




NEW PERSPECTIVES

A continuum of
BONE
HEALTH

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The relation of bone mineral density (BMD) to fracture risk is established. What may not be as clearly appreciated is the contribution of bone quality to skeletal fragility. Beyond the years of peak bone accrual, a slow sustained attrition in BMD parameters accompanies aging; postmenopausal exacerbations in this loss of BMD are well recognized and parallel a rising propensity for fragility fractures.

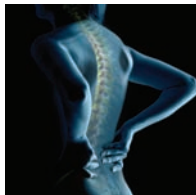
This article describes how skeletal deteriorations associated with reproductive and chronological aging occur as a continuum throughout the woman's life rather than as a sudden phenomenon after the cessation of menses. By viewing bone health as a continuum, clinicians may be better able to identify individuals at risk for skeletal compromise, either because of suboptimal peak bone accrual or secondary to premature bone loss.

Although low premenopausal BMD does not translate into enhanced fracture risk for young women, as it does for an older population,^{1,2} a BMD nadir is likely to be reached during the early postmenopausal years for women who entered menopause with low bone mass. Hence, women diagnosed with low BMD in the pre- and perimenopausal years may well be likely candidates for an enhanced lifetime risk for fracture.

A secondary aim of this discussion is to place the data about calcium and vitamin D supplementation from the Women's Health Initiative in the context of our present understanding of skeletal health.³ A "common sense" preventive health approach will benefit both the patient and the provider by optimizing skeletal health and minimizing the need to revert to aggressive interventions.

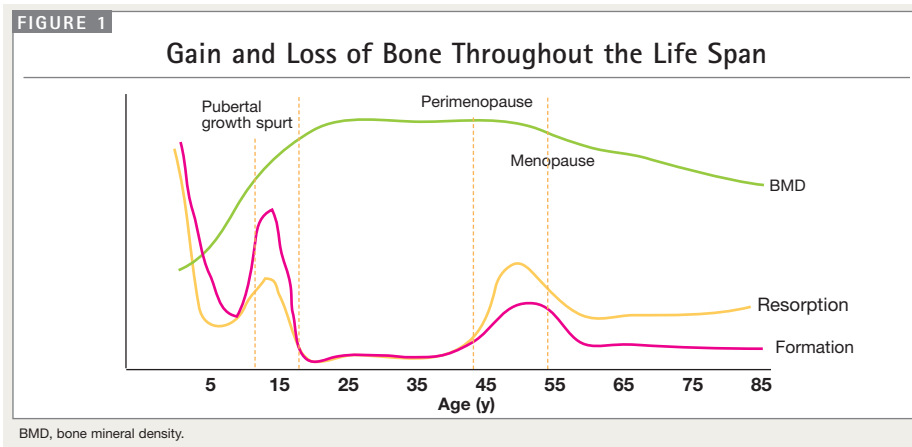
The bone health continuum over the female reproductive life span

The finely orchestrated process of bone resorption and formation known as bone turnover characterizes bone health. Bone turnover is sensitive to the reproductive hormone milieu (FIGURE 1). Both peak bone accrual and bone maintenance



KEY POINT

Diminished ovarian reserve and vasomotor symptoms correlate with low BMD in premenopausal women.



are markedly influenced by the reproductive physiology. The exaggerated bone loss in peri- and postmenopause is attributable to an enhanced bone turnover secondary to declining estrogen levels.⁴ Interestingly, in regularly cycling premenopausal women, an up-regulation of bone resorption is described during periods in the menstrual cycle of relative hypoestrogenism, namely, the early follicular and the late luteal phases.^{5,6} These latter observations underscore the influences of ovarian estrogen on bone metabolism.

Recent data suggest that estrogen may not be the only player in this context. Elevated levels of follicle-stimulating hormone (FSH) are a hallmark of reproductive aging. A correlation has been shown between serum levels of FSH and bone turnover markers in the premenopausal as well as the postmenopausal population.⁷⁻⁹ More recently, direct effects of FSH at the level of the osteoclasts have been demonstrated. These *in vitro* data are important because they suggest that declining estrogen and increasing FSH are independent mechanisms at play in mediating the bone loss accompanying reproductive senescence.¹⁰ Future studies hopefully will elucidate the individual contributions of high FSH and low estrogen in skeletal attrition.

BMD and ovarian reserve

Recent data highlight the implications of declining ovarian reserve parameters on skeletal metabolism and mass. There is an emerging appreciation that both “ovarian reserve” and “skeletal reserve” can be viewed as a continuum of progressive decline over the reproductive life span.

Indeed, factors, such as smoking, that are known to adversely influence ovarian reserve are also recognized detractors to skeletal health.

The positive influence of replete ovarian reserve on BMD parameters in premenopausal women has been noted.^{11,12} An ongoing cross-sectional study at the Montefiore Institute for Reproductive Medicine and Health in New York suggests the converse to also be true: Diminished ovarian reserve and symptoms of vasomotor instability in the premenopausal period may be associated with low BMD. In this study, researchers are offering BMD assessment to premenopausal patients (mean age 36 ± 3 years) presenting for infertility consultation. A linear association has been found between BMD, assessed using quantitative heel ultrasound, and early follicular-phase inhibin B levels, a recognized marker of ovarian reserve.

The investigators also have looked at an association between serum levels of FSH, which reflect ovarian reserve status, and the bone resorption marker N-telopeptide (NTx). FSH levels above 13 mIU/mL were noted to associate with significantly higher NTx levels, reflecting enhanced bone turnover. The prevalence of low BMD—Z score of <1 standard deviation (SD) below the population mean—was noted to be significantly higher in women diagnosed with diminished ovarian reserve (defined as FSH >10 mIU/mL) compared with women with normal ovarian reserve (47% vs 17%, $P=0.04$) (FIGURE 2).

As additional evidence supporting the relation of ovarian function to BMD, a significantly higher prevalence of low BMD was noted in those reporting symptoms of vasomotor instability than in asymptomatic women (63% and 14%, respectively)

Dr Pal reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

(FIGURE 3). The study is ongoing to better elucidate this emerging relation between ovarian reserve and bone metabolism in the premenopausal period.

Bone health assessment and technological constraints

BONE MINERAL DENSITY. Dual energy x-ray absorptiometry (DXA) remains the gold standard tool for determining BMD in clinical practice, but the technology does have constraints. DXA provides an estimate of the skeletal mineral content and thereby bone strength, but it offers limited insight into additional aspects of bone quality, which are known to influence fracture risk, such as osteomalacia. Terminology in DXA reports varies with the age and gender of the patient.

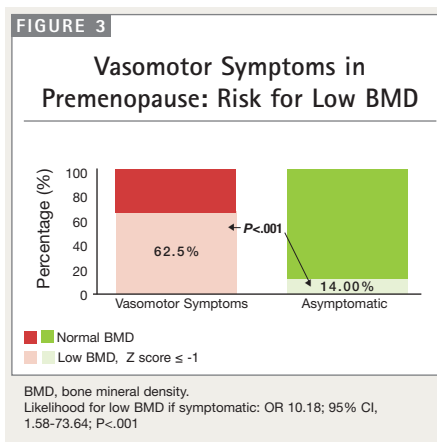
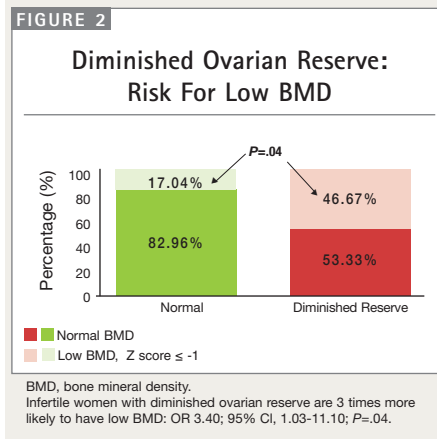
T scores describe the patient's bone mass in SD compared with the mean peak bone mass for healthy young adults, and are used to interpret BMD exclusively in postmenopausal women. Although low BMD parameters do translate into fracture risk in the entire aging population, the terms osteoporosis and osteopenia based on T scores are applicable strictly to the postmenopausal population.

Z scores are the patient's BMD in SD compared with the mean BMD for age- and gender-matched population controls. BMD in men and premenopausal women is best reflected by Z scores.

Although osteoporosis and osteopenia are defined by specified T scores, it is important to realize that the fracture risk does not jump dramatically only at these thresholds, but rather increases steadily as the BMD decreases; a 2-fold increase in fracture risk accompanies each SD decrease in BMD.¹³

BONE QUALITY. Bone quality is known to affect fracture risk. The number, width, and volume of trabeculae, cortical bone thickness as well as the quality of bone collagen influence fracture risk independent of age and gender. At present, technologies that may provide insight into these aspects of bone quality, such as quantitative bone computed tomography (CT), high resolution CT, magnetic resonance imaging, and even quantitative ultrasound, are not routinely used in clinical practice.

RISK FACTOR ASSESSMENT. Individual risk factors, such as low body weight, current smoking, lifelong low calcium intake, alcohol excess, among others, have been associated with low BMD and osteoporotic fractures.¹⁴ Treatment with Depo-



TABLE

Lifestyle and Bone Health

In the context of identifying pathologic processes detrimental to skeletal integrity, the role of covert influences cannot be minimized. The following list of factors should be considered:

Exercise

Exogenous detriments

- Excessive alcohol
- Smoking

Nutritional constraints

- Celiac disease
- Dairy intake
- Excessive protein consumption
- Lactose intolerance
- Vegetarian diet

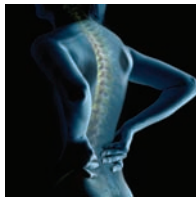
Psychodynamics

- Depression
- Stress

Provera, corticosteroids, chemotherapy, and radiation therapy contributes to low BMD in premenopausal years (TABLE). Despite the evolving awareness of risk factors for

KEY POINT

T scores decline with age: even if a patient's BMD is exactly the same at a 2-year follow-up, her T score will be lower.



KEY POINT

Meta-analyses and subset analyses of the WHI Ca plus D trial show a trend toward benefit with calcium and vitamin D.

skeletal compromise, clinical risk factor assessment demonstrates poor sensitivity in identifying patients at risk for future fractures.¹⁵

In the postmenopausal and aging population, high bone turnover itself is an independent risk factor for fracture and especially so when it accompanies low BMD.^{16,17} It is important to appreciate that in a setting of enhanced bone turnover, the actual changes in BMD may lag by years and a single BMD assessment may not fully communicate the dynamics of skeletal events. As resorption exceeds bone formation over a period of time, the net bone loss will eventually translate into a compromised skeleton. Clinical vigilance is crucial, as these phenomena may not be apparent until a fragility fracture is sustained.

Treatment decisions

Once low BMD is identified in a young woman, the critical question is whether she has a low but stable peak bone accrual or excessive bone loss and, therefore, a pathologic phenomenon.

Low but stable BMD in the absence of any identifiable risk factors or evidence of excess bone turnover is reassuring; such a patient does not need an aggressive medical intervention. This patient should be counseled regarding a healthy lifestyle that includes weight-bearing and moderate impact exercise for 10 to 30 minutes at least 3 times per week and elimination of any identified detriments. She will benefit from a nutritional assessment to determine whether her protein intake is excessive and she should optimize her dietary calcium and vitamin D. These measures should suffice and may even improve BMD; her skeletal health should be reassessed as she ages.

The urgency of therapeutic intervention needs to be assessed on the basis of the individual patient's risk profile, including BMD assessment (SIDEBAR).¹⁴ An assessment of serum markers of bone turnover may be useful in determining the timing and the choice of a therapeutic approach. Testing for a single marker of resorption (eg, NTx) and a marker of formation (eg, bone-specific alkaline phosphatase) can provide a sense of the skeletal dynamics.

The many pharmaceutical options for treatment are beyond the scope of this article; a useful review was published in 2006.¹⁸

The calcium and vitamin D question

Adequate calcium and vitamin D are essential for bone health at any age.

Testing and Treatment

Treatment is indicated for a patient with a fracture or a T score of -2 or below. For moderate-risk patients, guidelines for re-evaluating bone mineral density (BMD) are below.

Testing moderate-risk patients (T score of -1.5 to -2)

- ▶ Repeat testing at 1 year, unless there is an enhanced risk for rapid bone loss.
- ▶ Use the same device in repeat tests.
- ▶ Evaluate for secondary causes of bone loss and consider an intervention if:
 - BMD declines in excess of the least significant change for the device *and*
 - Nutrition and lifestyle changes have been tried

Testing patients on pharmacologic therapy

- ▶ Wait a minimum of 1 year to retest in order to detect meaningful changes.
- ▶ In a non-urgent situation, wait 2 years before repeating a BMD test.
- ▶ Test every 3 to 4 years once therapeutic effect is established, provided the patient's clinical status remains unchanged.

Considerations for repeat testing

- ▶ Obtain follow-up readings at the same facility as the first reading so that readings can be compared.
- ▶ Assess interval change in BMD by the actual bone density in grams per cm² and NOT by the T score.
- ▶ Note that T scores decline with advancing age: if a patient is 2 years older at follow-up, her T score will be lower even if her bone density is exactly the same.

Although recent data from the Women's Health Initiative calcium plus vitamin D (WHI Ca plus D) trial do not support fracture risk reduction with calcium plus vitamin D supplementation, these findings need to be placed into perspective.³

The older age of the participants (mean age 62.4 years), the use of supplements by a majority of the study population (including the placebo group), and the poor adherence to medications are factors that limit extrapolation of these findings to the general population. Only 59% of the participants took the intended dose of calcium with vitamin D throughout the study; post hoc analysis of the trial limited to adherent participants demonstrated a statistically significant (29%) reduction in risk of hip fractures (absolute benefit was 4 fewer hip fractures per 10,000 women), reconfirming the biologically plausible beneficial role of calcium and vitamin D in skeletal integrity.

A meta-analysis of earlier research demonstrated a positive, albeit small, influence of calcium supplementation on BMD and a trend toward reduction in fracture risk.¹⁹ A similar meta-analysis of skeletal effects of vitamin D demonstrated

definite risk reduction for vertebral fractures.²⁰ Although the results of the individual studies included in these meta-analyses often were not statistically significant, the trend favored calcium and vitamin D over placebo.

The decision to supplement calcium and vitamin D needs to be based on the individual's health, nutritional, and supplemental status. Supplementing a patient who is nutritionally replete may even be harmful, as reflected in the higher incidence of renal calculi in the WHI Calcium plus D trial.

There has been a left shift in the serum 25 (OH) vitamin D levels that distinguish "deficient" from "replete" vitamin reserves. Indeed, levels between 20 and 30 ng/mL that were recently regarded as "normal" now are considered to reflect "insufficiency"; levels lower than 15 ng/mL are associated with evidence of secondary hyperparathyroidism and hence states of "deficiency."²¹

Clinicians must be sensitive to the magnitude of the population prevalence of vitamin D insufficiencies and deficiencies, as well as recognize the ethnic disparities in this regard.²² Particularly for someone whose requirements may be high because of racial predisposition or limited sunlight exposure, the commonly prescribed doses of 400 to 600 IU/d may not be adequate; general recommendations are currently 800 IU/d. Vitamin D toxicity is extremely rare, so clinicians do have leeway for using higher doses of vitamin D for treatment of states of insufficiency and deficiency.

Conclusion

Osteoporosis represents an end point in the continuum of skeletal health and is clearly a risk factor for fragility fracture. Once low bone density is diagnosed, the various therapeutic modalities in the clinician's armamentarium should be aimed at minimizing further bone loss, as well as possibly improving bone quality.

Appreciating skeletal deterioration as a continuum allows clinicians to identify an individual's risk and intervene much before the disease process sets in, an approach that is a hallmark of primary care and preventive medicine. Studies in young and premenopausal populations are beginning to identify previously unrecognized risk factors that contribute to skeletal compromise that sets in well before natural menopause. This informa-

tion will help clinicians individualize non-pharmacologic intervention strategies, which, if instituted early enough, could reduce the need for eventual pharmacologic treatment. ■

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KEY POINT

Appreciating that osteoporosis is an end point in the bone health continuum may facilitate intervention before the disease process begins.