HHS Public Access

Author manuscript

Obstet Gynecol Clin North Am. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Obstet Gynecol Clin North Am. 2018 December ; 45(4): 695–708. doi:10.1016/j.ogc.2018.07.012.

Bone Health during the Menopause Transition and Beyond

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Keywords

Perimenopause; bone strength; bone turnover markers; transmenopausal bone loss; race/ethnicity differences; bone loss trajectories; osteoporosis; fracture

Introduction

The Study of Women's Health Across the Nation (SWAN) has significantly added to our understanding of changes in women's bone health over the menopause transition (MT), advancing the knowledge base regarding a critical period that has major impact on osteoporosis risk in older ages. SWAN is one of a few, large, race/ethnically diverse, cohorts with comprehensive longitudinal measures of bone health over the MT, and serves as a primary source for this review. Conducted in a large multi-ethnic population of more than 2000 women followed for over 20 years across five clinical centers in the United States, the SWAN Bone Study has also contributed greatly to understanding race/ethnicity differences in both pre- and post-menopausal bone health. We start this review of recent findings on bone health over the MT with a discussion of racial/ethnic differences in various aspects of bone health, and then go on to provide a broad overview of changes in bone metabolism and strength during the MT, and briefly summarize new data on factors that influence fracture risk in the perimenopause and postmenopause.

Racial/Ethnic Differences

The incidence of low-trauma fracturevaries substantially across race/ethnicity groups, both nationally and worldwide. Low-trauma fractures of the hip for instance, which are a major cause of morbidity, physical disability, and early mortality in older Americans [1], are

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The authors would like to thank Gail A. Greendale, MD (David Geffen School of Medicine at UCLA) for her expert review and suggestions for improvement of this chapter.

considerably more common in White women than in Asian, Black, and Hispanic women in the US [2,3,4]. Although low bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is the most reliable predictor of hip fracture risk *within* race/ethnicity groups[5,6,7,8], BMD does not account for the differences in fracture risk *between* race/ethnicity groups. Japanese women for example, who have lower risk of hip fracture than White women, also have lower BMD on average than White women[9,10]. On the other hand, Black women have fewer fractures than White women, even after controlling for differences in BMD[6].

At the SWAN baseline, BMD in the femoral neck, which is considered the best bone site at which to measure BMD for hip fracture prediction [11], was significantly higher in Black women than in White women and lower still in Chinese and Japanese women, with mean differences of 14–24% between Black women and the other groups [12,13]. While some of these differences in BMD can be explained by body weight, the discrepancy between BMD and fracture rate differences by race/ethnicity is not completely explained by body weight differences between the groups.

Racial/Ethnic Differences in Bone Size and Geometry

Differences by race/ethnicity in bone size and geometry might add explanatory power. Hip structural analysis showed that although Black women have greater BMD in the femoral neck (the site of 45% of osteoporotic hip fractures) than White women in SWAN, the width (or outer diameter) of the femoral neck is smaller in Black women[14]. At a given BMD, a smaller femoral neck width (FNW) means there is less bone mineral content in a cross section, and thus less strength to resist fracture forces[15]. It appears that the BMD advantage in Black women may be offset by their smaller FNW. In contrast, Japanese women had lower BMD in the femoral neck than White women, but this relative disadvantage was offset by their larger FNW, demonstrating the importance of not examining BMD in isolation.

In addition to the amount of bone mineral in a cross section of the femoral neck, which is determined by both BMD and FNW, the ability of the femoral neck to resist fracture is also affected by how the bone mineral content is distributed in the cross section. If it is mostly confined to a thin cortical shell, it increases the likelihood of buckling like a thin straw. The buckling ratio, the ratio of outer diameter to width of the cortical shell, is a measure of susceptibility to fracture from buckling[16]. Compared to White women in SWAN, the buckling ratio in the femoral neck was higher on average in Black and Japanese women and lower in Chinese women[14].

Racial/Ethnic Differences in Composite Indices of Femoral Neck Strength

Other than the bone's ability to resist fracture forces, risk of fracture also depends on the magnitude of the forces on bone during a fall. These forces increase with both body weight and body height, which implies that a level of BMD and bone size/geometry that is adequate to prevent fractures in a lighter or shorter individual may not be adequate in a taller or heavier one[17]. Composite indices of femoral neck strength integrate these major determinants of fracture risk (namely, BMD and FNW obtained from routinely obtained DXA scans and body height and weight) to capture bone strength relative to the load that

bone would be exposed to in a fall from standing height. They have been shown to be inversely associated with hip fracture risk in community-dwelling older adults[18]. We found in SWAN using data from the baseline visit when all women were either premenopausal or in early perimenopause, that despite having lower BMD in the femoral neck, both Japanese women and Chinese women had higher average values of femoral neck composite strength indices than White women, consistent with the lower risk for fracture in Asian women[13].

Not only do the racial/ethnic differences in femoral neck strength indices explain the paradox of lower fracture risk in Asian women despite their lower BMD, they also reduce the importance of race/ethnicity as a determinant of fracture risk. Each standard deviation (SD) increment in the composite strength indices measured at the SWAN baseline visit was associated with a 34–41% decrement in fracture hazard over the 9 years of follow up. In addition, while race/ethnicity predicted incident fractures independent of BMD, it did not add independent prediction or discrimination ability over that provided by the femoral neck composite strength indices[19].

Racial/Ethnic Differences in Trabecular Microstructure

Not only do macrostructural aspects of bone contribute to bone strength, so does bone microarchitecture. Thinned trabecula and diminished connectivity are seen in the bones of postmenopausal women, which lead to reduction in load bearing capacity of older bones[20]. Femoral neck composite strength indices may capture aspects of cortical bone strength relative to load, but like BMD, they ignore the contribution of trabecular microarchitectural integrity to bone strength, especially in vertebral bodies in the spine, which are the site of compression deformities, also a significant source of morbidity in older men and women. Not surprisingly, trabecular bone score (TBS), an index of trabecular thickness and connectivity obtained from DXA images of the lumbar spine[21], predicts incident fracture risk independent of BMD[22,23].

Several studies have documented racial/ethnic differences in trabecular microarchitecture, starting in premenopause. One study found TBS is lower in Japanese women than in age-matched White women, and that the difference increases with age[24]. Data from NHANES 2005–08 show that non-Hispanic Whites have higher TBS than non-Hispanic Blacks or Mexican Americans in all age groups[25]. These TBS comparisons need to be considered in light of body mass index (BMI) differences between race/ethnicity groups, because TBS, as currently measured, is underestimated in individuals with more soft tissue around the lumbar spine[26].

There are also differences by race/ethnicity in the shape and structure of individual trabeculae, with post-menopausal Black women in SWAN having more plate-like trabeculae and White women having more rod-like trabeculae, as imaged using high-resolution peripheral quantitative computed tomography (HR-pQCT) [27].

Bone Loss During The Menopause Transition

The MT is a critical period of change in bone strength in women, which sets the stage for development of osteoporosis and fracture susceptibility in older ages[28]. It has been

suggested that the MT represents a time-limited window of opportunity to intervene to prevent rapid bone loss and microarchitectural damage to stave off osteoporosis in later years[29]. Data from SWAN have provided substantial new knowledge and insights about these changes during the MT.

Changes in Bone Mineral Density over the Menopause Transition

Several prospective cohorts have documented declines in BMD over the MT[30,31], andSWAN established that there is a *rapid phase of bone loss* in a 3-year period around the final menstrual period (FMP); BMD begins to decline around 1 year prior to the FMP, and continues to decrease in early postmenopause, with a slight reduction in loss rate around 2 years after the FMP[32] (Figure 1). This pattern of initial acceleration of change before the FMP and a deceleration after the FMP, is seen in a variety of hormonal, metabolic, and other indicators of health, which has led researchers to refer to this interval as the *transmenopause*. This interval includes both perimenopause and early postmenopause but is best defined using the date of the FMP and not menstrual bleeding patterns, because of the large between-women variability in the length of the different menstrually defined MT stages. In fact, even in the year after the FMP, 30% of women could be classified as early perimenopausal based on bleeding patterns[32].

During the 3-year-long rapid bone loss phase in the transmenopause, the average rate of decline in BMD in White women was 2.5% per year in the lumbar spine and 1.8% per year in the femoral neck[32]. Prior to the transmenopause, there was no appreciable change in BMD at either bone site. Adjusted for BMI, Black women had smaller percentage losses at both bone sites (2.2% per year in the spine, 1.4% in the femoral neck) and Japanese and Chinese women had larger losses at the femoral neck (2.1% and 2.2% per year, respectively)[32].

Not surprisingly, changes in estradiol and follicular stimulating hormone (FSH) levels during the MT appear to be driving these changes in bone mass. The pattern of hormonal changes mirror those in BMD, with the most rapid increases in FSH and decreases in estradiol occurring in the years around the FMP (Figure 1). Every doubling of FSH level during the transmenopause was associated with an additional 0.3% decline per year in BMD at both the femoral neck and lumbar spine[33]. Consistent with a causal role for estrogen is the finding from at least two studies that women with vasomotor symptoms (hot flashes and night sweats), which have been etiologically linked to declining estradiol levels, have lower BMD[34,35]. Also consistent with a causal role for hormones, women in SWAN who initiated sex steroid hormone therapy during the MT had 0.4% per year less decline in BMD[36].

Analysis of initiation of other medications in SWAN also suggest that the women who use thiazide diuretics may lose less bone mass at the femoral neck than women who women who use ACE inhibitors or don’t use antihypertensive medications [37]. Similar analysis of initiation of proton pump inhibitors, H2 receptor antagonists, and antidepressants by participants did not reveal any links between these medications and the rate of bone loss over the MT[36].

Changes in Composite Strength Indices over the Menopause Transition

Declines in cortical bone mass during the transmenopause result from endosteal resorption by osteoclasts, which leads to compensatory bone formation at the outer periosteal surface. This results in increases in the outer diameter of long bones such as the radius and the femoral neck[38,39]. The width of the femoral neck increases on average by 0.4% per year during the MT, but it is not adequate to compensate for the decline in BMD, so that the composite indices of femoral neck strength decline on average by 0.7% per year[40]. The compensatory increase in external bone size (the outer diameter) of cortical long bones during the MT comes at a cost; it increases the susceptibility of long bones to failure by buckling[16]. In SWAN, the buckling ratio - a measure of this susceptibility, increased during the transmenopause by 2% each year[40].

The composite indices reflect bone strength relative to load borne, and load is proportional to body weight; thus, changes in the composite indices are also affected by changes in body weight. Body weight generally increases in midlife; the average increase in White women in SWAN was 0.4% per year. There were racial/ethnic differences in the rate of change in both bone size (femoral neck width) and body weight. Both Japanese and Chinese women had smaller increases in body weight than White women, but the increase in femoral neck width was also smaller in Japanese women. The combined effect was that the composite strength indices declined at the slowest rate in Chinese women and the fastest in Japanese women. Despite these differences in decline rate, the strength indices remained consistently lower in White women than in Black, Chinese, and Japanese women throughout the study[40].

Because the external bone size of cortical bones reflects cortical bone remodeling, correlations have been observed between femoral neck width and both cortical thickness and intracortical porosity [41]. This has led to the hypothesis that women who start with a wider femoral neck at baseline experience greater bone loss during and after the MT. An analysis of longitudinal SWAN data from the Pittsburgh study site did indeed show that bone lost over 14 years of follow up was greater in women who had wider femoral necks[42], pointing to the importance of measuring bone size in addition to BMD in assessing a woman's risk for osteoporosis and fractures.

Changes in Bone Turnover Markers over the Menopause Transition

The pattern of bone loss over the MT parallels changes in markers of bone turnover: Markers of both bone resorption and formation increase over the MT[31]. Urinary N-terminal telopeptide of type I collagen (U-NTX), a marker of type I collagen breakdown, starts increasing 2 years before the FMP, peaks approximately 1.5 years after the FMP, and plateaus thereafter[43] (Figure 1). Decreases in levels of circulating estradiol and increases in FSH occur on nearly the same time frame, while decreases in BMD lag by about 6 months, consistent with a causal pathway from hormones to bone resorption to bone mass (Figure 1). Further support comes from the observation that women who report frequent vasomotor symptoms (6 or more days in 2 weeks), which may indicate either larger declines in circulating estradiol levels or heightened sensitivity to the decline, have significantly higher levels of U-NTX[44].

After restricting the comparisons to women with BMI under 29 kg/m^2, Japanese women had the highest, and Black women the lowest, level of peak (postmenopausal) U-NTX[43], consistent with the rate of BMD decline being greatest in Japanese women and smallest in Black women[32].

If the increase in bone resorption during the MT is indeed causally related to transmenopausal bone loss, then measurement of U-NTX during the MT might be useful in estimating the magnitude of bone loss in the rapid phase. SWAN longitudinal data show that U-NTX measured both in early postmenopause (when U-NTX has peaked and plateaued) and in late perimenopause (when U-NTX has risen considerably but not yet peaked) does indeed strongly predict the rate of bone loss in transmenopause in the femoral neck and lumbar spine. However, U-NTX measured when women were still premenopausal or in early perimenopause, did not predict the rate of transmenopausal bone loss[45].

Because bone formation and resorption are coupled, markers of both formation and resorption increase when there is bone turnover, regardless of whether there is net bone gain (as after initiating an exercise regimen) or bone loss. Therefore, in younger women, some of whom may yet have entered the rapid phase of MT-related bone loss, bone resorption markers such as U-NTX may not be able to predict who is losing bone and how much. SWAN measured serum levels of bone formation marker, osteocalcin, from fasting morning blood. The in-balance relationship between osteocalcin and U-NTX was estimated from measurements of the two turnover markers in 685 women who were more than 5 years before their FMP at the time, and presumably in a state of balance between bone formation and resorption. This estimated in-balance relationship was used to create, for every woman in the cohort, a bone balance index (BBI) that reflects her level of bone formation that is in excess of bone resorption. Not only was the BBI smaller (less favorable) in women who were closer to the FMP (0.3 SD smaller for every year closer to the FMP; P = 0.007), BBI also predicted the rate of BMD decline in the lumbar spine over the next 3–4 years. Each SD decrement in BBI was associated with a 38% higher odds of faster-than-average loss of BMD in the lumbar spine (P=0.008, c-statistic 0.76)[46].

Fracture Risk During and After The Menopausal Transition

Fractures during the MT are not uncommon, although women are still in midlife and very few meet criteria for osteoporosis. Between the ages of 42 and 58 years, which included a median of 6 years after the FMP, one in six women in SWAN had one or more fractures, at a rate of 11 first fractures per 1000 person-years. The majority (59%) of these fractures were *not* minimum-trauma fractures attributable solely to osteoporosis. Yet, low BMD, low indices of femoral neck composite strength, and high levels of U-NTx, did strongly predict the risk of fracture in this midlife period[19,47]. Inaddition, 3.2% of women had a vertebral compression deformity by the 8th to 10th follow up visit when mean age was 54 years, and as expected, low BMD at the SWAN baseline visit was a major risk factor, with the odds increasing by 61% per SD decrement in BMD in the lumbar spine. Over the next 7 years (until the 13th follow up visit) the observed incidence of new vertebral deformities was 2 per 1000 person-years[48].

In addition to low BMD, a number of other factors increase the risk of fracture over the MT. Among indicators of socioeconomic status (SES), low education, but not low income, was associated with greater incidence of fracture in non-White women[49]. That this association was seen only in non-White women may be partly explained by the increased prevalence of risk factors for low bone accrual in childhood and young adulthood (such as inadequate vitamin D intake, smoking, and depression) in underprivileged minority communities in the US; the combination of low SES and minority race/ethnicity status may be synergistically deleterious to bone health. Increased parity is often seen in low SES and minority women, and both parity and lactation have been linked to poor bone health. In SWAN, lifetime parity was associated *positively* with composite indices of femoral neck strength, while accumulated duration of lactation was associated negatively with BMD in the lumbar spine; yet there were no associations between either lifetime parity or accumulated duration of lactation with fracture hazard after age 42[50]. Both low SES and minority race/ethnicity status are also associated with obesity and increased prevalence of chronic inflammation and diabetes, all of which have been linked to increased fracture risk.

Metabolic Risk Factors and Fracture Risk

Several observational studies have noted that diabetics have more fractures despite having higher BMD than matched non-diabetics. Women with diabetes at the baseline SWAN visit had higher BMD at both the hip and spine than non-diabetics, yet they had twice as many fractures over the first 8 years of follow up. This can only be partly explained by the observed faster rate of decline in hip BMD in diabetic women but is inconsistent with their slower rate of decline in spine BMD[51]. Consistent with their higher fracture risk, diabetic women in SWAN did have lower levels of femoral neck composite strength indices (0.2 SD lower) at the baseline visit than non-diabetic women. In those without diabetes, there was a graded inverse relationship between insulin resistance and femoral neck strength indices, such that each doubling of HOMA-IR was associated with 2.4% decline in the strength indices[52]. There are also differences in bone microarchitecture which are not captured by either BMD or the strength indices. In postmenopausal SWAN women, although there were no differences in BMD at the radius by diabetes status, diabetic women had 26% greater cortical porosity measured by HR-pQCT than women without diabetes[53].

Chronic inflammation is also a risk factor for osteoporosis and fractures, but in the absence of inflammatory conditions like rheumatoid arthritis and inflammatory bowel disease, associations have not been consistently found between sub-clinical chronic inflammation and low BMD. In SWAN, in the general population of women going through the MT, fracture hazard increased monotonically with serum levels of inflammatory biomarker, C-reactive protein (CRP), above a threshold level of 3 mg/L, yet there was no association between CRP level and BMD at the baseline visit. However, CRP level was inversely associated with the femoral neck composite strength indices (0.04 SD decrement per doubling of CRP level), and the association explained the link between high CRP and increased fracture hazard[54]. Increased plasma levels of triglycerides, another component of the metabolic syndrome, is also an independent risk factor for fracture in midlife. Women with triglycerides level at the SWAN baseline visit higher than 300 mg/dL had a 2.5-fold

greater hazard for non-traumatic fractures than women with baseline TG lower than 150 mg/dL [55].

Pleiotropic Effects of Obesity on Fracture Risk

Obesity has multiple effects on bone health, some positive, others negative. Greater body weight in an obese individual can stimulate bone formation and lead to greater BMD, and the increased tissue padding at potential sites of impact in a fall (such as over the greater trochanter) can also protect against fractures, but other aspects of an obese body habitus increase fracture risk, e.g., by increasing impact forces in a fall from standing height. In SWAN, greater BMI was associated with greater BMD but smaller composite indices of femoral neck strength, suggesting that although BMD increases with greater skeletal loading in heavier individuals, the increase may not be sufficient to compensate for the increase in fall impact forces. Indeed, after controlling for BMD, greater BMI was associated with increased fracture risk, consistent with the greater impact forces in a heavier individual. With controls for the femoral neck composite strength indices (which also account for greater impact force in heavier individuals), greater BMI was associated with *reduced* fracture risk (5% reduction in fracture hazard per unit increment in BMI), consistent with a protective role for soft tissue padding in obese women. This protective association was eliminated when a control for hip circumference, a surrogate marker for soft tissue padding over the hip, was added to the model, confirming the multiple ways by which obesity influences fracture risk in women[56].

Summary and Clinical Implications

In summary, the prospective assessment of bone health in a large, multi-ethnic cohort of women through and after the MT has confirmed previously seen differences by race/ethnicity in older women, pointed out the importance of looking beyond traditional BMD measurement to include macro and microstructural aspects of bone in the context of body size, and documented the trajectories of change in various aspects of bone health across the MT. It has also highlighted the role of SES and metabolic risk factors in bone health during this critical period, and illuminated the pleiotropic effects of obesity on fracture risk in women.

These findings point to the importance of early intervention, including but not necessarily limited to life style modification, to ward off osteoporosis and fractures in later years. To this end, data from SWAN show that greater physical activity in midlife in each of the domains of home, work, active living (daily routine), and sports, is associated with larger femoral neck composite strength indices[57]. The importance of a healthy diet cannot be ignored, especially the need to maintain an adequate calcium and vitamin D intake. In longitudinal follow up of the Aberdeen Prospective Osteoporosis Screening Study, greater dietary intake of calcium was associated with smaller loss of BMD in the femoral neck during the MT[58]. In SWAN women, levels of serum 25-hydroxy vitamin D below 20 ng/mL at the third follow up visit (when mean age was 48.5 years) were associated with 85% higher hazard for incident non-traumatic fractures[59]. Greater intake of isoflavones (such as from soy products) was also associated with greater BMD at the baseline visit[60,61]. However, more of a good

thing is not always better. Just as excessive exercise may have deleterious effects on health[62], excessive calcium and vitamin D supplementation can also be harmful: Excess calcium intake can lead to nephrolithiasis[63], and high-dose Vitamin D supplementation in older ages can increase falls[64,65] and raise the risk of fractures[66].

Screening and Treatment

Current guidelines (from the United States Preventive Services Task Force) for osteoporosis screening in midlife (between the ages of 50 and 64 years) recommend using the Fracture Risk Assessment calculator (https://www.sheffield.ac.uk/FRAX/) to estimate the 10-year risk for osteoporotic fracture as a first step, and to proceed only if the estimated 10-year risk exceeds 9.3%. However, in those 50–64 year old, only about one third of the women who would meet treatment criteria by BMD (T score ≤−2.5) and only one quarter of the women who experience a fracture over the next 10 years would meet the FRAX-based threshold for screening[67,68]. As a result, the current clinically used strategy for screening does not identify the majority of women who could benefit from treatment. Unfortunately, data on treatment options in midlife are also limited. Currently available drugs for treating osteoporosis have significant adverse effects that increase with duration of treatment. Data on the benefits vs. harms of pharmacotherapy beginning in the 50s and continued for multiple decades are not available. Use of drug treatment in younger ages may also leave women with fewer options for pharmacotherapy in their 70s, when their risk for hip fracture begins to increase[69].

Future Work

Because bone mass declines rapidly during the transmenopause and it is accompanied by deleterious changes in trabecular and cortical microarchitecture (including decreased trabecular number, increased trabecular spacing, conversion of trabecular plates to rods, and increased cortical thinning and porosity)[70,71] which may be irreversible, the start of the transmenopause may be the optimal, but time-limited, window for early interventions to prevent osteoporosis and reduce the risk of debilitating fractures in older ages. To develop and test such a strategy, we need to be able to determine, before substantial bone loss has occurred, whether transmenopausal bone loss is imminent (to be able to time the intervention optimally) and which women will lose the most bone during the transmenopausal rapid loss phase (to select the women who will gain the most from early intervention). The rapid bone loss phase of transmenopause begins 1 year before the FMP, but the FMP date is not knowable until 1 year after it has passed, by which time 2 of the 3 years of the rapid bone loss phase will have passed. Sex steroid hormones, bone turnover markers, and anti-Mullerian hormone measurements are all potential indicators of the onset of the transmenopause, and future work will examine their ability to jointly do so. The same biomarkers, in combination with metabolic risk factors, may be of use in identifying the women who are likely to lose the most bone mass over the MT.

Acknowledgements

SWAN has grant support from the National Institutes of Health (NIH), Department of Health and Human Services, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The content of

this review chapter is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

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Synopsis

The menopause transition is a critical period for bone health, with rapid losses in bone mass and strength occurring in a 3-year window bracketing the date of the final menstrual period. Declines in bone mass are accompanied by deleterious changes in bone macrostructure and microarchitecture, which may be captured by changes in composite strength indices and indices of trabecular thickness and connectivity. The onset of the rapid bone loss phase is preceded by changes in sex steroid hormones and increases in markers of bone resorption, measurements of which may be clinically useful in predicting the onset of the rapid loss phase.

Key Points

- The substantial differences in fracture risk between race/ethnicity groups are not explained by between-group differences in bone mineral density.
- Composite indices of femoral neck strength capture the combined impact of bone density, bone size, and body size on fracture risk, and explain observed racial/ethnic differences in fracture risk.
- Bone resorption begins increasing 2 years *before* the final menstrual period (FMP), peaks approximately 1.5 years after the FMP, and then plateaus.
- In concert with increases in bone resorption, there is a rapid phase of bone loss during the menopause transition, in a 3-year period around the FMP.
- Metabolic factors during the menopause transition, such as insulin resistance, inflammation, and obesity, are associated with lower bone strength and increased fracture risk.

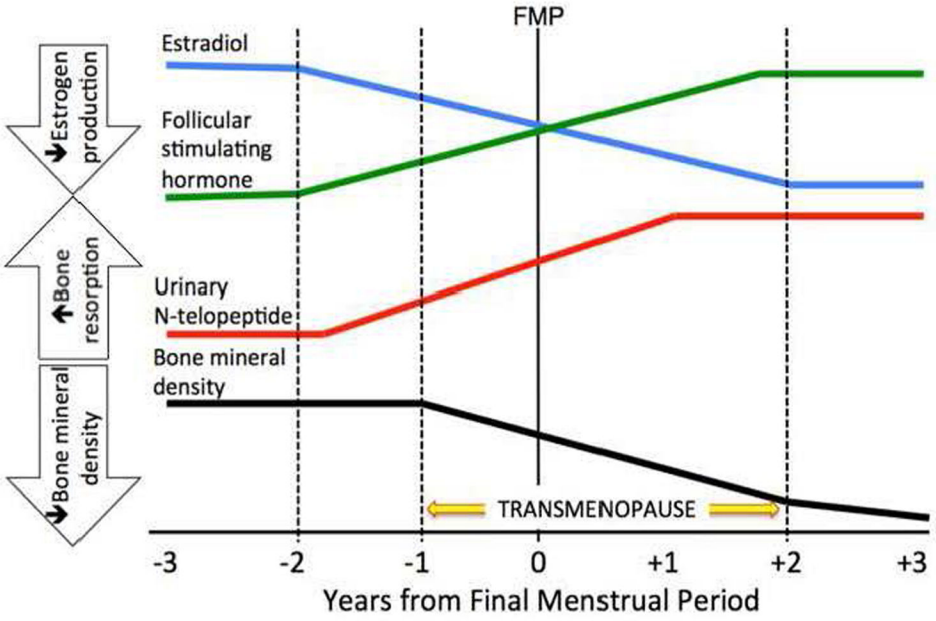

Figure 1:

Schematic depiction of the trajectories of sex steroid hormones (estradiol (blue) and follicular stimulating hormone (green)), bone resorption marker urinary N-telopeptide (U-NTX) (red), and bone mineral density (black) over the menopause transition. Rapid bone loss occurs during transmenopause, a period that lasts from 1 year before to 2 years after the final menstrual period (FMP). Changes in hormone levels and in U-NTX start about 1 year before the transmenopause. *Courtesy of* A. Shieh, MD, Los Angeles, CA.