bone volume and trabecular connectivity decreased by 20.3% and 13.1%, respectively. In SWAN, TBS, an indirect measure of trabecular microarchitecture, decreased by 6.3% from 5 years before until 5 years after the FMP^[10]. These transmenopausal changes in BMD and TBS, accounting for 40–50% of the total changes observed between premenopause and age 80

years, are important contributors to the development of postmenopausal osteoporosis and related fractures.

Based on the SWAN and the US National Health and Nutrition Examination Survey, American women who approach menopause with an average total hip (TH) BMD value (T-score = 0) would be predicted to meet the BMD criteria for osteoporosis (T-score -2.5) at a mean age of about 82 years, after losing 28–30% of their bone mass. In contrast, women with a peak bone mass 1 standard deviation below average (T-score -1.0) would be predicted to meet the criteria for osteoporosis at about age 64 years, after a decrease of only 18%. Consistent with these predictions, 13.1% of American women aged 50–64 had osteoporosis based on BMD testing ^[11].

Can transmenopausal bone loss be prevented?

For more than 30 years, estrogen, tibolone, and low-dose bisphosphonate therapy have been known to prevent postmenopausal bone loss, and both estrogen and bisphosphonates are also recognized to prevent perimenopausal bone loss ^[8,12-17]. Drugs approved in North America for preventing postmenopausal bone loss are listed in Table I. Note that doses of alendronate and zoledronate approved for prevention of bone loss are half the doses used for treating osteoporosis.

Treatment options to prevent transmenopausal bone loss

General measures

Medical societies emphasize the roles of good nutrition (especially adequate intakes of calcium and vitamin D), regular physical activity, and avoidance of unhealthy habits such as smoking in the prevention of osteoporosis but rarely discuss the use of drugs to prevent bone loss. Although general health measures are appropriate for all postmenopausal women, they do not prevent the rapid transmenopausal bone loss related to estrogen deficiency. BMD is not associated with calcium intake in women aged 40–60 ^[18,19]. In SWAN, average dietary calcium intake was about 750 mg daily, and taking at least 300 mg of a calcium supplement daily was not associated with either less bone loss or fewer fractures in early perimenopausal women ^[20]. In young postmenopausal women, rates of bone loss over 2 years were not influenced by daily calcium intake ^[21]. A systematic review found that Tai Chi, endurance training, and strength training did not prevent loss of BMD in perimenopausal women ^[22]. In SWAN, vigorous leisure time activity reduced the rate of FN BMD decline from 1.5% to 1.3% per year but did not prevent transmenopausal bone loss ^[23].

Estrogen(s)

Both oral and transdermal estrogen prevent postmenopausal bone loss in a dose-dependent manner ^[13,24,25]. In early postmenopausal women, BMD increased with daily doses up to 2.0 mg of oral estradiol and 0.1 mg of transdermal estradiol with progressively smaller proportions of women experiencing bone

loss as doses increased ^[24,26]. These larger estrogen doses may be required during the period of rapid transmenopausal bone loss or in the presence of acute estrogen deficiency, after which smaller doses appear capable of maintaining BMD. Conjugated estrogen given alone or with either medroxyprogesterone acetate or micronized progesterone induced similar changes in BMD, whereas the androgenic progestin norethindrone acetate provided small additional BMD benefits when given with estradiol ^[13,25]. In the low-fracture-risk population of the Women's Health Initiative, conjugated estrogen, with or without a progestin, reduced clinical fracture risk by more than 24% with reductions in hip and spine fracture of about 35% ^[27,28].

In perimenopausal women, combined continuous oral contraceptives preserve BMD while providing contraception, inhibition of ovarian hormone production, and control of irregular bleeding ^[14]. The BMD response was similar with oral contraceptives containing 20 mcg ethinyl estradiol and different progestins ^[29]. When contraception is no longer needed, switching to standard menopausal hormone therapy is appropriate.

Bone protection persists as long as estrogen is given, but bone density and fracture protection are quickly lost when therapy is discontinued ^[30,31]. Women who discontinue estrogen therapy should transition to low-dose alendronate or zoledronate for 2–3 years to maintain the skeletal benefit ^[32].

Previous breast cancer is the most common contraindication to estrogen therapy. A two-fold increased risk of venous thrombosis and very rare pulmonary embolism occur with oral but not transdermal estrogen therapy ^[33]. The overall benefit/risk profile of estrogen begun within 10 years of menopause in the Women's Health Initiative studies was favorable ^[34]. For women over the age of 60 or more than 10 years postmenopause, an individualized evaluation of risks and benefits is appropriate.

Selective estrogen receptor modulators (SERMs)

Raloxifene and bazedoxifene have weak estrogen-like effects on bone while inhibiting estrogen action in the breast and endometrium. Raloxifene 60 mg daily and a combination treatment—bazedoxifene 20 mg/conjugated estrogen 0.45 mg—are both approved for preventing postmenopausal bone loss in the United States. These drugs induce small increases (1–2%) in bone density over 1–3 years ^[35,36]. However, neither treatment has been evaluated in perimenopausal women. Because raloxifene may increase vasomotor symptoms and SERMs do not provide contraception or suppression of ovarian hormone secretion, they are not appropriate for preventing perimenopausal bone loss but may have roles in the long-term management of postmenopausal women.

Bisphosphonates

Four nitrogen-containing bisphosphonates are available for osteoporosis prevention, based on studies showing a 5–6% improvement in LS BMD over 24 months of therapy compared with placebo in early postmenopausal women (Table I). No direct comparisons have been made among the bisphosphonates when used for prevention. Postmenopausal use of alendronate 5 mg daily was compared to menopausal hormone therapy (conjugated estrogen 0.625 mg or oral estradiol 2 mg daily, with a progestin in the women with a uterus). After 4 years of

alendronate, LS and TH BMD increased by 3.5% and 2.9%, respectively, while women in the placebo group experienced losses of 2.9% at the LS and 1.5% at the TH [37]. In women randomized to conjugated equine estrogen or estradiol, increases in LS BMD were 5.1% and 7.5%, respectively, while increases of 2.9% and 4.8% were seen at the TH. BMD changes after 6 years of continuous alendronate were similar to the 4-year results [38]. Intravenous zoledronate given every 2 years or less frequently prevents postmenopausal bone loss [39,40].

Oral bisphosphonates are contraindicated in women with swallowing disorders, including esophageal stricture and achalasia, while zoledronate is contraindicated in women with seriously impaired renal function [41]. Continuous oral bisphosphonate use for more than 5 years is associated with rare but important adverse events including osteonecrosis of the jaw and atypical femoral fracture.

When should screening occur?

If transmenopausal bone loss is to be prevented, intervention should begin in perimenopause, before the onset of rapid bone loss. Consequently, assessment must occur at the onset of perimenopause to identify the subset of women at high risk of developing osteoporosis. In SWAN, the strongest predictors of developing osteoporosis by the 10-year follow-up visit were low body weight and low BMD at study entry [42]. These factors are related since low body weight is strongly correlated with low BMD in premenopausal and young postmenopausal women [43]. Bone density testing at the onset of perimenopause is, then, appropriate in women with low body weight, a family history of osteoporosis, or medical problems associated with decreased BMD [44]. American guidelines recommend bone density screening in all peri- and postmenopausal women whose weight is <58 kg [44,45] (Table II). Based on a systematic review of the literature, Canadian experts recommend BMD testing for those weighing <70 kg [18].

The objective of BMD screening at perimenopause is to identify women at high risk of osteoporosis despite a low current fracture risk. In such cases, preventive therapy would aim to maintain bone mass and strength, prevent the development of high fracture risk, and reduce the risk of future fractures. This contrasts with the strategy for osteoporosis treatment, which focuses on identifying individuals at high current fracture risk who require therapy to reduce that risk.

Who should receive therapy to prevent transmenopausal bone loss?

Since all women experience estrogen deficiency-related bone loss, they would all likely benefit from therapy designed to prevent bone loss and structural deterioration during the transmenopausal interval. Treatment would be especially useful in women at high risk of developing osteoporosis. Most osteoporosis guidelines either do not address or do not endorse the use of drugs for osteoporosis prevention [46,47]. An exception is the Osteoporosis Position Statement of the North American

Menopause Society (now The Menopause Society) [44]. Their recommendation, found in Table III, is that estrogen therapy is appropriate to prevent transmenopausal bone loss in women who approach menopause with risk factors for osteoporosis, even in the absence of vasomotor symptoms.

How long should therapy be taken?

Both the prevention and the treatment of postmenopausal osteoporosis require long-term if not lifelong management. While there is no fixed limit to the duration of estrogen ther-

Table I Drugs approved in North America for preventing postmenopausal osteoporosis.

ESTROGEN AGONISTS		BISPHOSPHONATES	
Drug	Approved dose	Drug	Approved dose
Estrogen, oral and transdermal	Multiple doses	Alendronate	35 mg PO weekly
Conjugated estrogen plus bazedoxifene	0.45 mg + 20 mg daily	Risedronate	35 mg PO weekly
Raloxifene	60 mg daily	Ibandronate	150 mg PO monthly
Tibolone*	2.5 mg daily	Zoledronate	5 mg IV every 2 years

* Tibolone is not approved in the United States

Table II Indications for bone density testing.

ESTROGEN AGONISTS	BISPHOSPHONATES
Bone density should be measured in postmenopausal women with risk factors for osteoporosis or fracture where knowing the result will influence clinical management. This includes postmenopausal women: • with a history of fracture since menopause • with one or more of these risk factors: - body weight less than 127 lb (57.7 kg) or BMI less than 21 kg/m² - history of hip fracture in a parent - current smoker - aged 65 years and older • with medical causes of bone loss or fracture • discontinuing estrogen	USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in postmenopausal women • aged 65 years and older • younger than 65 years with 1 or more risk factors for osteoporosis

Table III Indications for the use of drugs to prevent bone loss (adapted from the NAMS Osteoporosis Position Statement) [11].

Pharmacological therapy to prevent bone loss is indicated in peri- or postmenopausal women with • Premature menopause, at least until the average age of natural menopause • Low BMD (T-score < 1.0), especially if they are experiencing relatively rapid bone loss because of acute estrogen deficiency in perimenopause or upon discontinuing ET • Low BMD with other risk factors for bone loss or fracture (e.g., family history) but who do not meet the criteria for osteoporosis treatment

apy, discontinuation should be followed by at least 2 years of alendronate or at least one dose of zoledronate to preserve bone density.

The optimal duration of bisphosphonate therapy begun in perimenopause has not been evaluated. The period of rapid transmenopausal bone loss lasts for 5–6 years [4]. Continuous bisphosphonate therapy for more than 5 years at a time is not recommended as its benefits plateau and the risk of atypical femoral fracture increases [48]. In young postmenopausal women, BMD benefits persist, remaining well above pre-treatment levels for at least 2–3 years after discontinuation of alendronate [49, 50]. With zoledronate, two doses, perhaps two years apart, would be appropriate for preventing bone loss in perimenopausal women.

Following bone loss prevention therapy with either estrogen or a bisphosphonate, long-term maintenance of bone density is required. After a relatively short course of alendronate or zoledronate in patients who discontinue estrogen, or after 3–5 years of bisphosphonate begun during perimenopause, patients at low fracture risk could be transitioned to intermittent bisphosphonate therapy to maintain BMD. Based on studies in young postmenopausal women, alendronate could be given in cycles of two years on and three years off therapy [49, 50]. Alternatively, zoledronate once every 5 years could be used [40]. If breast cancer risk reduction is desired in addition to prevention of bone loss, raloxifene could also be considered between the perimenopausal or post-estrogen bisphosphonate use and the maintenance therapy phase [35].

Which therapy to prevent osteoporosis during perimenopause?

Choosing between estrogen and bisphosphonate therapy is an individualized decision. For most women, estrogen therapy, beginning in perimenopause, is the best treatment option. Managing perimenopause involves multiple components: preventing bone loss, managing vasomotor symptoms, controlling abnormal vaginal bleeding, and providing contraception. Continuous estrogen/progestin contraceptives offer therapy for all four concerns and, in early perimenopause, when estrogen levels may vary chaotically, suppress ovarian production and provide stable hormone levels. For women who cannot take estrogen, low-dose bisphosphonate therapy for 3–5 years beginning in perimenopause is an excellent alternative, although additional therapy to provide contraception and control of menopausal symptoms may be required.

Summary

The rapid bone loss and damage to bone structure that occur during transmenopause transition are significant contributors to the development of postmenopausal osteoporosis but can be prevented with estrogen or bisphosphonates. This strategy should be considered in all women as they enter perimenopause, especially those at increased risk of developing osteoporosis.

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