Published in final edited form as:
Obstet Gynecol Clin North Am. 2011 September ; 38(3): 503–517. doi:10.1016/j.ogc.2011.07.001.

Bone and the Perimenopause

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Abstract

The loss of ovarian function during the menopausal transition has a profound impact on female skeletal health. Currently it is estimated that one in every two Caucasian women will experience an osteoporotic fracture during her lifetime,[1] contributing to considerable morbidity and an enormous economic burden within the aging female population. However, most studies have been conducted in postmenopausal women, with fewer investigations focusing specifically on perimenopausal bone health. The Study of Women's Health Across the Nation (SWAN) is the largest prospective cohort to date where changes in bone mineral density and bone turnover have been examined in relation to ovarian aging among women followed across the menopause transition.[2–3] As defined by bleeding pattern in SWAN, early perimenopause is characterized by increasing menstrual irregularity but less than 3 months of amenorrhea, late perimenopause by amenorrhea lasting greater than 3 months but less than 1 year, and postmenopause by the absence of menstrual bleeding for twelve consecutive months or more.[3–4] A recent multi-study collaboration has further recommended that the early menopause transition be defined by a persistent 7+ day difference in consecutive cycle lengths and the late menopause transition by at least 60 days of amenorrhea.[5–6] A serum follicle-stimulating hormone (FSH) level of 40 IU/L or greater has also been found to be an independent marker of the transition that may facilitate predicting the time to the final menstrual period.[6–7]

Keywords

osteoporosis; perimenopause; menopause; bone; fractures

Conducted in a large multi-ethnic population of more than 2000 women across five clinical centers in the United States, the SWAN bone study has contributed greatly to our

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understanding of both early and late changes in bone metabolism during perimenopause, associated clinical and race/ethnic differences, and the implication of these findings for optimization of postmenopausal bone health. This review will focus on bone loss during the menopausal transition, changes surrounding the final menstrual period, and the role of endogenous hormones and ethnic variation in predicting bone density and bone loss. Specific findings from SWAN and other studies, data on perimenopausal fractures, fracture risk and implications for clinical management will also be discussed.

Bone Loss During the Menopausal Transition

Changes in Bone Mineral Density (BMD)

While there is a large body of literature examining bone mineral density among postmenopausal women, and a moderate body of literature examining bone mineral density among premenopausal women, fewer studies have monitored bone mineral density (BMD) serially in a cohort of women who were initially premenopausal and continued monitoring BMD until women experienced their final menstrual period.[8–11] Some of these earlier studies reported that BMD remained stable in premenopausal women while others found that BMD begins to decline well before the final menstrual period.[3, 12–17] However, many of the early studies lacked clear definitions of menopausal status, and prior studies often examined bone density as a function of chronologic age instead of menopause stage or time from the final menstrual period. SWAN investigators examined changes in BMD of the lumbar spine and total hip across six annual visits in nearly 2000 participants with carefully characterized perimenopausal stage.[3] There was little change in BMD during the pre- or early perimenopausal period. Bone loss accelerated dramatically during late perimenopause and continued through the early postmenopause.[3] This acceleration in bone loss during the late perimenopause (Figure 1) was characterized by a 1.8- 2.3% annual rate of bone loss in the lumbar spine and 1.0–1.4% in the hip.[3] Body weight was found to be an important predictor of the rate of bone loss, independent of differences in race/ethnicity. Compared with women in the highest tertile of body weight, rate of bone loss was 35–55% higher in women in the lowest tertile of body weight.[3]

Similar rates of accelerated bone loss have also been reported in the Melbourne Women's Midlife Health Project where an average annual rate of BMD decline of 2.5% in the lumbar spine and 1.7% in the femoral neck occurred in the time surrounding the final menstrual period.[18] These findings are comparable to early data obtained in perimenopausal women residing in France where the average annual decline in vertebral BMD was in the range of 2.35%.[19] The association of higher body mass or body mass index with slower rates of bone loss at various skeletal sites (including the forearm, hip and spine) has also been described in several studies, consistent with the known protective effect of body size and adiposity on bone loss and fracture risk.[11, 17–18, 20]

The Role of Endogenous Hormones

Bone loss in postmenopausal women has historically been attributed to estrogen deficiency. A detailed review of changes in ovarian and pituitary hormones during the menopausal transition is described elsewhere in this issue of Obstetrics and Gynecology Clinics of North America (Reproductive Hormones and Menopause). There are numerous studies in older postmenopausal women demonstrating a significant association between circulating estrogen levels, BMD and fracture risk.[21–22] However, in pre- and perimenopausal women, it is difficult to extrapolate a single estradiol level, even when obtained during a well-defined portion of the menstrual cycle, to an entire menstrual cycle or series of menstrual cycles. This is because estradiol levels change from day to day and vary over a range of more than 10-fold across the course of a normal menstrual cycle.[23]

There is also evidence that fluctuations in estradiol may be more pronounced in the perimenopause, at least in its earlier stages.[24] Thus, in contrast to the postmenopause when estradiol levels are quite stable, perimenopausal estradiol levels might not be expected to correlate well with bone density and bone loss during the perimenopause, more because of the difficulty in assessing estrogen status rather than a lack of a true relationship. Moreover, the effect of fluctuating estradiol on bone density and bone loss is not well understood. It is possible that the periods of normal-to-high estradiol followed by periods of low estradiol that are characteristic of the perimenopause may relate differently to bone than the more stable and consistent levels seen in midreproductive-aged women.

Perimenopause is characterized by an increase in bone resorption and reduction in BMD.[25] These findings are accompanied by higher serum FSH levels, although estrogen levels may remain within the premenopausal range during the early transition.[25] In pre- and early perimenopausal Australian women examined across the menopausal transition, estradiol level measured at the final time point was significantly associated with perimenopausal bone loss.[26] In a separate examination of Swedish women undergoing prospective measurement of distal radius BMD at menopause, postmenopausal serum estradiol level was also found to correlate with changes in BMD.[27]

In SWAN, significant cross-sectional associations were observed between baseline serum FSH levels and BMD, but not between baseline serum estradiol levels and BMD, in pre- and early perimenopausal women.[28] Baseline FSH levels and changes in FSH levels were associated with longitudinal changes during the menopause transition[29] whereas annual measures of serum estradiol did not predict bone loss. Estradiol concentrations below 35 pg/mL were associated with lower BMD levels during the transition, however.[29] Examination of BMD change in the context of FSH staging in the Michigan Bone Health and Metabolism Study (Figure 2) showed that bone loss in the lumbar spine and femoral neck became evident when FSH increased into the range of 34–56 IU/l, which occurred approximately two years before the final menstrual period.[17] The annualized rate of bone loss in the lumbar spine increased from 1.7% in perimenopausal women with FSH levels of 34–56 IU/l to 3.3% during the two years after the final menstrual period and then declined to 1.1% per year in subsequent postmenopausal years.[17]

There has also been increasing awareness of other potential hormones that may contribute to bone loss during ovarian aging.[30] For example, it has been reported that mice with null mutations in the FSH receptor gene do not manifest bone loss despite the atrophic ovaries and uterus and disordered estrous cycles, suggesting that FSH is required in order for bone loss to occur in states of estrogen deficiency.[31–32] However, because mice with null mutations in the FSH receptor gene have elevated testosterone levels,[33] the lack of bone loss may be due to direct effects of testosterone on bone. Other gonadal peptides, such as inhibin A, inhibin B and activin have also been purported to contribute to changes in BMD with ovarian aging. Both inhibin A and inhibin B suppress osteoblast and osteoclast development and they oppose the stimulatory effects of activin and bone morphogenetic proteins on bone formation.[34] Whether any of these compounds truly contributes to the regulation of bone homeostasis during the perimenopause is currently unclear. Progesterone has also been implicated in the regulation of bone mass. The decline in progesterone concentrations associated with anovulation or luteal phase deficiency[35] and the reduction in inhibin secretion evident during the perimenopause may represent an additional mechanism for bone loss independent of circulating estrogen.[30, 34, 36] In a subset of pre- and early perimenopausal SWAN women in whom urinary excretion of estrogen and progesterone metabolites was assessed daily for one menstrual cycle each year, no association between measures of luteal function and BMD was observed;[37] however, larger studies are needed to examine the specific impact of changes in ovulatory function on BMD in midlife women.

Finally, new data have led some experts to hypothesize that other intrinsic age-related factors may be important in the pathogenesis of postmenopausal osteoporosis, particularly with regard to loss of trabecular bone.[30]

Changes in Bone Turnover

Bone turnover markers have been used for many years in the research setting to monitor the response to specific osteoporosis therapies.[38] Peptides made by osteoblasts, including bone-specific alkaline phosphatase, osteocalcin and procollagen type I N-propeptide (P1NP) are often used to assess bone formation while products of type I collagen degradation, including the cross-linked N-terminal and C-terminal telopeptides of type I collagen [N-telopeptide (NTX) or serum C-telopeptide (CTX)] are often used to assess bone matrix degradation. In cross-sectional analyses, bone resorption markers are consistently higher in untreated postmenopausal osteoporotic women than in premenopausal women whereas bone formation markers are more variable.[39–42] Higher levels of bone turnover markers have been shown in many, but not all studies,[40, 43–45] to predict subsequent bone loss[40, 46–47] or fracture risk[40–41, 44, 48] (independent of bone density changes) in postmenopausal women not receiving anti-osteoporosis treatment.

There are still, however, many gaps in knowledge that hinder the utilization of bone turnover markers in clinical practice. Few studies have measured bone turnover markers in perimenopausal women or in a racially diverse cohort of women. In a cross-sectional analysis, urinary NTX and osteocalcin were measured in 2,375 SWAN participants who were either pre-or early perimenopausal.[49] Mean NTX and osteocalcin levels were slightly higher in the perimenopausal women as compared with the premenopausal women; however, these differences were not statistically significant. Another cross-sectional analysis of 2313 pre- or early perimenopausal SWAN subjects demonstrated ethnic/racial differences in osteocalcin and urinary NTX levels wherein Caucasian subjects had the highest levels of both markers, even after adjusting for anthropometric and lifestyle differences.[50] The increased bone turnover observed in Caucasian subjects may explain the lower BMD, as discussed later in this chapter, seen in these subjects as compared with women from other racial groups. Additionally, only a few studies have assessed longitudinal changes in bone turnover markers during the menopause and the published reports have been limited by small cohort size. In a three year study of fifteen pre-menopausal women where six women became post-menopausal, bone resorption markers were unchanged prior to the final menses but started to increase six months after the final menstrual period.[51] The mean within-subject increase in bone resorption markers was 30–50%.[51] In an eight year study of 104 pre-menopausal women, 34 women became menopausal over the observation period with significant within-individual increases in bone resorption markers.[52] Longitudinal changes in bone resorption markers in the SWAN study are currently being analyzed; given SWAN's cohort size and racial diversity, these data will add substantively to our knowledge of the effect of the menopause on bone turnover markers. Because of significant within-individual variability of these markers, lack of uniform reference standards and challenges with interpretation, the use of bone turnover markers has been limited primarily to the research domain. However, with increasing knowledge of the hormonal and physiologic factors that affect bone turnover markers, a stronger clinical role for bone turnover measurements may become evident in the future.[38, 40]

Race/Ethnic Differences

It is well known that BMD and osteoporotic fracture risk vary by race/ethnicity, with unadjusted BMD values typically lowest in Asian women, intermediate in Caucasian women, and highest in African-American women. Fracture rates follow a different pattern, however, with the highest rates in Caucasians, intermediate rates in Asians, and the lowest

rates in African-Americans. Some of the observed differences in BMD among race/ethnic groups could be due to differences in bone size (one of the limitations of dual energy x-ray absorptiometry which measures areal and not three-dimensional BMD). However, race/ethnic differences have similarly been reported in population studies utilizing quantitative computed tomography (QCT) which measures volumetric BMD[53] and adjusting BMD values in SWAN for bone size did not eliminate race/ethnic differences in BMD.[54]

The specific sampling structure of the SWAN Bone Study across five clinical centers, each with approximately half the participants selected based on being of non-Hispanic Caucasian race and the remaining based on African-American, Chinese and Japanese race with annual BMD measurements during follow-up provides one of the few population-based studies able to examine race/ethnic differences in BMD and bone loss across the menopausal transition.[2] At the baseline evaluation, the racial variation in BMD (highest in African-Americans followed by Caucasians and lowest in Chinese and Japanese women) was found to be largely due to differences in body weight.[54] After adjustment for weight and other confounders, there were minimal differences in lumbar spine BMD among African-American, Chinese, or Japanese women, all of whom had higher adjusted BMD compared to Caucasian women.[54] Unadjusted femoral neck BMD was highest in African-Americans, intermediate in Caucasians, and lowest in Japanese and Chinese women with mean differences of 14–24% between African-American's and the other groups. After careful weight matching, the difference in femoral neck BMD between African-Americans and the other groups was reduced to 8–9% and the difference between Asians and Caucasians was eliminated. It is only because SWAN has large numbers of women from each of these racial/ethnic groups that weight matching and adjustment was possible, thus allowing new insights into racial/ethnic differences in BMD. Across the menopausal transition, rates of bone loss were greatest among Chinese and Japanese women, intermediate among Caucasian women and lowest among African-American women; however, like the baseline differences in BMD, these variations were also largely accounted for by differences in body weight rather than race/ethnicity *per se*.[3] Taken together, SWAN has helped to reinforce the finding that Caucasian race is a risk factor for bone loss, and that adjusting for body weight is critical in the determination of peak bone mass as well as a woman's risk of bone loss during the menopausal transition.

Perimenopausal Fracture Risk

Population-based studies, conducted mainly in Caucasian women, have contributed substantially to our understanding of fracture patterns across the aging lifespan. Among 10,902 middle-aged Swedish women followed for up to 11 years, the largest proportion of low-energy fractures occurred in the forearm (37%) followed by the ankle (12%), spine and proximal humerus (9% each), hands or feet (8%) and hip (8%).[55] Overall, the incidence of fracture was quite low, estimated at 5.5 per 1000 person-years for forearm fractures and approximately 3 per 1000 person-years for the proximal humerus.[55] Risk factors for incident fracture included older age, prior fracture, diabetes mellitus and poor health status; higher body mass index was associated with an increased risk of proximal humerus and ankle fractures but lower risk of forearm fractures.[55] Among 3068 perimenopausal women aged 47–53 years residing in Finland, 8.5% sustained a fracture during a mean follow-up period of 3.6 years, with most fractures again occurring in the extremities (26% wrist, 16% ankle, 19% hands or feet, and 15% rib).[56] The presence of low BMD, prior fracture history, nonuse of hormone replacement therapy, three or more chronic illnesses and smoking were found to be independent risk factors for perimenopausal fracture.[56] In a similarly aged cohort of 1857 women undergoing BMD screening in Scotland, the two year incidence of self-reported fracture was 2.4%; risk factors associated with an increased fracture risk included low spine BMD, prior fracture history, family history of hip fracture and postmenopausal status.[57]

Among 2171 women enrolled in SWAN followed for up to eight years, 245 reported an incident fracture.[58] The subset of women with diabetes (5%) underwent an earlier menopause transition and experienced a two-fold increased risk of incident fracture compared to women without diabetes.[58] Fracture risk is also influenced by other predisposing conditions, including genetic factors, relevant comorbidities and exposures (e.g., rheumatoid arthritis, malabsorptive syndromes, systemic glucocorticoids, aromatase inhibitors), differences in structural bone geometry and risk of falls.[1]

Clinical Management Considerations

Diet and Lifestyle Factors

The dietary and lifestyle recommendations for optimal bone health and fracture prevention during perimenopause are the same as those recommended for postmenopausal women. These include a well-balanced diet, regular exercise, smoking cessation, avoidance of excessive alcohol consumption, and fall prevention measures.[1, 59] Attention should also be given to changes in weight, particularly in light of the known association of weight loss with increasing rates of bone loss and subsequent fracture risk.[60]

Calcium and Vitamin D

Maintenance of adequate calcium and vitamin D intake remain an important component of preventive bone health. Several studies have shown that calcium and vitamin D supplementation improves BMD and reduces fracture risk in late postmenopausal women.[61–65] The Women's Health Initiative (WHI) trial found that calcium (500 mg twice daily) and vitamin D (400 IU daily) supplementation in healthy postmenopausal women increased hip BMD modestly but did not reduce hip fracture risk significantly in the cohort as a whole, though fracture risk was reduced significantly in women who adhered to study treatment.[66] However, it should be noted that women in the WHI trial received a relatively low dose of vitamin D (400 IU) and more than half were concurrently receiving hormone replacement therapy.[67] In early postmenopausal women (within the first five years of their final menstrual period), calcium administration slows bone loss from sites comprised largely of cortical bone but has little effect on skeletal sites comprised largely of trabecular bone.[67–70] The relationship between calcium supplementation and fracture risk in perimenopausal or early postmenopausal women is less clear.[67, 70]

Even though the beneficial effects of calcium administration in perimenopausal women are not well established, most experts recommend that perimenopausal women should be counseled regarding optimal calcium intake. Currently, both the National Academy of Sciences and the National Osteoporosis Foundation recommend a total daily intake of 1200 mg elemental calcium (combining dietary and supplement sources) for women over age 50.[1, 59, 71] Dietary calcium sources are preferred due to greater calcium absorption and, possibly, because of a lower risk of vascular disease, particularly in light of a recent meta analysis which reported that calcium supplementation increases the risk of cardiovascular events.[72–73] Calcium supplements, when taken, should be in conjunction with meals to maximize gastrointestinal absorption. Select populations at higher risk for reduced dietary calcium intake include older individuals and those with lactose intolerance, vegetarian diet or poor eating habits.[59, 74] A list of calcium-rich foods can be found through the Office for Dietary Supplements, National Institutes of Health (http://ods.od.nih.gov/factsheets/calcium/).

Vitamin D may reduce fracture risk through a number of mechanisms. Correcting vitamin D deficiency can improve calcium absorption and thereby treat secondary hyperparathyroidism and osteomalacia.[75–76] Additionally, correcting vitamin D deficiency can decrease fracture risk by improving muscle strength and reducing the risk of falls.[77] There is ongoing debate

as to the minimum 25-hydroxyvitamin D level required for skeletal benefits. A meta-analysis of seven clinical trials with 9,820 subjects suggested that a daily dose of vitamin D 700–800 IU is required to achieve a 25-hydroxyvitamin D level of 40 ng/mL, which is associated with 26% and 23% reduction in hip and non-vertebral fracture risk, respectively.[62] However, the findings of this meta-analysis are discordant with the 2010 National Academy of Sciences recommendations that women younger and older than 50 years should consume 600 and 800 IU of vitamin D daily, respectively, and that the minimum desired 25-hydroxyvitamin D level for skeletal benefits is 20 ng/mL.[71] Even with the ongoing debate, certain populations are at increased risk for vitamin D deficiency and may require higher doses of vitamin D (1000–2000 IU per day or pharmacologic therapy). Serum 25-hydroxyvitamin D levels reflect the dietary intake of vitamin D and the synthesis of vitamin D in response to ultraviolet B (UV-B) exposure of the skin.[78–79] Thus, women with pigmented skin or limited sun exposure due to use of sunscreen or occlusive clothing are at particular risk for vitamin D deficiency.[80] Dietary sources of vitamin D can be found through the Office for Dietary Supplements, National Institutes of Health (http://ods.od.nih.gov/factsheets/vitaminD/).

Bone Mineral Density Screening in Perimenopausal Women

Dual energy x-ray absorptiometry is the most widely available and validated modality for measurement of BMD and continues to be the preferred method for assessing osteoporosis.[81] The National Osteoporosis Foundation recommends BMD testing for women in the menopausal transition *if there is a specific risk factor associated with increased fracture risk* (e.g. prior fragility fracture or high-risk medication), but recognizes that BMD assessment may not be indicated if the results will not influence treatment decisions.[1] When BMD measurements are performed, The World Health Organization (WHO) criteria for osteoporosis apply to postmenopausal women, using the reference range for young adult Caucasian women for calculation of BMD T score.[81–82] The North American Menopause Society advises that the WHO criteria can be used for classification of perimenopausal women, but that care should be taken to interpret bone mineral density results appropriately in this setting.[59] For premenopausal women, the International Society for Clinical Densitometry advises that race-adjusted Z score (instead of T score) be used, with a Z-score of −2.0 or lower defined as “below the expected range for age” and a Z-score above −2.0 defined as “above the expected range for age” for women prior to menopause.[82]

There are currently no recommendations for osteoporosis screening in healthy perimenopausal women. The recent 2011 U.S. Preventive Task Force recommends screening for osteoporosis in postmenopausal women below age 65 years if their fracture risk is equivalent to that of a 65 year old white woman with no other risk factors.[83] This screening threshold translates to a 9.3% ten-year risk of major osteoporotic fractures calculated using the web-based World Health Organization Fracture Risk Assessment Tool FRAX, accessible at www.shef.ac.uk/frax. Using these recommendations, the majority of healthy perimenopausal women would likely not be recommended for BMD screening. Alternatively, women with low body weight comprise a higher risk subgroup where BMD testing during late perimenopause has been suggested.[3, 84] As yet, there are no controlled studies examining the benefit of early detection and intervention for low bone mineral density[83] with the exception of specific premenopausal patient subsets (e.g. breast cancer, chronic glucocorticoid therapy).

Fracture Risk Assessment

Few studies have examined the application of FRAX in perimenopausal and early postmenopausal women, most of whom will have relatively low fracture risk.[85] For the U.S. population, early revisions to FRAX were made in 2009 based on updated U.S. fracture

incidence rates, resulting in lower rates of major osteoporotic fracture, particularly at the younger ages.[86] Other risk factors considered in FRAX include age, gender, race/ethnicity, parental history of hip fracture, other clinical risk factors, and femoral neck bone mineral density. A recent study conducted in France, using data from 2651 peri- and early postmenopausal women with DXA measurements and an average follow-up of 13 years, suggested that FRAX may not improve the discriminatory value of hip BMD alone for fracture risk prediction.[87] At an individual level, FRAX is a useful clinical risk assessment tool that may also aid in patient counseling. For the U.S. population, the National Osteoporosis Foundation has recommended cost-effective osteoporosis treatment thresholds of 3% for 10-year risk of hip fracture or 20% for 10-year risk of major osteoporotic fracture using the WHO FRAX model in women with osteopenia.[88]

Treatment Considerations

There are currently no established guidelines pertaining to the treatment and prevention of osteoporosis in perimenopausal women. For perimenopausal women who have a high fracture risk or for those in whom osteoporosis treatment is indicated, the selection of therapy should be considered on an individual basis. A detailed discussion of available osteoporosis therapies and their risks and benefits is beyond the scope of this chapter. In brief, bisphosphonate drugs are considered first-line drugs for the treatment of postmenopausal osteoporosis, with evidence for reduction in risk of hip, vertebral and non-vertebral fractures.[59] However, since the optimal duration of bisphosphonate treatment remains unknown, practitioners may weigh consideration of other antiresorptive therapies for postmenopausal women with osteoporosis who are relatively young, depending on osteoporosis disease severity. Use of antiresorptive agents in perimenopausal women carries a potential hazard of prenatal exposure. Although fertility is rare and rarely desired in this age group, non-contracepting, sexually active perimenopausal women require specific counseling prior to taking bisphosphonates. Raloxifene, a selective estrogen receptor modulator shown to prevent bone loss and reduce vertebral fracture risk in elderly postmenopausal women, may be an option for younger postmenopausal women with osteoporosis, although its efficacy in preventing non-vertebral fractures and hip fractures is uncertain.[59] Because raloxifene administration may reduce BMD in premenopausal women,[89] it should not be used for the prevention of bone loss in perimenopausal women. For perimenopausal women with menopausal symptoms, treatment with estrogen plus progestin (or estrogen alone if the woman has had a hysterectomy) can be considered, although when hormone replacement therapy is assessed solely for osteoporosis indications, the risks and benefits should be weighed in conjunction with other non-estrogen based therapies,[1, 59] There are currently no recommendations with regard to estrogen therapy for prevention of postmenopausal bone loss. Once estrogen is discontinued, there does not appear to be a persisting benefit on BMD, bone loss or fracture risk.[90–92]

Summary

The findings from prospective examination of BMD change across the menopausal transition demonstrate an early and accelerated rate of bone loss, particularly in the lumbar spine. Bone loss begins to accelerate 1–2 years before menopause, concurrent with the prolonged amenorrhea that characterizes the late menopausal transition.[3, 17] Importantly, these rates of bone loss are also influenced by body size, with greater bone loss in non-obese women and those with lower body mass, independent of differences in race/ethnicity.[3, 17] The greatest reduction in BMD occurs in the year before the final menstrual period and the first two years after the final menstrual period, with lower rates of loss during the ensuing 1–7 years.[17] Clinical management considerations during the perimenopause include maintenance of adequate dietary calcium and vitamin D intake, attention to modifiable risk factors and consideration of osteoporosis screening in high risk populations with assessment

of fracture risk. The indication, benefits and risks of pharmacologic osteoporosis therapy should be individually assessed as there are currently no established guidelines addressing the treatment and prevention of osteoporosis in perimenopausal women.

Acknowledgments

The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health, Kaiser Permanente, the University of California or Massachusetts General Hospital.

Disclosures: Drs. Lo and Burnett-Bowie have received research funding from Amgen, Inc.

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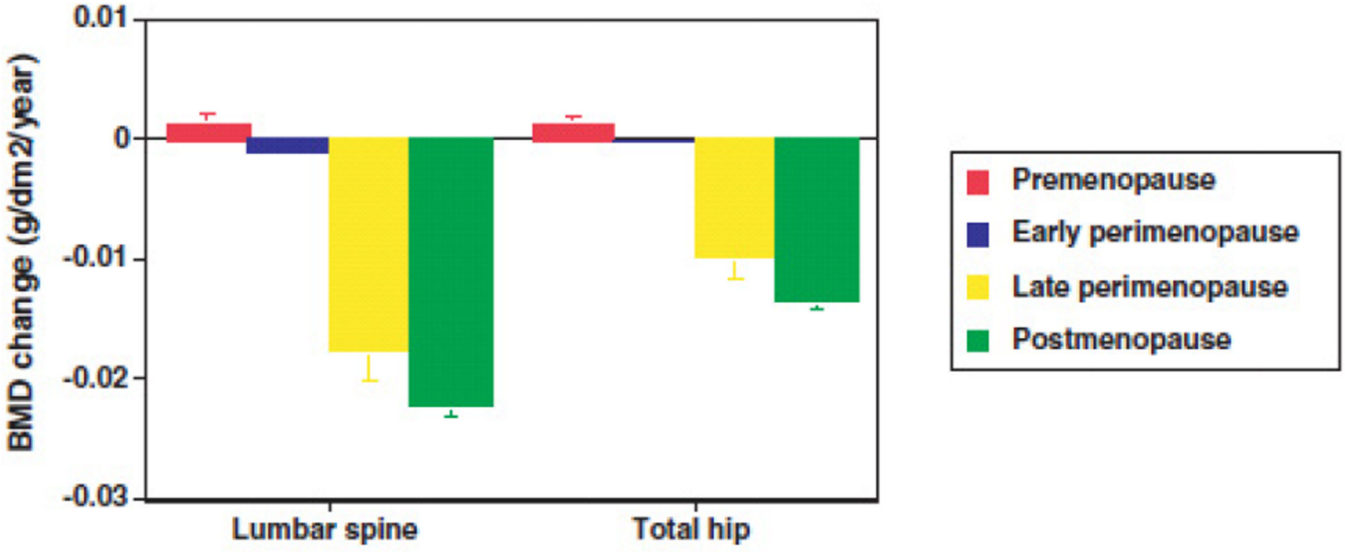

Figure 1.

Annual adjusted rates of change in bone mineral density (BMD) of the lumbar spine and total hip during the menopausal transition among 1902 SWAN participants. Error bars represent 95% confidence limits. (*Data from* Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopausal transition in a multiethnic cohort of women. Journal of Clinical Endocrinology and Metabolism 2008; 93:861–868, with permission)

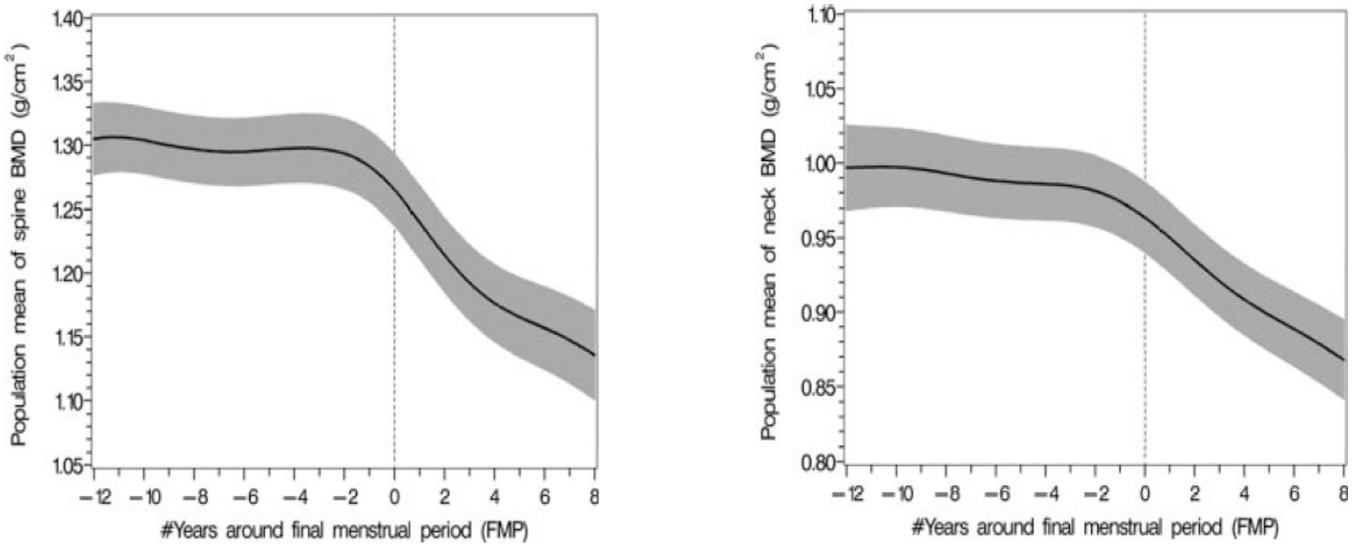

Figure 2.

The pattern of population mean lumbar spine and femoral neck bone mineral density (BMD) values in relation to the final menstrual period with 95% upper and lower confidence intervals (black solid line with shaded areas). The Michigan Bone Health and Metabolism Study. (*Data from* Sowers MR, Zheng H, Jannausch ML, et al. Amount of bone loss in relation to time around the final menstrual period and follicle-stimulating hormone staging of the transmenopause. Journal of Clinical Endocrinology and Metabolism 2010; 95:2155–2162, with permission)