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Treatment of Premenopausal Women with Low Bone Mineral Density

Adi Cohen, MD, MHS and Elizabeth Shane, MD

Abstract

Interpretation of bone mineral density (BMD) results in premenopausal women is particularly challenging, because the relationship between BMD and fracture risk is not the same as for postmenopausal women. Z scores rather than T scores should be used to define “low BMD” in premenopausal women. The finding of low BMD in a premenopausal woman should prompt an evaluation for secondary causes of bone loss. If a secondary cause is found, management should focus on treatment of this condition. In some cases in which the secondary cause cannot be addressed, such as glucocorticoid therapy or cancer chemotherapy, treatment with a bone-active agent to prevent bone loss should be considered. In women with no fractures and no known secondary cause, low BMD may not signify compromised bone strength. BMD is likely to remain stable in these women, and pharmacologic therapy is rarely justified. Assessment of markers of bone turnover and follow-up bone density measurements can help to identify those with an ongoing process of bone loss that may indicate a higher risk for fracture, and possible need for pharmacologic intervention.

Introduction

The finding of low bone mineral density (BMD) in a premenopausal woman presents specific diagnostic and management challenges that are quite different from those in postmenopausal women. We discuss BMD interpretation in premenopausal women, the relationship between BMD and fracture risk in young women, evaluation of premenopausal women with low BMD, and management issues that pertain to this particular population.

BMD Testing in Premenopausal Women

The International Society for Clinical Densitometry (ISCD) recommends BMD testing in women with a known secondary cause of osteoporosis or bone loss [1]. However, routine screening of bone density in healthy premenopausal women is not recommended because the low yield of abnormal measurements does not justify the expense. Nevertheless, many healthy women are referred for BMD testing for various reasons. When results are lower

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Corresponding author: Adi Cohen, MD, MHS, Columbia University, College of Physicians and Surgeons, Department of Medicine, PH8-864, 630 West 168th Street, New York, NY 10032, USA., ac1044@columbia.edu.

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than expected, these women may consult their physician for evaluation and advice regarding treatment options.

BMD and the Diagnosis of “Osteoporosis” in Premenopausal Women

In postmenopausal women, osteoporosis and osteopenia may be diagnosed based on BMD T scores measured by dual energy X-ray absorptiometry (DXA), with or without the presence of a fragility fracture. Low BMD T scores predict future fractures in postmenopausal women [2].

However, low BMD in a premenopausal woman may not have the same clinical implications. When interpreting BMD measurements in young women, the clinician should be cognizant that, based on the Gaussian distribution of BMD measurements, approximately 0.5% of the normal population of young women would be expected to have T scores -2.5 or less, and 16% would be expected to have T scores between -1 and -2.49 [3]. In addition, it is important to consider that the incidence and prevalence of fractures in premenopausal women is much lower than in postmenopausal women [4,5]. As seen in Figure 1, the relationship between BMD and fracture risk is not the same in premenopausal and postmenopausal women, and fracture incidence rates are low in premenopausal women (even in those with low BMD measurements) [6]. In other words, the predictive relationship between BMD and fracture risk is much weaker in young than in older women. Young women with low BMD, but without other risk factors for fracture (eg, previous fracture, glucocorticoid therapy), usually have very low short-term risk for fracture.

For these reasons, the ISCD does not recommend using T scores to categorize BMD measurements in premenopausal women. Although T and Z scores are similar in young individuals, the ISCD recommends using Z scores, which compare a young woman's BMD with the mean of an age-, gender-, and ethnicity-matched reference population [1]. Young women with BMD Z scores below -2 should be categorized as having BMD that is “below expected range for age,” and those with Z scores above -2 should be categorized as having BMD that is “within the expected range for age” [7]. The term “osteoporosis” should be used with restraint in premenopausal women, particularly when the diagnosis is based on BMD alone, when the BMD is at the low end of or just below the normal range, and there is no history of fracture. In certain clinical contexts, when BMD is below expected range for age and the individual has a known secondary cause of osteoporosis (such as steroid use or premenopausal estrogen deficiency), a diagnosis of “osteoporosis” can be considered in the absence of a fracture history. The diagnosis of “osteopenia” based on bone density should not be applied to premenopausal women.

Low-Trauma Fracture and the Diagnosis of “Osteoporosis” in Premenopausal Women

A low-trauma fracture is defined as that which occurs with force equivalent to a fall from a standing height or less. This definition leaves some room for interpretation by the patient and the clinician, and the “low-trauma” categorization of a fracture may not be clear in all cases. Taking this into account, premenopausal women with a history of one or more low-

trauma fractures are defined as having osteoporosis, regardless of BMD. These women have clinical evidence of decreased bone strength.

Several studies have shown that risk of a post-menopausal fracture is increased in women who have experienced a fracture before menopause [8–10]. In the Study of Osteoporotic Fractures, women with a history of premenopausal fracture were 35% more likely to fracture during the early postmenopausal years than women without a history of premenopausal fracture [8], even after controlling for a number of potential confounding variables. These findings suggest that certain lifelong traits, perhaps including fall frequency, neuromuscular protective response to falls, bone mass, or various aspects of bone quality, can affect the lifelong risk of fracture [9].

Bone Fragility May Relate to Conditions Other than Osteoporosis

Low-trauma fracture in a premenopausal woman may also be due to bone fragility from osteomalacia, metastatic disease, or transient osteoporosis of the hip (TOH). TOH is a rare condition, presenting with hip pain in the absence of prior trauma. It can occur in men and women, but often occurs in previously healthy women during the third trimester of pregnancy. MRI may show marrow edema of the femoral head and neck [11], and radiographs may show regional demineralization. Although some pregnant women develop femoral fractures related to TOH, others have resolution of hip pain over an average of 6 months postpartum without the development of fractures [12]. The etiology of this condition is unknown but may be related to pelvic nerve compression, vascular insufficiency, or fibrinolytic system changes with pregnancy [12].

Low BMD Is Not Necessarily Evidence of Bone Fragility

Although premenopausal women with a history of low-trauma fracture have evidence of decreased bone strength, the same cannot necessarily be said for premenopausal women with low BMD who do not have a history of fracture. This is because, as noted earlier, fractures are much less common in premenopausal women, and the relationship between BMD and fracture is different in younger than in older women.

However, although the relationship between low BMD and fracture is not nearly as robust as in older women, there is evidence that it exists in premenopausal women. Several studies have shown that young women with low BMD are at higher risk for fractures than are young women with normal BMD [13,14,15•]. In this regard, premenopausal women with Colles' fractures have been found to have significantly lower BMD at the nonfractured radius [16], lumbar spine, and femoral neck [17•], compared with age-matched controls without fractures. In addition, stress fractures in female military recruits and athletes are associated with lower BMD than in controls [13,15•].

However, many premenopausal women with low BMD have no history of fracture. Current available data do not allow us to use BMD to predict fracture risk in this population. In premenopausal women without a history of fracture or known secondary cause of osteoporosis, low BMD (Z score ≤ -2) may not signify compromised bone strength. In some

cases, low bone mass may be related to genetic factors that determine peak bone mass, or to small bone size.

Low peak bone mass

Peak bone mass is defined as the maximum BMD achieved by age 30 years, as measured by DXA. In healthy girls, the peak period of bone mass gain occurs between ages 11 and 14 years [18]. Although approximately 95% of peak bone mass is acquired by the late teens, there are small gains from ages 20 to 29 years [18,19]. Therefore, when interpreting low BMD measurements in premenopausal women aged younger than 30 years, one must consider the possibility that they may not yet have reached their peak bone mass. Genetic, nutritional, and environmental factors clearly affect the peak BMD attained. Everyone attains a peak bone density, but not necessarily an optimal peak bone density.

Women with genetically determined low peak bone mass may have no evidence of excessive bone loss, and no abnormalities in bone microarchitecture, turnover, or mineralization. Low peak bone mass can also result from a past nutritional, environmental, or medication-related insult to bone that is no longer operative or leading to an active process of bone loss. Alternatively, some women may have a persistent cause of bone fragility and bone loss that could lead to low peak bone mass as well as ongoing bone loss in adulthood.

Small bone size

Small stature and body size (and therefore bone size) also influence DXA measurements. DXA provides a two-dimensional areal projection (g/cm^2) rather than a true volumetric BMD (g/cm^3). Thus, using DXA, it is not possible to distinguish between a bone that is small but of normal density and one that is of low density. Although equations are available that convert BMD to bone mineral apparent density (BMAD; g/cm^3), a calculation made by dividing the bone mineral content by a reference bone volume [20,21], these calculations are not incorporated within DXA software and are not widely used. Thus, one may underestimate true volumetric BMD in petite individuals.

Pregnancy and lactation are associated with physiologic BMD decreases in premenopausal women

Physiologic changes in bone mass occur in association with pregnancy and lactation. Small decreases in bone density are expected during pregnancy, and lactation is associated with rapid bone loss of 3% to 10% over 3 to 6 months, with recovery of bone mass during and after weaning [22,23]. Interpretation of BMD in premenopausal women must always take the timing of recent pregnancy and lactation into account.

Pathological Processes (Secondary Causes) of Low BMD in Premenopausal Women

Most premenopausal women with low BMD measurements or low-trauma fracture have an underlying disorder or medication exposure that has interfered with bone mass accrual during adolescence and/or has caused excessive bone loss after peak bone mass has been

reached. The same “secondary causes” may be associated with bone loss in older women. In a population study from Olmstead County, MN, 90% of men and women aged 20 to 44 years with established osteoporosis (ie, fractures) were found to have a secondary cause [24]. In contrast, several other case series records of young women with osteoporosis evaluated in tertiary referral centers have found that only 44% to 56% had secondary causes [25–27]. However, this discrepancy likely reflects referral bias of more obscure cases to specialists.

Potential secondary causes are listed in Table 1. The main goal of the clinician who encounters a premenopausal woman with low BMD measurements is to diagnose and treat any correctable contributing secondary cause. Often this can be accomplished by performing a detailed history and physical examination, but in some circumstances an exhaustive biochemical evaluation is necessary.

Evaluation

In premenopausal women, the finding of low BMD (Z score ≤ -2) should lead to further evaluation for secondary causes of osteoporosis and bone loss. A secondary cause of osteoporosis can be found in a substantial proportion of premenopausal women with low BMD or fractures [24,25,27], and identification of a contributing condition often helps to guide management of the affected individual.

The cornerstone of the evaluation is a careful medical history. The physician should elicit information about family history, fractures, kidney stones, amenorrhea or evidence of premenopausal estrogen deficiency, timing of any recent pregnancies and lactation, dieting and exercise behavior, subtle gastrointestinal symptoms that may suggest celiac disease or other causes of malabsorption, and medications, including over-the-counter supplements. Physical examination can identify signs of Cushing’s syndrome, thyroid hormone excess, or connective tissue disorders (eg, blue sclerae in some forms of osteogenesis imperfecta). In women with low BMD who are less than 63 inches tall, it may be useful to measure volumetric BMD of the spine or hip by central quantitative CT, if available. Alternatively, one can calculate BMAD [28].

The laboratory evaluation should also be aimed at identifying secondary causes of osteoporosis. Biochemical evidence of hyperthyroidism, hyperparathyroidism, Cushing’s syndrome, early menopause, renal or liver disease, celiac disease and other forms of malabsorption, or idiopathic hypercalciuria should be sought. Table 2 lists suggested initial and additional laboratory tests. If other disease processes are suspected, further specific evaluations may be appropriate.

Evaluation of markers of bone turnover and follow-up bone density testing may help to distinguish those with stable low BMD from those who are experiencing ongoing bone loss and who therefore may be at higher short-term risk for fracture.

In premenopausal women with evidence of ongoing bone loss, in whom no secondary cause can be found after extensive evaluation, bone biopsy may be indicated to identify other sources of bone loss and to guide therapeutic intervention.

Management Issues

General measures

For all patients, it is appropriate to recommend a set of general measures that generally benefit bone health. Such measures include getting adequate amounts of weight-bearing exercise, protein, calories, calcium, and vitamin D, as well as lifestyle modifications such as smoking cessation and avoidance of excess alcohol [29–31,32•,33].

In premenopausal women with isolated low BMD and no history of fractures, in whom no secondary cause can be identified after thorough evaluation, pharmacologic therapy is rarely justified. This is particularly true if the Z score is greater than -3.0 . Low BMD in such young women may be due to genetically determined low peak bone mass, or to past insults to the growing or adult skeleton (poor nutrition, medications, estrogen deficiency) that are no longer operative. Such young women usually have low short-term risk of fracture.

Moreover, Peris et al. [34•] recently reported that BMD improved slightly on average in women with unexplained osteoporosis managed with only calcium (to achieve a total intake of 1500 mg/day), vitamin D (400–800 IU/daily), and exercise and followed over time. Bone density should be remeasured after 1 or 2 years to reassure the patient and physician that BMD is stable and, conversely, to identify the unusual patient with ongoing bone loss.

In premenopausal women with low BMD (or low-trauma fractures) and a known secondary cause of osteoporosis, management should address the underlying cause whenever possible. For example, those with estrogen deficiency should be treated with estrogen (unless contraindicated), those with celiac disease should begin a gluten-free diet, those with primary hyperparathyroidism may benefit from parathyroidectomy [35], and those with idiopathic hypercalciuria may benefit from thiazide diuretics.

In some women, it is not possible to address or alleviate the secondary cause directly. Premenopausal women who require long-term glucocorticoids and those being treated for breast cancer may require pharmacologic therapy to prevent excessive bone loss or fractures. Options for treatment include antiresorptive drugs, such as estrogen or bisphosphonates, or anabolic agents such as teriparatide. Selective estrogen receptor modulators, such as raloxifene, should not be used to treat bone loss in menstruating women because they block estrogen action on bone and lead to further bone loss [36,37].

Bisphosphonates

The US Food and Drug Administration has approved the use of bisphosphonates only for premenopausal women who are receiving glucocorticoids. Because bisphosphonates accumulate in the maternal skeleton, cross the placenta, and also accumulate in the fetal skeleton [38], and because they have been reported to cause toxic effects in pregnant rats [39], they should be used with caution in premenopausal women who may later become pregnant. Although several reports document normal pregnancies and no fetal abnormalities in women receiving bisphosphonates [40•,41–43], one report of two women with osteogenesis imperfecta treated with long-term intravenous pamidronate before conception documented mild neonatal abnormalities (transient hypocalcemia and bilateral talipes equinovarus) [44]. Thus, the potential for future fetal abnormalities should be carefully

considered when choosing bisphosphonate therapy for any premenopausal woman. In general, bisphosphonate therapy should be reserved for premenopausal women who have had or continue to have fragility fractures, and those with ongoing bone loss due to a known secondary cause that cannot be addressed directly, such as glucocorticoid-induced osteoporosis or cancer chemotherapy. The following text summarizes the few studies that have rigorously examined the effects of bisphosphonates in premenopausal women with secondary causes of bone loss.

Glucocorticoid-induced osteoporosis—Bisphosphonates are very effective for prevention and treatment of glucocorticoid-induced osteoporosis. However, relatively few premenopausal women have been included in the large clinical trials of glucocorticoid-induced osteoporosis [45]. Some studies specifically examining premenopausal women with autoimmune and connective tissue diseases have demonstrated the protective effects of intermittent cyclical etidronate and oral pamidronate [46–48]. Guidelines from the American College of Rheumatology recommend bisphosphonate therapy for prevention and treatment of glucocorticoid-induced osteoporosis in premenopausal women taking at least 5 mg of prednisone or equivalent per day [49]. However, because of the potential for harm to the fetus in women who may become pregnant, they also urge great caution with bisphosphonate use in premenopausal women [49].

Cancer—Bisphosphonates, including intravenous pamidronate and zoledronic acid, oral risedronate, and oral clodronate, have been shown to prevent bone loss in premenopausal women experiencing ovarian failure in the setting of chemotherapy for breast cancer [50•, 51,52] and in those with leukemia who are undergoing stem cell transplant [53]. Additionally, in a randomized study of 401 premenopausal women with breast cancer who were receiving adjuvant endocrine-suppressive therapy with either goserelin and tamoxifen or goserelin and anastrozole, bone loss seen with these therapies was prevented in those receiving zoledronic acid (4 mg every 6 months) [54••]. However, because these women have been rendered prematurely menopausal in most cases, there is less reluctance to expose them to bisphosphonates.

Pregnancy-associated osteoporosis—In a report of nine premenopausal women with a history of fracture(s) and a diagnosis of pregnancy- and lactation-associated osteoporosis, use of bisphosphonates over an average of 24 months was associated with substantial increases of 11% to 23% in lumbar spine bone density [40•]. Because bone density is expected to increase postpartum and after weaning in normal women, it is not clear to what extent bisphosphonate use provided an incremental benefit for these patients.

Anorexia nervosa—Although body weight and nutritional recovery are thought to be the most important determinants of BMD in women with anorexia nervosa [55••,56], both alendronate and risedronate have been shown to significantly increase BMD in young women with anorexia [55••,57].

Teriparatide/parathyroid hormone (1–34)

There are even fewer data regarding the effects of teriparatide or parathyroid hormone (PTH) (1–34) in premenopausal women. About half of 43 young women treated with the gonadotropin-releasing hormone analog nafarelin for endometriosis were randomly assigned to receive PTH(1–34), 40 µg daily, during the 12-month period of nafarelin treatment [58]. PTH(1–34) prevented bone loss at the femoral neck. At the spine, BMD decreased by 4.9% in those treated with nafarelin alone and increased by 2.1% in the PTH(1–34) group ($P < 0.001$). Markers of bone resorption (urinary hydroxyproline and deoxypyridinoline) and formation (serum bone-specific alkaline phosphatase and osteocalcin) increased significantly more in the PTH(1–34) group, peaking at 6 to 9 months, followed by partial decline. It is not clear whether these results would apply to premenopausal women with normal gonadal status.

A recent study of teriparatide for glucocorticoid-induced osteoporosis included a few premenopausal women. In this 18-month active-comparator double-blind randomized trial comparing teriparatide, 20 µg/day, with alendronate, 10 mg/day, in 528 patients on long-term glucocorticoids (81% women, age range 22–89 years), teriparatide was associated with significantly greater increases in lumbar spine and total hip BMD and resulted in significantly fewer incident vertebral fractures than did alendronate [59].

Because the long-term effects of teriparatide in young women are not known, use of this medication should be reserved for those at highest risk for fracture.

Conclusions

The finding of low BMD (Z score -2) in a premenopausal woman, in the absence of fracture history, may or may not predict bone fragility. This finding may be the result of genetically determined low peak BMD, past insults to the skeleton, or currently active causes of continuing bone loss. Because secondary causes are commonly found and many potential causes of low BMD are treatable, the finding of a Z score of -2 or less at the spine, hip, or forearm should lead to evaluation for potential secondary causes of osteoporosis and bone loss. For premenopausal women in whom a secondary cause is known or found, treatment of this underlying cause is the focus of management to improve bone health. Pharmacologic intervention with a bone-active agent can be considered, on a case-by-case basis, for women with fragility fractures, documented persistent bone loss, or in cases of ongoing glucocorticoid treatment, treatment of cancer, or other conditions that may result in a high short-term risk for bone loss and fracture. Some data are available suggesting beneficial effects of bisphosphonates and teriparatide in women in certain clinical settings. Although some bisphosphonates are approved for use in premenopausal women in the setting of ongoing glucocorticoid exposure, these medications should be used with caution in women who may have future pregnancies. For women with stable low BMD, no fractures, and no known secondary cause, the relationship between BMD and fracture risk is not clear. In such women, pharmacologic therapy is rarely justified.

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Figure 1.

Radial bone mass was measured using single-photon absorptiometry in this 6.5-year prospective study of 521 white women. (From Hui et al. [6]; with permission.)

Table 1

Secondary causes of low BMD in premenopausal women

Amenorrhea (eg, anorexia nervosa, pituitary diseases, medications)
Cushing's syndrome
Hyperthyroidism
Primary hyperparathyroidism
Vitamin D, calcium, and/or other nutrient deficiency
Gastrointestinal malabsorption (celiac disease, inflammatory bowel disease, cystic fibrosis, postoperative states)
Anorexia nervosa
Rheumatoid arthritis, SLE, other inflammatory conditions
Renal disease
Liver disease
Hypercalciuria
Alcoholism
Medications
Glucocorticoids
Immunosuppressants (eg, cyclosporine)
Antiepileptic drugs (particularly cytochrome P450 inducers such as phenytoin, carbamazepine)
Cancer chemotherapy
GnRH agonists (when used to suppress ovulation)
Heparin
Idiopathic low BMD

BMD—bone mineral density; GnRH—gonadotropin-releasing hormone; SLE—systemic lupus erythematosus.

Table 2

Laboratory evaluation in premenopausal women with unexplained low BMD

Initial laboratory evaluation
Complete blood count
Electrolytes, renal function
Serum calcium, phosphate
Serum albumin, transaminases, total alkaline phosphatase
Serum TSH
Serum 25-hydroxyvitamin D
24-hour urine for calcium and creatinine
Additional laboratory evaluation
Estradiol, LH, FSH, prolactin
PTH
1,25-dihydroxyvitamin D
24-hour urine for free cortisol
Iron/TIBC, ferritin
Celiac screen
Serum/urine protein electrophoresis
ESR or CRP
Bone turnover markers
Transiliac crest bone biopsy—consider in cases of unexplained ongoing bone loss

BMD—bone mineral density; CRP—C-reactive protein; ESR—erythrocyte sedimentation rate; FSH—follicle-stimulating hormone; LH—luteinizing hormone; PTH—parathyroid hormone; TIBC—total iron-binding capacity; TSH—thyroid-stimulating hormone.