Clinical Considerations in Premenopausal Osteoporosis

Margaret L. Gourlay, MD; Sue A. Brown, MD

Osteoporosis can occur at any age. In premenopausal osteoporosis, full achievement of peak bone mass may be curtailed, and accelerated bone loss may occur in young adulthood. Premenopausal osteoporosis may be associated with chronic glucocorticoid therapy, prolonged amenorrhea, anorexia nervosa, rheumatoid arthritis, and diseases that affect calcium and vitamin D metabolism. Lesser degrees of bone loss may be associated with common conditions such as dieting, low calcium intake, smoking, and oligomenorrhea. Owing to a paucity of prospective studies on screening and treatment in younger age groups, few practice recommendations exist to guide the management of osteoporosis in young adults. We review the most important clinical concerns in premenopausal osteoporosis, including measurement of bone mass, normal bone accrual, risk factors for premature bone loss, clinical outcomes, and management issues. We emphasize clinically relevant information for primary care physicians, who are usually the first to encounter premenopausal patients with risk factors for early bone loss.

Although low bone mass and accelerated bone loss can occur early in life, osteoporosis is usually considered a disorder of postmenopausal women. The most serious consequences of osteoporosis occur in this age group, and treatment outcomes may be poor after a fracture late in life. Hip fractures cause the most morbidity and mortality; the hip fracture incidence in white women increases 10-fold from 50.1 per 100,000 per year between ages 50 and 54 years to 530.5 per 100,000 per year between ages 70 and 74 years. Vertebral fractures and distal forearm (Colles) fractures occur more commonly after menopause and are associated with a higher subsequent rate of hip fracture.

Certain groups of premenopausal women are at high risk of osteoporosis, including those with disease states or exogenous influences that promote accelerated bone loss. The 2001 National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy specified peak bone mass in children and secondary osteoporosis in young adults as important areas for future research. Relatively little is known about early-onset osteoporosis, and, to our knowledge, no general practice recommendations exist to guide diagnosis and therapy.

We present an overview of the most important clinical concerns in premenopausal osteoporosis, with the goal of increasing awareness of high-risk patients, who often are first seen by primary care physicians. This review addresses measurement of bone mass, normal bone accrual, risk factors for premature bone loss, clinical outcomes, and management issues in premenopausal women.

METHODS

We searched the MEDLINE/PubMed database (January 1984 to August 2002) using the following MeSH terms and keywords: “osteoporosis” AND “premenopause” for articles on premenopausal osteoporosis and “bone diseases, metabolic” OR “low bone mass” OR...
“bone density” OR “osteopenia,” AND “premenopause” NOT “osteoporosis” for articles on premenopausal osteopenia. We reviewed abstracts for all English-language citations in peer-reviewed journals and excluded the following: studies that only included perimenopausal or postmenopausal women; studies with premenopausal women as a reference group/control only, without analysis and discussion of relevant outcomes in premenopausal patients; studies with a lack of osteoporosis-related health outcomes; studies with the purpose of verifying an experimental radiologic diagnostic tool; and studies of insufficient length to assess significant change in outcome.

Our initial search yielded 287 articles on premenopausal osteoporosis, 176 of which were excluded, and 202 articles on osteopenia, 126 of which were excluded; the remaining 187 articles were reviewed for relevance and quality. An additional 185 articles from supplementary searches and hand searches of reference lists were evaluated. Owing to the broad scope of this review and the general paucity of prospective studies from our searches, we considered all study designs except case reports and diagnostic test verification studies. One of us (M.L.G.) used a checklist to evaluate the internal validity of scientific studies, systematic reviews, and meta-analyses.

RESULTS

BONE DENSITY IN YOUNGER PATIENTS

The National Institutes of Health Consensus Panel 2000 adopted a definition of osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength is determined by bone density and bone quality.

Because fragility fractures are rare in young patients, they are usually not used as outcomes in studies of premenopausal bone loss, and they do not serve as the basis for the diagnosis of early-onset osteoporosis. Instead, bone densitometry measurements are used as surrogate indicators of fracture risk. The relationship between bone mineral density (BMD) measures and fracture risk is unclear in premenopausal women. In postmenopausal women, a strong relationship exists between BMD and fracture risk, such that a 10% decrease in BMD confers a 1.6- to 2.6-fold increased risk for spine and hip fracture.

BMD Measurement in Younger Patients

Bone mineral density is a 2-dimensional, areal projection measurement defined as the average concentration of mineral per unit area, expressed in grams per square centimeter. It is usually measured using dual-energy x-ray absorptiometry (DXA) or, in some cases, single-energy x-ray absorptiometry.

Bone mineral density is reported using 2 scores based on SD measurements: the Z score and the T score. The Z score compares the patient’s BMD with the mean value in age-matched normal individuals. This is the most appropriate measure to use for children and young adults, who have yet to achieve their lifetime peak bone mass. The T score compares the patient’s BMD to the mean value in a healthy young reference population, assumed to represent a standard for peak bone mass. Both scores may be adjusted for race and sex. A T score of –2.5 or lower represents osteopenia; however, because fracture risk may vary widely based on age and other factors for patients with osteopenia, this categorization is of limited clinical value.

Several factors should be considered when assessing bone density during periods of longitudinal growth. First, bone density measurements obtained using DXA reflect a 2-dimensional rather than a 3-dimensional projection and may inaccurately capture geometric changes or increases in bone size that occur during growth. In addition, the 2-dimensional DXA measure may suggest a falsely lower BMD in small-framed individuals, which could be particularly important in evaluating premenopausal women. Other techniques, such as quantitative computed tomography, measure bone volume (in grams per cubic centimeter) and may better characterize changes in total bone mass that occur during growth; however, their use is limited owing to cost and radiation exposure. Second, bone density and calcium accrual vary by site of measurement, with a general trend toward earlier bone density accrual in the proximal femur and vertebral body and later accrual at other sites. Finally, small changes in BMD may be due to the random variability in the DXA test; changes of less than approximately 5.6% can often be due to precision error and should be interpreted cautiously.

Bone mineral density is most often measured at the lumbar spine and proximal femur because measures at these sites have been best validated against fracture in postmenopausal women. Discordance in BMD scores at these sites is common in young women, probably because of differing rates of bone accrual and loss. Bonnick et al studied BMD values in 237 premenopausal women and reported that a difference in Z score of more than 1 occurred between the spine and the proximal femur in 20% to 24% of women aged 20 to 29 years and in 32% to 46% of women aged 30 to 45 years. Peripheral DXA measurements of the distal radius and calcaneus can be performed; however, these values may not correlate with spine and hip measures and do not predict hip fractures as well as hip BMD. Until peripheral DXA has been further validated against fracture, abnormal peripheral measures should be followed up with additional measurements of the spine and hip to confirm a diagnosis of osteoporosis.

Attainment of Peak Bone Mass

Peak rates of calcium accrual occur before age 30 years. Longitudinal studies have demonstrated that calcium utilization increases during early puberty and that the highest rates of calcium accrual may occur at a mean age of 12½ years in girls and 14 years in boys. After this period of rapid calcium accretion, a period of bone consolidation is thought to ensue between ages 20 and 30 years. Calcium accrual rates change little during this period, but periosteal expansion (outer surface of bone) may be increasing. These periosteal changes could theoretically confer greater structural integrity and would not...
be adequately detected by bone density measurements using DXA. One study found that the independent determinants of BMD during growth are Tanner stage in girls and weight in boys. Owing to the complex processes that occur during bone development, changes in bone mass in growing individuals may be difficult to interpret. Several investigators have begun to develop normative databases to more accurately define expected BMD values for younger age ranges.

Factors affecting the attainment of peak bone mass have recently been reviewed. The precise age at which peak bone mass occurs is unknown. Population-based, cross-sectional studies indicate that women may attain peak bone mass in their 20s at the proximal femur and near age 30 years at the spine and forearm; however, age of attainment could vary in healthy individuals. A cross-sectional study of 265 premenopausal white females aged 8 to 50 years showed that most of the bone mass at multiple skeletal sites is accumulated by late adolescence.

Multiple factors affect attainment of peak bone mass, including genetic background, nutritional influences, and activity level. Twin and family studies suggest that 50% to 80% of the variance in bone mass is heritable. A strong association has been noted between bone densities in mother/daughter pairs, which may be apparent before the daughter has begun puberty.

**Bone Mass in Premenopause**

Sowers and Galuska published a comprehensive review of the epidemiology of bone mass in premenopausal women in 1993. They reported conflicting findings regarding BMD status after the attainment of peak bone mass and before the onset of menopause. Most cross-sectional studies from the 1980s and early 1990s reported stable BMD in the premenopausal period. However, most prospective and cross-sectional studies since 1994 have reported a small degree of loss (0.5% per year) during this period, especially at the proximal femur and more often in women with subclinical or clinical ovulation disturbances or menopausal symptoms (Table 1).

**RISK FACTORS FOR PREMENOPAUSAL OSTEOPOROSIS**

Risk factors for low bone mass and osteoporotic fractures have been well studied in perimenopausal and postmenopausal patients. Few studies have comprehensively examined predictors in younger patients. Moreira-Kulak et al studied 111 premenopausal and perimenopausal women younger than 55 years with T scores of -2.0 or less at 1 or more anatomic sites who were referred to a tertiary care center for metabolic bone disorders. Seventy-three of these women (66%) had an identifiable cause of bone loss. Conditions associated with estrogen deficiency and the use of glucocorticoid therapy were the most common known causes of osteoporosis. However, 38 women (34%), 21 of whom were premenopausal, had no identifiable cause of low bone mass. Peris et al studied 52 premenopausal osteoporotic women aged 20 to 51 years who were referred to an outpatient rheumatology clinic for osteoporosis evaluation and similarly found that 29 (56%) had no identifiable predisposing condition.

Tudor-Locke and McColl recently reviewed risk factors for variation in bone status in premenopausal women aged 20 to 50 years. Nonmodifiable risk factors include genetic effects and race and ethnicity. Potentially modifiable categories of risk include hormonal and nutritional factors, physical activity, medications, and smoking. Certain disease states known to be associated with early bone loss can be secondary causes of osteoporosis.

**Genetic Influences**

Twin and family studies have shown that genetic factors play an important role in determining BMD. Candidate genes under study include vitamin D receptor (VDR) genes, the estrogen receptor gene, the collagen type I alpha 1 (COL1A1) gene, and genes that

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**Table 1. Prospective Studies of BMD in Premenopausal Women**

<table>
<thead>
<tr>
<th>Source</th>
<th>Length of Follow-up</th>
<th>Participants</th>
<th>Change in Femoral Neck BMD, Mean ± SD</th>
<th>Change in Lumbar Spinal BMD, Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bainbridge et al</td>
<td>6 y</td>
<td>614 Women aged 24-44 y</td>
<td>-0.003†</td>
<td>Varied with time</td>
</tr>
<tr>
<td>Hui et al</td>
<td>1-9 y (mean, 3.9 y)</td>
<td>130 Premenopausal white women aged 31-50 y</td>
<td>-0.00357 ± 0.0025†</td>
<td>-0.000209 ± 0.0050 -0.19</td>
</tr>
<tr>
<td>Salamone et al</td>
<td>30 mo</td>
<td>290 Premenopausal white women aged 44-50 y</td>
<td>-0.00357 ± 0.0025†</td>
<td>-0.0043†</td>
</tr>
<tr>
<td>Stemenda et al</td>
<td>2-8 y</td>
<td>96 Premenopausal women aged 30-48 y</td>
<td>-0.0021 ± 0.013†</td>
<td>+0.0036 ± 0.012 ±0.32</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; NA, not assessed.

*Some values are given as mean only because the SD was not reported and could not be calculated.
†P<.05 for follow-up value vs baseline value.
regulate the growth hormone/insulin-like growth factor 1 axis. Their role in bone mass development is under investigation, but this has not been adequately characterized to date.

Race and Ethnicity

Owing to racial and ethnic differences in BMD values, population norms have been established for use as DXA reference standards. As a group, African American women achieve a higher peak bone mass than whites, show a slower subsequent rate of bone loss, and have a lower incidence of postmenopausal hip fracture. Asian Americans tend to have lower BMD values than whites, but they also have a lower rate of hip fracture.

Hormonal Factors

Endogenous Hormones. Bone loss can occur in the setting of prolonged amenorrhea and estrogen deficiency. Davies et al measured lumbar spinal bone mass in 200 white women aged 16 to 40 years seen in a reproductive medicine clinic for amenorrhea of a median duration of 3 years (range, 6 months to 24 years). Lumbar spinal BMD was 15% lower in the women with amenorrhea than in 57 age-matched controls (95% confidence interval [CI], 12%-18%; absolute BMD values, 0.89 g/cm² vs 1.05 g/cm²). Patients who reported a history of fracture had 6.6% lower mean BMD than those who never had a fracture (n = 57; P = .003). A prospective study of 54 professional dancers and 57 nondancers found lower lumbar spinal BMD values at baseline and during the subsequent 2 years in exercising and nonexercising women with amenorrhea. An increased incidence of stress fractures was associated with delayed menarche and lower spinal BMD.

A small study of elite athletes indicated that premature bone loss might occur in women with lesser degrees of hypoestrogenism, as evidenced by prolonged menstrual irregularity. Micklesfield et al measured BMD in 25 premenopausal ultramarathon runners aged 29 to 39 years (4 had current oligomenorrhea, 2 had current amenorrhea, and 4 had a history of mixed oligomenorrhea/amenorrhea). Mean lumbar spinal BMD in women with a history of oligomenorrhea alone was 12.4% lower than in controls (P < .005) but did not differ from the mean value in women with a history of oligomenorrhea and amenorrhea.

Exogenous Hormones. In some studies, oral contraceptive (OC) use has been associated with bone mass increases in premenopausal women. Interpretation of these studies is difficult for several reasons. The indication for OC use is usually unspecified, and women taking OCs for oligomenorrhea or amenorrhea would be more likely to have low bone mass at baseline than would those taking OCs for contraception only. Use of OCs could potentially have a different effect on bone mass in women with low vs normal bone mass at baseline. Also, OC users have been found to have a lower body mass index and to be more likely to smoke than controls in some studies, making confounding more likely.

Two prospective studies of early premenopausal women who take OCs have failed to show consistent gains in bone mass in response to estrogen therapy. Prior et al examined OC use in 524 women aged 25 to 45 years participating in a multicenter, population-based cohort study, of whom had taken OCs. Mean BMD values adjusted for age, body mass index, and height were 0.02 to 0.04 g/cm² (2.3%-3.7%) lower in women who had ever used OCs compared with controls; differences were statistically significant at the lumbar spine and femoral trochanter. Results were similar for current and past OC users. The investigators postulated that comorbid lifestyle factors (more smoking and alcohol consumption in OC users) or a confounding effect of OCs prescribed for oligomenorrhea/amenorrhea may have contributed to these findings. An earlier cohort study of 200 healthy women aged 19 to 22 years showed that 76 participants who took an oral monophasic contraceptive (ethinyl estradiol [20 µg] ± desogestrel [0.150 mg]) for 5 years experienced no mean change in spinal BMD, whereas 71 nonusers showed a 7.8% increase in spinal BMD by the end of the study. Considering the young age range of the participants, the lack of change in BMD associated with OC use suggested that exogenous estrogen may have attenuated the potential peak bone mass in users, whereas nonusers achieved normal gains. These findings need to be further validated to clarify the impact of OC use on bone mass in eumenorrheic women.

Past prospective studies have shown conflicting results regarding the effect of depot medroxyprogesterone acetate administration on bone mass. Most of these studies involved small patient populations followed for as little as 6 months. A recent 3-year population-based cohort study of 457 women aged 18 to 39 years (183 depot medroxyprogesterone acetate users and 274 nonusers) showed an annual mean rate of BMD change of –0.87% at the spine for the treatment group vs +0.40% for controls. Annual BMD change at the hip was –1.12% for the test group vs –0.05% for controls. The differences at both sites were statistically significant and seemed to be reversible after discontinuation of depot medroxyprogesterone acetate use. Use of depot medroxyprogesterone acetate may cause lower endogenous estrogen levels, an effect that may not be generalizable to other forms of progestin-only contraception. Ongoing multicenter studies will examine the impact of depot medroxyprogesterone acetate on bone loss and reversibility after discontinuation of use.

In summary, delayed menarche and amenorrhea are associated with lower spinal bone mass in premenopausal women. Limited evidence indicates that prolonged oligomenorrhea can have a similar effect on lumbar spinal BMD. Two prospective studies of premenopausal women did not show BMD increases in response to OC use. A recent population-based prospective study indicated that long-term administration of depot medroxyprogesterone acetate is associated with bone density loss but that the loss may be reversible. Further studies are needed to support these conclusions.

Nutritional Factors

Cross-sectional studies and a limited number of small prospective studies have examined the impact of
nutrition on bone mass in premenopausal women. Although dietary effects have been the focus of numerous studies of postmenopausal osteoporosis, they are often secondary measures in premenopausal studies. For example, the effect of calcium intake on bone mass might be studied when calcium supplementation is provided during an exercise intervention or a dieting program. As for all studies based on dietary histories, these studies are limited by recall bias and extrapolation of short-term data on food consumption.

**Calcium.** Ramsdale et al\(^72\) examined the relationship between BMD and calcium intake in 56 healthy premenopausal women aged 21 to 47 years. Statistically significant correlations were found between calcium intake and BMD at 3 femoral sites (neck: \(r = 0.41\); Ward’s triangle: \(r = 0.40\); and trochanter: \(r = 0.47\); \(P < .001\)) and at the spine (\(r = 0.27\); \(P < .05\)).\(^73\) A cross-sectional study by Teegarden et al\(^74\) showed a more complex relationship between bone mass and nutrient intake. Dietary intake was assessed from food frequency interviews in 215 white women aged 18 to 31 years recruited for an exercise intervention study. The statistical model indicated that adequate intakes of calcium, protein, and phosphorus were all required for significant bone density changes to occur.

Prospective studies have shown different findings in cohorts of different ages. A cohort study\(^64\) of 156 healthy white college students followed for up to 5 years found an increase of 5.9% in lumbar spinal BMD. Spinal BMD showed a weak positive correlation with calcium intake that was not statistically significant; however, a modest but statistically significant correlation was seen with the calcium-protein ratio (\(r = 0.20\); \(P = .02\)). Citron et al\(^74\) examined the effect of calcium intake on spinal and radial BMD in a 4-year prospective study of 41 older premenopausal women, aged 38 to 42 years at baseline. Spinal bone mass declined \(-0.86\% \pm 0.15\%\) per year (\(P < .001\)); the rate of decline was not attenuated by calcium intake.

Thus, several cross-sectional and prospective studies have not shown a statistically significant association between BMD and calcium intake alone. However, calcium intake analyzed in conjunction with other nutrients seems to be a better predictor of spinal BMD in some studies.

**Protein.** Cooper et al\(^72\) studied the relationship of 6 key nutrients to axial and appendicular BMD in a cross-sectional, population-based study of premenopausal and postmenopausal women based on a 7-day dietary record. In the analysis of 72 premenopausal women, statistically significant positive associations were found between protein intake and BMD in the proximal femur and distal radius; these associations remained statistically significant after BMD values were adjusted for age, weight, and physical activity. Adjusted BMD values were not associated with calcium and phosphorus intake. The 4 premenopausal women who had a history of fractures at the hip, distal forearm, or spine had significantly lower intakes of protein and phosphorus and borderline lower intakes of calcium relative to other premenopausal women. These results suggest that protein intake may be an important determinant of bone mass in premenopausal women.

**Dieting and Weight Cycling.** The effect of voluntary weight loss on BMD has been studied in several settings. Two small prospective studies of obese premenopausal patients participating in physician-supervised weight loss interventions, including phases of very-low-calorie dieting, demonstrated small but statistically significant decreases in bone mineral content at the distal radius\(^76\) and hip\(^77\) after 8 to 36 months of follow-up. A randomized clinical trial\(^60\) examined bone mass in 236 healthy premenopausal women aged 44 to 50 years recruited from the community to participate in a lifestyle intervention program for weight loss (dietary behavior modification and exercise recommendations). After 18 months of participation, the intervention group (\(n = 115\)) had lost 3.2 \(\pm 4.7\) kg vs a weight gain of 0.42 \(\pm 3.6\) kg in controls (\(n = 121\)). The annual rate of hip BMD loss was significantly higher in the intervention group vs controls (0.81\% \(\pm 1.3\%\) loss vs 0.42\% \(\pm 1.1\%\) loss; \(P < .001\)), despite the fact that intake of dietary calcium and calcium supplements increased in the intervention group but decreased in controls. In contrast, Shapses et al\(^79\) reported that lumbar spinal BMD increased by 1.7% from baseline in premenopausal obese women participating in a moderate weight loss plan with calcium supplementation (1000 mg/d) (\(n = 14\)). No significant change in lumbar spinal BMD was seen in dieters who did not receive calcium supplementation (\(n = 14\)) or in controls who maintained their body weight (\(n = 10\)).

Subtler degrees of eating restraint may also affect bone mass. Van Loan and Keim\(^80\) measured significantly lower bone mineral content in women who had high scores on a cognitive eating restraint questionnaire compared with women who had low cognitive eating restraint scores. This effect was seen only in women who weighed less than 71 kg. Menstrual and hormonal differences were not assessed. Participants with high cognitive eating restraint scores reported higher numbers of lifetime weight loss cycles (episodes of weight loss \(>2.25\) kg). A cross-sectional study\(^60\) of 169 premenopausal women aged 29 to 46 years showed lower lumbar spinal BMD (−0.062 g/cm\(^2\)) vs controls; \(P = .01\) in participants who reported a history of weight cycling (weight loss of at least 5 kg, followed by regain of at least 50% of the loss).

Thus, small degrees of bone loss have been observed in obese patients on very-low-calorie diets. Results of 2 cross-sectional studies suggested that a high level of eating restraint and a history of repeated weight loss followed by regain may be associated with slightly lower bone mass.

**Physical Activity**

Attempts to analyze the effect of physical activity on bone mass have been hampered by methodological problems in exercise intervention studies. These studies show wide variation in interventions and outcome measures, small effect sizes, frequent high dropout rates, and variable compliance with test or control regimens. Wallace and Cumming\(^81\) re-
cently published a systematic review of randomized trials of the effect of exercise on bone mass in premenopausal and postmenopausal women published between 1966 and 1997. They included 8 randomized trials of premenopausal women; pooled results of these studies showed 1.5% (95% CI, 0.6%-2.4%) less bone loss per year in the lumbar spine after impact exercise (n=143; 73 exercisers and 70 controls) and 1.2% (95% CI, 0.7%-1.7%) less loss after nonimpact exercise (n=203; 95 exercisers and 108 controls). At the femoral neck, impact exercise was associated with 0.9% (95% CI, −0.2% to 2.0%) less bone loss, which approached statistical significance (n=143; 73 exercisers and 70 controls). There were insufficient data to analyze the effect of nonimpact exercise on bone mass at the femoral neck.

Two studies published since the previously mentioned systematic review have shown statistically significant increases in BMD from baseline in premenopausal women with high levels of physical activity; however, neither of these studies showed statistically significant differences in BMD in physically active women compared with controls. Two earlier randomized controlled trials showed statistically significant increases in lumbar spinal BMD in women who participated in exercise interventions compared with controls; all participants took a calcium supplement throughout both of these trials. Relevant prospective studies of exercise are summarized in Table 2.

### Disease Factors

Anorexia Nervosa and Associated Eating Disorders. Low bone mass is highly prevalent in patients with chronic anorexia nervosa (AN), especially those with the binge-eating/purging subtype. In a cohort analysis of 130 women with AN recruited from the community, Grinspoon et al found that 92% of participants met the World Health Organization criteria for osteopenia (BMD re-

### Table 2. Physical Activity and BMD in Premenopausal Women

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>Exercise</th>
<th>Participants</th>
<th>Change in Femoral Neck BMD, Mean ± SD*</th>
<th>Change in Lumbar Spinal BMD, Mean ± SD*</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/cm² per Year From Baseline per Year, %</td>
<td>g/cm² per Year From Baseline per Year, %</td>
</tr>
<tr>
<td>Ito et al, 2001</td>
<td>24-mo observational study</td>
<td>Volleyball</td>
<td>26 Premenopausal Asian women aged 42-49 y</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Exercise group (n=13)</td>
<td>NA</td>
<td>NA</td>
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<tr>
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<td></td>
<td>Sedentary controls (n=13)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Goto et al, 2001</td>
<td>12-mo prospective cohort study</td>
<td>Walking</td>
<td>12 Premenopausal Asian women aged 35-42 y</td>
<td>0.022 ± 0.014†</td>
<td>2.67†</td>
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<tr>
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<td>Exercise group (n=6)</td>
<td>−0.006 ± 0.014</td>
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<td></td>
<td>Sedentary controls (n=6)</td>
<td>0.022 ± 0.014†</td>
<td>2.67†</td>
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<tr>
<td>Winters and Snow, 2000</td>
<td>18-mo nonrandomized controlled trial</td>
<td>Jumping and resistance exercises</td>
<td>49 Premenopausal women aged 30-45 y</td>
<td>0.008†</td>
<td>1.2 ± 3.2†</td>
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<td>Exercise group (n=29)</td>
<td>0.002</td>
<td>−0.03 ± 1.9</td>
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<td>Sedentary controls (n=20)</td>
<td>0.002</td>
<td>−0.03 ± 1.9</td>
</tr>
<tr>
<td>Dornemann et al, 1997†</td>
<td>6-mo unblinded randomized controlled trial</td>
<td>Resistance exercises</td>
<td>35 Premenopausal women aged 40-50 y; all participants took a calcium supplement (500 mg/d) throughout the study</td>
<td>0.020†</td>
<td>2.62†</td>
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<tr>
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<td>Exercise group (n=18, 6 dropouts)</td>
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<td>2.62†</td>
</tr>
<tr>
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<td></td>
<td>Sedentary controls (n=17, 3 dropouts)</td>
<td>0.022†</td>
<td>2.44†</td>
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<tr>
<td>Lohman et al, 1995</td>
<td>18-mo unblinded randomized trial</td>
<td>Weight lifting</td>
<td>106 White premenopausal women aged 28-39 y; all participants took a calcium supplement (500 mg/d) throughout the study</td>
<td>−0.003</td>
<td>−0.32</td>
</tr>
<tr>
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<td></td>
<td>Exercise group (n=59, 35 dropouts)</td>
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<td>−0.32</td>
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<td></td>
<td></td>
<td>Sedentary controls (n=47, 13 dropouts)</td>
<td>−0.015</td>
<td>−1.57</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; NA, not assessed.

*Values were calculated if not reported in the study. Some values are given as mean only because the SD was not reported and could not be calculated.
†$P<.05$ for posttraining value vs pretraining value.
‡Values were extrapolated from 6-month follow-up data.
§$P<.05$ for exercise group vs control group.
duced by ≥1.0 SD) and that 38% met the criteria for osteoporosis (BMD reduced by ≥2.5 SD) at 1 or more skeletal sites. Weight was a significant independent predictor of BMD at all skeletal sites; age at menarche and time since last menstrual period were significant predictors of spinal BMD. Undernutrition, hyperprolactinemia, type 1 diabetes mellitus, AN, pernicious anemia, and previous osteoporotic fracture. Moderate-risk diseases (relative risk of fracture 1–2) included hyperthyroidism, diabetes mellitus (type 2 or not specified), and rheumatoid arthritis.

Accelerated bone loss may be associated with endocrine diseases that lead to hypoestrogenism (eg, hyperprolactinemia and Sheehan syndrome). Diseases for which glucocorticoid therapy is commonly prescribed (eg, collagen vascular diseases and cystic fibrosis) and conditions causing high endogenous levels of glucocorticoids (eg, Cushing’s syndrome) may be associated with premature bone loss. Malabsorption syndromes, inflammatory bowel disease, and lactose intolerance can affect bone health in part by altering calcium and vitamin D absorption and intake. A recent population-based study of 322 women with a history of major depression compared with 644 controls showed that a lifetime history of major depression may be associated with earlier transition to perimenopause and its associated hypoestrogenic state, which could potentially lead to premature bone loss. A National Institutes of Health–sponsored clinical trial is currently examining whether premenopausal women aged 21 to 45 years with major depression lose bone mass at a faster rate than women without depression and whether alendronate therapy can preserve bone mass in premenopausal women with major depression and osteoporosis.

**Medications**

**Glucocorticoids.** A meta-analysis of 56 cross-sectional studies and 10 longitudinal studies (a total of 2891 corticosteroid users, 71.5% women, average age of 55.2 years, age range and menopausal status not specified) concluded that oral doses of prednisolone greater than 5 mg/d or an equivalent led to a reduction in BMD and a rapid increase in fracture risk as early as 3 to 6 months after initiation of therapy. As discussed in this analysis, the increased fracture risk seems to be primarily due to a decline in bone density, but it is probably also due to a deterioration in bone quality. The decline in quality is evidenced by higher fracture rates than expected based on bone density changes alone in patients with corticosteroid-induced osteoporosis. Prolonged use of inhaled corticosteroids may also contribute to bone loss. Long-term corticosteroid use can cause a decline in muscle mass, which could potentially increase fall risk. Although the American College of Rheumatology has published guidelines for BMD monitoring and preventive management in patients receiving long-term corticosteroid therapy, many patients taking chronic exogenous corticosteroids do not receive preventive therapy for bone loss.

**Other Medications.** Although long-term thyroid supplementation has been associated with significant osteopenia in cross-sectional studies, a recent systematic review of cohort studies and case-control studies and a large cohort study of postmenopausal white women did not indicate an independent association with fracture risk. In the latter study, current use of anticonvulsant drugs was associated with increased hip fracture risk in an age-adjusted model (relative risk, 2.8; 95% CI, 1.2-6.3), although a previous analysis did not show an association between use of anticonvulsant drugs and lower appendicular bone mass.

**Smoking**

Two meta-analyses since 1997 have reported statistically significantly lower BMD at the hip in long-term smokers compared with nonsmokers. Smoking may exert its effect on bone by altering calcium and vitamin D metabolism.

**CLINICAL OUTCOMES**

Osteoporosis itself is clinically silent; the disorder has clinical and public health importance only because it increases the risk of disabling osteoporotic fractures. These outcomes are well studied in postmenopausal women. Although certain high-risk young adults may have BMD in the osteoporotic range, these patients have a low fall risk and greater muscle strength and dexterity to protect themselves from higher-impact falls. How often, and how early, do complications occur in premenopausal patients? Immediate and long-term clinical outcomes should be considered.

**Immediate Clinical Outcomes**

Premenopausal osteoporotic fractures are rare; however, early fragility fractures have been documented. In a descriptive study of 52 consecutive premenopausal women aged 20 to 51 years referred to an outpatient rheumatology clinic primarily for osteoporosis management, Peris et al found 15 patients (29%) with vertebral fractures and 12 with perivertebral fractures. Low bone mass has been associated with an increased incidence of stress fractures in female athletes and military recruits. Certain occupational groups, such as ballerinas, are at increased risk of delayed menarche and hypothalamic amenorrhea leading to osteopenia and stress fractures. A survey of 75 dancers found that 61% (n=46) reported a history of fracture, and 69%...
of the fractures described were stress fractures. Early stress fractures and vertebral fractures were documented in case series of patients with AN. A retrospective, population-based cohort study assessed long-term fracture risk in 208 patients with AN followed for a total of 2689 person-years. Forty-five patients sustained 88 fractures; the cumulative incidence of any fracture 40 years after the diagnosis of AN was 57%. Fractures of the hip, spine, and forearm occurred long after disease onset (average, 24–38 years after diagnosis).

Adolescent idiopathic scoliosis has been associated with persistent osteopenia in a small cohort study, and with low body mass index due to presumed disordered eating in a cross-sectional study of 44 young women. A 24% prevalence of scoliosis was reported in an early study of young ballet dancers; this value is substantially higher than the 2% prevalence of scoliosis reported in school-aged children and adolescents.

### Late Clinical Outcomes

Retrospective data from postmenopausal studies suggest that fractures in early adulthood may predict fractures in the perimenopausal and postmenopausal period. A recent report from the Study of Osteoporotic Fractures cohort of 9086 white women aged 65 years and older indicated that premenopausal fracture is an independent risk factor for postmenopausal fracture. For women with a history of premenopausal fracture, the hazard ratio of fractures of all types during 12 years of follow-up was 1.25 (95% CI, 1.03-1.50) after adjustment for age, BMD, body mass index, use of corticosteroid and anticonvulsant medications, number of falls, and maternal fracture history. This effect persisted after stratification by estrogen use, propensity to fracture, and maternal fracture history. Similarly, a large retrospective, population-based study by Honkanen et al found that a history of any fracture

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### Table 3. Relationship Between Premenopausal and Postmenopausal Fracture

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>Participants</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosmer et al, 2002</td>
<td>12-y prospective, population-based cohort study</td>
<td>9086 Ambulatory white women aged ≥65 y</td>
<td>Fractures that occurred after study enrollment</td>
<td>Women with a history of premenopausal fracture were more likely to sustain a fracture during the study than were women without a history of fracture (adjusted hazard ratio, 1.25; 95% CI, 1.03-1.50)</td>
</tr>
<tr>
<td>Wu et al, 2002</td>
<td>Cross-sectional</td>
<td>1284 Women ≥10 y postmenopausal (mean ± SD age, 73 ± 4 y)</td>
<td>Retrospective self-report of fracture</td>
<td>Women with a history of fractures between ages 20 and 50 y had 1.74 times the odds of sustaining a fracture after age 50 y (OR, 1.74; 95% CI, 1.12-2.70)</td>
</tr>
<tr>
<td>Goulding et al, 1997</td>
<td>Cross-sectional</td>
<td>59 Eumenorrheic premenopausal women aged 40-55 y</td>
<td>DXA, BMD, and BMC of LS</td>
<td>Women with a history of fractures had significantly lower BMD (6% less) than women who never had a fracture</td>
</tr>
<tr>
<td>Honkanen et al, 1997</td>
<td>Retrospective, population-based study</td>
<td>12,162 Women aged 47-56 y in total study population; 2412 women in BMD substudy (mean ± SD age, 53.24 ± 8.80 y)</td>
<td>Retrospective self-report of fracture</td>
<td>Women with a history of fractures between ages 20 and 34 y were more likely to sustain a fracture between ages 35 and 57 y than were women without this history (hazard ratio, 1.9; 95% CI, 1.6-2.3)</td>
</tr>
<tr>
<td>Torgerson et al, 1996</td>
<td>2-y prospective, population-based cohort study</td>
<td>1857 Perimenopausal women aged 47-51 y</td>
<td>Fractures that occurred after study enrollment</td>
<td>Women with a history of a fracture had 2 times the odds of sustaining a fracture during the study (95% CI, 1.31-3.03)</td>
</tr>
</tbody>
</table>

Abbr: BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; LS, lumbar spine; OR, odds ratio.
at ages 20 to 34 years was associated with an increased risk of fracture at ages 35 to 57 years (hazard ratio, 1.9; 95% CI, 1.6-2.3).

In summary, descriptive studies have shown low bone mass and a higher incidence of stress fractures in premenopausal women with certain disease states associated with prolonged amenorrhea, nutritional deprivation, or excessive exercise. Premenopausal fragility fractures are rare; however, premenopausal fractures of any type are an independent predictor of postmenopausal fractures.

MANAGEMENT

Treatment Issues

Early treatment interventions have been studied in premenopausal patients with secondary osteoporosis from a variety of causes. A Cochrane Review126 assessed the efficacy of bisphosphonates in preventing or delaying bone loss in a single-blind, randomized controlled trial129 of 100 premenopausal women receiving treatment for uterine leiomyomas.

Safety of bone-protective agents for women of reproductive age must be considered. For example, bisphosphonates have a category C rating for safety in pregnancy, based on toxic effects at parturition in the rat model.130 Bisphosphonates have been shown to pass through the rat placenta and accumulate in fetuses.131 These agents may be stored in bone for long periods, and the long-term implications for women of childbearing age are uncertain. Potential risks and lack of efficacy data on fracture risk reduction in premenopausal women must be weighed against the proven efficacy of bisphosphonates to decrease fractures in postmenopausal women.132,133 Bisphosphonate use should be limited in premenopausal women until further research clarifies its safety and efficacy.

Screening Issues

Although some clinical outcomes may occur early, screening for premenopausal osteoporosis in the general population is not feasible. The US Preventive Services Task Force134 considers screening in women younger than 60 years a grade C recommendation, that is, although the Task Force found at least fair evidence that this process can improve health outcomes (prevent fractures), it concluded that the balance of benefits and harms is too close to justify a general recommendation. The National Osteoporosis Foundation mentions that current data are insufficient to formulate specific recommendations for premenopausal women, nonwhite women, or men. However, the National Osteoporosis Foundation recommends that risk factors be used on an individual basis to determine the need for bone density testing and treatment and that all people should follow universal recommendations for bone health.

A case-finding strategy could be considered for premenopausal women with disease conditions known to be strongly associated with accelerated bone loss. Early detection of osteoporosis could allow interventions at an age when appropriate measures could maximize bone accrual and minimize loss over a much longer period before menopause. Some interventions are more likely to be effective in younger women; for example, more strenuous physical activity can be recommended to younger patients, and they may be more likely to comply with exercise prescriptions than premenopausal and postmenopausal women. Moreover, older patients are more likely to have already sustained fractures or to have comorbid conditions that could limit their ability to comply with an exercise regimen.

However, advantages of early detection must be weighed against potential harms, which include treatment-associated morbidity, inappropriate treatment of patients with false-positive test results, prolonged psychological distress in some patients over misperceived fracture risk, and misallocation of resources if more lives could be saved or improved through other preventive measures. Existing evidence regarding the balance of benefits and harms is insufficient to allow reasonable cost-effective analyses of screening strategies for premenopausal osteoporosis.

Guidelines

A search of the National Guidelines Clearinghouse in November 2002 revealed 8 practice guidelines directly relating to osteoporosis management. Four of these guidelines offer some diagnostic or treatment information for premenopausal patients101,136,137; the fifth mentions that its prevention guidelines apply to adults of all ages.138 The 2001 update of the American College of Rheumatology Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis mentions that prevention of bone loss with anti-resorptive agents should be considered for premenopausal women receiving glucocorticoid therapy.101

Evidence to date does not support screening for osteoporosis in premenopausal women in the general population. However, certain patient populations are at higher risk of accelerated bone loss at an early age;
a systematic method for identifying these patients in primary care is lacking. Further research must clarify the relative importance of risk factors for early bone loss and better document the potential benefits and harms of screening before a useful approach to selective screening can be developed. Until then, we will rely on heightened knowledge of primary care physicians to identify young women who may need early bone health assessment and preventive interventions. The evidence reviewed in this article supports consideration of risk assessment and bone density testing for premenopausal women with the following conditions: frequent or prolonged use of corticosteroid medications (>5 mg of oral prednisolone or the equivalent per day for >3 months), past or current AN, prolonged or recurrent anorexia nervosa, hyperparathyroidism, rheumatoid arthritis, and hyperthyroidism. Patients with abnormally low bone density will often require additional laboratory workup, nutritional evaluation, or specialty referral.

Future research should focus on prevention in addition to therapeutic interventions. Health care practitioners also need to increase patient education on modifiable disease factors, including optimal nutrition from birth, age-appropriate regular weight-bearing exercise, smoking cessation, and minimization of environmental risk factors for fracture. The goal should be to institute age-appropriate interventions at a stage when bone quality is intact and future loss can be minimized.

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