

Clinical Considerations in Premenopausal Osteoporosis

By

Margaret L. Gourlay, MD

A Master's Paper submitted to the faculty of
The University of North Carolina at Chapel Hill
In partial fulfillment of the requirements for
The degree of Master of Public Health in
The Public Health Leadership Program.

(Manuscript published in Archives of Internal Medicine, March 22, 2004:
Gourlay ML, Brown SA. Clinical considerations in premenopausal
osteoporosis. Arch Int Med 2004;164:603-614)

Chapel Hill

2004

Abstract

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.

Due to a paucity of prospective studies on screening and treatment in younger age groups, few practice recommendations exist to guide 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.

CLINICAL CONSIDERATIONS IN PREMENOPAUSAL OSTEOPOROSIS

Introduction

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; hip fracture incidence in white women increases tenfold from 50.1 per 100,000 per year at ages 50-54, to 530.5 per 100,000 per year at ages 70-74.¹ Vertebral fractures and distal forearm (Colle's) fractures occur more commonly after menopause and are associated with a higher subsequent rate of hip fracture.²⁻⁴

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 NIH 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.⁵ At present, relatively little is known about early-onset osteoporosis, and 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 present first to 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 (1984 to August 2002) using the following MeSH terms: osteoporosis, premenopause (for articles on premenopausal osteoporosis); 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 references for the following reasons: studies that included perimenopausal and/or postmenopausal women only; studies with premenopausal women as a reference group/control only, without analysis and discussion of relevant outcomes in premenopausal patients; lack of osteoporosis-related health outcomes; purpose of study was to verify an experimental radiological diagnostic tool; insufficient length of study to assess significant change in outcome.

Our initial search yielded 287 articles on premenopausal osteoporosis of which 176 articles were excluded, and 202 articles on osteopenia of which 126 were excluded; the remaining 185 articles were reviewed for relevance and quality. An additional 187 articles from supplementary searches and hand searches of reference lists were evaluated. Due 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 author (MLG) used a checklist to evaluate the internal validity of scientific studies, systematic reviews and meta-analyses.

Results

Bone density in younger patients

The NIH Consensus Panel 2000 adopted a definition of osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.⁶ Bone strength is determined both by bone density and bone quality.

Since fragility fractures are rare in young patients, they are usually not used as outcomes in studies of premenopausal bone loss, nor do they serve as the basis for 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 bone mineral density and fracture risk, such that a 10% decrease in BMD confers a 1.6-2.6 fold increased risk for spine and hip fracture.⁷

MEASUREMENT OF BONE MASS IN YOUNGER PATIENTS

Bone mineral density (BMD) is a two-dimensional, areal projection measurement defined as the average concentration of mineral per unit area, expressed in grams/cm².⁸ It is usually measured by dual-energy x-ray absorptiometry (DXA), or by single-energy x-ray absorptiometry in some cases.

BMD is reported using two scores based on standard deviation measurements: the Z score and the T score. The Z score compares the patient's BMD to the mean value in age-matched normal subjects. 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 in a healthy young reference population, assumed to represent a standard for peak bone mass. Both scores may be adjusted for race and gender. A T score of -2.5 or lower meets World Health Organization criteria for osteoporosis.⁹ A T score between -2.5 and -1 represents osteopenia; however, since fracture risk may vary widely based on age and other factors for patients with osteopenia, this categorization is of limited clinical value.⁸

Several factors should be considered when assessing bone density during periods of longitudinal growth. First, bone density measurements obtained by DXA

reflect a two-dimensional rather than a three-dimensional projection and may inaccurately capture geometric changes or increases in bone size that occur during growth. Additionally, the two-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 (grams/cm³) and may better characterize changes in total bone mass that occur during growth; however, their use is limited due to cost and contrast dye 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 with later accrual at other sites.¹⁰ Finally, small changes in BMD may be due to the random variability in the DXA test; changes of less than about 5.6% can often be due to precision error and should be interpreted cautiously.⁸

BMD 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 due to 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 > 1 occurred between the spine and proximal femur in 20-24% of women ages 20-29, and 32-46% of women ages 30-45.¹¹ 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.¹² Until peripheral DXA has been further validated against fracture, abnormal peripheral measures should be followed up with additional measurements of the spine and/or hip to confirm a diagnosis of osteoporosis.

ATTAINMENT OF PEAK BONE MASS

Peak rates of calcium accrual occur earlier than age 30. Longitudinal studies have demonstrated that calcium utilization increases during early puberty¹³ and the highest rates of calcium accrual may occur at a mean age of 12.5 in girls and 14 in boys.¹⁴ After this period of rapid calcium accretion, a period of bone consolidation is thought to ensue between age 20 and 30. Calcium accrual rates change little during this period, but periosteal expansion (outer surface of bone) may be increasing¹⁰. 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 were Tanner stage in girls and weight in boys.¹⁵ Due 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 bone mineral density values for younger age ranges.^{16, 17}

Factors influencing the attainment of peak bone mass have recently been reviewed.^{18, 19} 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 at the spine and forearm^{20, 21}; however, age of attainment could vary in normal individuals.²² A cross-sectional study of 265 premenopausal white females ages eight to 50 years showed that most of the bone mass at multiple skeletal sites will be accumulated by late adolescence.¹⁰

Multiple factors affect attainment of peak bone mass including genetic background, nutritional influences and activity level. Twin and family studies suggest that 50-80% of the variance in bone mass is heritable.^{23, 24} A strong association has been noted between bone densities in mother/daughter pairs, which may be apparent before the daughter has begun puberty.²⁵⁻²⁷

BONE MASS IN PREMENOPAUSE

Sowers and Galuska published a comprehensive review of the epidemiology of bone mass in premenopausal women in 1993.²⁸ 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, the majority of prospective and cross-sectional studies since 1994 have reported a small degree of loss (<0.5% per year) during this time period, especially at the proximal femur, and more often in women with subclinical or clinical ovulation disturbances or menopausal symptoms (Table 1).²⁹⁻³²

Risk factors for premenopausal osteoporosis

Risk factors for low bone mass and osteoporotic fractures have been well studied in peri- and postmenopausal patients³³⁻³⁶ Few studies have comprehensively examined predictors in younger patients. Moreira-Kulak et al. studied 111 pre- and perimenopausal women under 55 years of age with T scores of -2.0 or below at one or more anatomic sites, who were referred to a tertiary center for metabolic bone disorders.³⁷ Seventy-three of these women (66%) had an identifiable cause of bone loss. Conditions associated with estrogen deficiency, and use of glucocorticoid therapy were the most common known causes of osteoporosis. However, thirty-eight women (34%), 21 of whom were premenopausal, had no identifiable cause of low bone mass. Peris et al. studied 52 premenopausal osteoporotic women ages 20-51 whom were referred to an outpatient rheumatology clinic for osteoporosis evaluation and similarly found that 56% (29 patients) had no identifiable predisposing condition.³⁸

Tudor-Locke and McColl recently reviewed risk factors for variation in bone status in premenopausal women ages 20-50.³⁹ Nonmodifiable risk factors include genetic influences, 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 study have shown that genetic factors play an important role in determination of bone mineral density.^{23, 24} Candidate genes under study include vitamin D receptor (VDR) genes,⁴⁰⁻⁴⁵ the estrogen receptor gene,⁴⁶⁻⁴⁹ the collagen type 1 alpha 1 (COL1A1) gene,^{50, 51} and genes that regulate the growth hormone/insulin-like growth factor-I (IGF-I) axis.^{52, 53} Their role in bone mass development is under investigation, but this has not been adequately characterized to date.

RACE AND ETHNICITY

Due to racial and ethnic differences in BMD values, population norms have been established for use as DXA reference standards.⁵⁴⁻⁵⁶ 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.^{57, 58} Asian Americans tend to have lower BMD values than whites, but they also have a lower rate of hip fracture.⁵⁹

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 16-40 seen in a reproductive medicine clinic for amenorrhea of a median duration of three years (range six months to 24 years).⁶⁰ Lumbar spinal BMD was 15% lower in the amenorrheic women than in 57 age matched normal volunteers

(95% 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 had never fractured (n=57, p=0.003). A prospective study of 54 professional dancers and 57 nondancers found lower lumbar spinal BMD at baseline and over the subsequent two years in both exercising and nonexercising amenorrheic women.⁶¹ 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 29-39 years, four of whom had current oligomenorrhea, two with current amenorrhea, and four with a history of mixed oligo/amenorrhea.⁶² Mean lumbar spinal BMD in women with a history of oligomenorrhea alone was 12.4% lower than in controls (p<0.005), but did not differ from the mean value in women with a history of both oligomenorrhea and amenorrhea

Exogenous hormones

In some past studies, oral contraceptive (OC) use was found to be associated with bone mass increases in premenopausal women.^{63, 64} Interpretation of these studies is difficult for several reasons. The indication for OC use is usually unspecified, and women taking OC for oligo- or amenorrhea would be more likely to have low bone mass at baseline than those taking OC for contraception only. OC use 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 lower BMI 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 OC have failed to show consistent gains in bone mass in response to estrogen. Prior et al. examined oral contraceptive use in 524 women ages 25-45 participating in a multicenter, population-based cohort study, 454 of whom had taken oral contraceptives.⁶⁵ Mean BMD values adjusted for age, BMI and height were 0.02-0.04 gm/cm² (2.3%-3.7%) lower in OC ever-users as compared to 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 OC prescribed for oligo/amenorrhea may have contributed to these findings. An earlier cohort study of 200 healthy women ages 19-22 years showed that 76 participants who took an oral monophasic contraceptive (ethinyl estradiol 20 µg ± desogestrel 0.150 mg) for five years experienced no mean change in spinal BMD, while 71 non-users showed a 7.8% increase in spinal BMD by the end of the study.⁶⁶ 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, while non-users 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 (DMPA) administration on bone mass. Most of these studies involved small patient populations followed for periods as short as six months.^{67, 68} A recent 3-year, population-based cohort study of 457 women ages 18-39 (183 DMPA users and 274 non-users) showed an annual mean rate of BMD change of -0.87% at the spine for the DMPA group vs. $+0.40\%$ for controls.⁶⁹ 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 appeared to be reversible after discontinuation of DMPA use. DMPA may cause lower endogenous estrogen levels, an effect that may not be generalizable to other forms of progestin-only contraception.^{70, 71} Ongoing multicenter studies will examine the impact of DMPA 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 indicates that long-term administration of DMPA 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. While dietary influences 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 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. examined the relationship between bone mineral density and calcium intake in 56 healthy premenopausal women, ages 21-47. Statistically significant correlations were found between calcium intake and BMD at three femoral sites (neck $r=0.41$, Ward's triangle $r=0.40$, trochanter $r=0.47$, $p < 0.001$) and at the spine ($r=0.27$, $p < 0.05$).⁷² A cross-sectional study by Teegarden et al. showed a more complex relationship between bone mass and nutrient intake.⁷³

Dietary intake was assessed from food frequency interviews in 215 white women ages 18-31 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 of 156 healthy white college students, followed for up to 5 years found an increase of 5.9% in lumbar spinal BMD.⁶⁴ Spinal BMD showed a weak positive correlation with calcium intake which was not statistically significant; however, a modest but statistically significant correlation was seen with the calcium/protein ratio ($r=0.20$, $p=0.02$). Citron et al. examined the effect of calcium intake on spinal and radial BMD in a 4-year prospective study of 41 older premenopausal women, aged 38-42 years at baseline.⁷⁴ Spinal bone mass declined $-0.86 \pm 0.15\%$ per year ($p < 0.001$); the rate of decline was not attenuated by calcium intake.

Thus, several cross-sectional and prospective studies have failed to show a statistically significant association between BMD and calcium intake alone. However, calcium intake analyzed in conjunction with other nutrients appears to be a better predictor of spinal BMD in some studies.

Protein

Cooper et al. studied the relationship of six key nutrients to axial and appendicular BMD in a cross-sectional, population-based study of pre- and post-menopausal women based on a 7-day dietary record.⁷⁵ 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 four 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 bone mineral density has been studied in several settings. Two small prospective studies of obese, premenopausal patients on 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 radius⁷⁶ and hip⁷⁷ after eight to 36 months of follow-up. A randomized clinical trial examined bone mass in 236 healthy premenopausal women ages 44-50 recruited from the community to participate in a lifestyle intervention program for weight loss (dietary behavior modification and exercise recommendations).⁷⁸ After 18 months of participation, the intervention group (n=115) had lost 3.2 ± 4.7 kg vs. a weight gain of 0.42 ± 3.6 kg in controls (n=121). The annual rate of hip BMD loss was significantly higher in the intervention group vs. the controls ($0.81\% \pm 1.3\%$ loss vs. $0.42\% \pm 1.1\%$ loss, $p < 0.001$), despite the fact that intake of both dietary calcium and calcium supplements increased in the intervention group but decreased in controls. In contrast, Shapses et al. reported that lumbar spinal BMD increased by 1.7% from

baseline in premenopausal obese women on a moderate weight loss plan with 1000 mg/day calcium supplementation (n=14).⁷⁹ 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 et al. measured significantly lower bone mineral content in women who had high scores on a cognitive eating restraint (CER) questionnaire as compared to women who had low CER scores.⁸⁰ This effect was only seen in women who weighed < 71 kg. Menstrual and hormonal differences were not assessed in the participants. Participants with high CER scores reported higher numbers of lifetime weight loss cycles (episodes of weight loss over 5 pounds). A cross-sectional study of 129 premenopausal women ages 29-46 showed lower lumbar spinal BMD (-0.062 g/cm² vs. controls, p = 0.01) 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. Two 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 recently published a systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women published from 1966 to 1997.⁸¹ They included eight 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, 70 controls), and 1.2% (95% CI; 0.7%-1.7%) less loss after non-impact exercise (n=203; 95 exercisers, 108 controls). At the femoral neck, impact exercise was associated with 0.9% less bone loss (95% CI; -0.2%-2.0%), which approached statistical significance (n=143; 73 exercisers, 70 controls). There were insufficient data to analyze the effect of non-impact exercise on bone mass at the femoral neck.

Two studies published since the above systematic review have shown statistically significant increases in BMD from baseline in premenopausal women with high levels of physical activity,^{82, 83} however, neither of these studies showed statistically significant differences in BMD in the physically active women as compared to controls. Two earlier randomized, controlled trials showed statistically significant increases in lumbar spinal BMD in women who

participated in exercise interventions as compared to controls; notably, all participants took a calcium supplement throughout both of these trials.^{84, 85} Relevant prospective studies of exercise are summarized in Table 2.⁸²⁻⁸⁶

DISEASE FACTORS

Anorexia nervosa and associated eating disorders

Low bone mass is highly prevalent among patients with chronic anorexia nervosa (AN), especially in those with the binge-eating/purging subtype.⁸⁷ In a cohort analysis of 130 women with AN recruited from the community, Grinspoon et al. found that 92% of participants met WHO criteria for osteopenia (BMD reduced by at least 1.0 SD) and 38% met criteria for osteoporosis (BMD reduced by at least 2.5 SD) at one or more skeletal sites.⁸⁸ 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, hypoestrogenism, and possibly endogenous cortisol excess are mechanisms for accelerated bone loss in these patients. Bone loss has the potential to be most severe in chronic AN when onset of disease is before attainment of peak bone mass.⁸⁹

Other diseases

A recent systematic review⁹⁰ classified the following disease states as high risk (relative risk ≥ 2) for fracture related to bone mass loss in predominantly postmenopausal women: primary hyperparathyroidism, type I diabetes mellitus,

anorexia nervosa, gastrectomy, pernicious anemia, prior osteoporotic fracture. Moderate-risk diseases (RR of fracture between 1 and 2) included hyperthyroidism, diabetes mellitus (type II or not specified), and rheumatoid arthritis.

Accelerated bone loss may be associated with endocrine diseases that lead to hypoestrogenism (e.g., hyperprolactinemia,⁹¹ Sheehan's syndrome). Diseases for which glucocorticoid therapy is commonly prescribed (e.g., collagen vascular diseases,⁹² cystic fibrosis⁹³) and conditions causing high endogenous levels of glucocorticoids (e.g., Cushing's Syndrome) may be associated with premature bone loss. Malabsorption syndromes, inflammatory bowel disease and lactose intolerance⁹⁴ 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 to 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.⁹⁵ An NIH-sponsored clinical trial is currently examining whether premenopausal women ages 21 to 45 with major depression lose bone mass at a faster rate than women without depression, and whether alendronate can preserve bone mass in premenopausal women with major depression and osteoporosis.⁹⁶

MEDICATIONS

Glucocorticoids

A meta-analysis of 56 cross-sectional studies and ten longitudinal studies (total 2891 corticosteroid users, 71.5% female, average age 55.2 years, age range and menopausal status not specified) concluded that oral doses greater than 5 mg per day of prednisolone or an equivalent lead to a reduction in bone mineral density and a rapid increase in fracture risk as early as 3 to 6 months after initiation of therapy.⁹⁷ As discussed in this analysis, the increased fracture risk appears to be primarily due to a decline in bone density, but 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 steroids may also contribute to bone loss.^{98,99} Long-term steroid 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 on long-term steroid therapy,¹⁰⁰ many patients taking chronic exogenous steroids fail to receive preventive therapy for bone loss.¹⁰¹

Other medications

Although long-term thyroid supplementation has been associated with significant osteopenia in cross-sectional studies,¹⁰² a recent systematic review of cohort studies and case controls studies⁹⁰ and a large cohort study of postmenopausal white women³⁴ 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 (RR 2.8; 95% CI, 1.2-6.3), even though a previous analysis did not show an association between use of anticonvulsant

drugs and lower appendicular bone mass.¹⁰³ A meta-analysis of nine cross-sectional studies of long-term oral anticoagulant exposure found a modest negative association with bone density in the ultradistal radius, but no significant association with bone density in the distal radius, spine or hip.¹⁰⁴

SMOKING

Two meta-analyses since 1997 have reported statistically significant lower BMD at the hip in long-term smokers as compared to nonsmokers.^{105, 106} Smoking may exert its effect on bone by altering calcium and vitamin D metabolism.^{107, 108}

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.¹⁰⁹ 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? Both 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 ages 20-51 referred to an outpatient rheumatology clinic primarily for

osteoporosis management, Peris et al. found 15 patients (29%) with vertebral fractures and 12 with previous peripheral fractures.³⁸

Low bone mass has been associated with an increased incidence of stress fractures in female athletes¹¹⁰ and military recruits.¹¹¹ Certain occupational groups, such as ballerinas are at increased risk of delayed menarche and hypothalamic amenorrhea leading to osteopenia and stress fractures.¹¹² A survey of 75 dancers found 61% (n=46) reported a history of fracture, and 69% of the fractures described were stress fractures.¹¹³ Early stress fractures¹¹⁴ and vertebral fractures¹¹⁵ were documented in case series of patients with anorexia nervosa (AN). A population-based retrospective cohort study assessed long-term fracture risk in 208 patients with AN followed for a total of 2689 person-years.¹¹⁶ Forty-five patients sustained 88 fractures; the cumulative incidence of any fracture at 40 years after the diagnosis of anorexia nervosa was 57%. Fractures of the hip, spine and forearm occurred long after disease onset (on average 24 to 38 years after diagnosis).

Adolescent idiopathic scoliosis has been associated with persistent osteopenia in a small cohort study,¹¹⁷ and with low BMI due to presumed disordered eating in a cross-sectional study of 44 young women.¹¹⁸ A 24% prevalence of scoliosis was reported in an early study of young ballet dancers¹¹³; this value is substantially higher than the 2% prevalence of scoliosis reported in school-age children and adolescents.^{119, 120}

LATE CLINICAL OUTCOMES

Retrospective data from postmenopausal studies suggest that fractures in early adulthood may predict fractures in the peri- and postmenopausal period (Table 3).^{3, 121-124} A recent report from the Study of Osteoporotic Fractures (SOF) cohort of 9086 white women aged 65 and older indicated that premenopausal fracture is an independent risk factor for postmenopausal fracture.¹²¹ 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, BMI, use of steroid 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 at ages 20-34 was associated with an increased risk of fracture at ages 35-57 (HR 1.9; 95% CI 1.6, 2.3).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 and/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 Review assessed the efficacy of bisphosphonates for prevention and treatment of corticosteroid-induced osteoporosis.¹²⁵ This systematic review included 13 controlled clinical trials of 842 adults, most of whom were taking chronic corticosteroids for collagen vascular diseases (esp. rheumatoid arthritis, lupus), asthma or COPD. The weighted mean differences of bone mineral density between the treatment and placebo groups were 4.3% (95% CI, 2.7, 5.9) at the lumbar spine and 2.1% (95% CI, 0.01, 3.8) at the femoral neck. Efficacy regarding fracture prevention could not be determined. Currently, treatment trials are underway examining the efficacy of bisphosphonates in preventing and/or treating bone loss in premenopausal women with premature ovarian failure due to chemotherapy for breast cancer, in cystic fibrosis patients, and in children with idiopathic juvenile osteoporosis.⁹⁶

A randomized, controlled trial by Klibanski et al. (n=48)¹²⁶ and a recent prospective cohort study (n=50)¹²⁷ showed that estrogen-progestin replacement therapy did not prevent progressive bone loss in premenopausal patients with anorexia nervosa. Raloxifene was found to prevent GnRH-agonist-related bone loss in a single-blind, randomized controlled trial of 100 premenopausal women receiving treatment for uterine leiomyomas.¹²⁸

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.¹²⁹

Bisphosphonates have been shown to pass through the rat placenta and accumulate in fetuses.¹³⁰ 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.^{131, 132}

Bisphosphonate use should be limited in premenopausal women and reserved for those individuals with fragility fractures or clearly accelerated bone loss rather than low peak bone mass alone.

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 Force considers screening in women younger than age 60 a Grade C recommendation, i.e., 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.¹³³

The National Osteoporosis Foundation mentions that current data are insufficient to formulate specific recommendations for premenopausal women, nonwhite women or men. However, the NOF 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.¹³⁴

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 time 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 peri- 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 tests, 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 eight practice guidelines directly relating to osteoporosis management. Four of these guidelines offer some diagnostic or treatment information for premenopausal patients^{6, 100, 135, 136}; the fifth mentions that its prevention guidelines apply to adults of all ages.¹³⁷ Notably, the 2001 update of the American College of Rheumatology Recommendations for the Prevention and Treatment of Glucocorticoid-induced Osteoporosis specifies that prevention of bone loss with antiresorptive agents should be considered for premenopausal women receiving glucocorticoid therapy.¹⁰⁰

Conclusion

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 ($\geq 5\text{mg}$ oral prednisolone or equivalent per day for

at least three months), past or current anorexia nervosa, prolonged or recurrent amenorrhea, hyperparathyroidism, rheumatoid arthritis, hyperthyroidism. Patients with abnormally low bone density will often require additional laboratory work-up, nutritional evaluation, or specialty referral.

Future research should focus on prevention in addition to therapeutic interventions. Health care providers 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.

Acknowledgments

Dr. Gourlay and Dr. Brown acknowledge David Ontjes, MD, Russell Harris, MD, MPH and Michael Pignone, MD, MPH for their review of this manuscript. Dr. Gourlay also thanks Jay Siwek, MD for his editorial advice.

Grant Support: Dr. Gourlay is supported by the Robert Wood Johnson Foundation. Dr. Brown is supported by the UNC NIH-sponsored Building Interdisciplinary Research Careers in Women's Health Program.

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Table 1: Prospective studies of bone mineral density in premenopausal women

Study	Length of follow-up	Participants		Change in femoral neck BMD		Change in lumbar spinal BMD	
				g/cm ² per year	% change from baseline per year	g/cm ² per year	% change from baseline per year
Bainbridge et al. 2002 ²⁹	6 years	614 women ages 24-44		-0.003*	-0.3%*	Varied with time	
Hui et al. 2002 ³⁰	1-9 years (mean 3.9)	130 premenopausal white women, ages 31-50		-0.00357 ± 0.0025*	-0.43%*	-0.00209 ± 0.0050	-0.19%
Salamone et al. 1998 ³¹	30 months	290 premenopausal white women, ages 44-50	No menopausal symptoms	—	—	-0.0018	-0.17% ± 1.1%
			At least one menopausal symptom	—	—	-0.0050*	-0.50 ± 1.3%*
Slemenda et al. 1996 ³²	2-8 years	96 premenopausal women, ages 30-48		-0.0021 ± 0.013*	-0.25%*	+0.0036 ± 0.012	+0.32%

BMD, bone mineral density

* p < 0.05 for comparison of follow-up value to baseline value

Table 2. Physical activity and bone mineral density in premenopausal women

Study	Type	Exercise	Participants		Change in femoral neck BMD [†]		Change in lumbar spinal BMD [†]	
					g/cm ² per year	% change from baseline per year	g/cm ² per year	% change from baseline per year
Ito et al. 2001 ⁸⁶	24-month observational study	Volleyball	26 premenopausal Asian women ages 42-49	Exercise group (n=13)	—	—	0.001	0.05%
				Sedentary controls (n=13)	—	—	-0.011	-0.94%
Goto et al. 2001 ⁸²	12-month prospective cohort study	Walking	12 premenopausal Asian women ages 35-42	Exercise group (n=6)	0.022 ± 0.015*	2.67%*	0.009 ± 0.015	0.90%
				Sedentary controls (n=6)	-0.006 ± 0.014	-0.78%	0.011 ± 0.027	1.06%
Winters et al. 2000 ⁸³	18-month nonrandomized controlled trial	Jumping and resistance exercises	49 premenopausal women ages 30-45	Exercise group (n=29)	0.008*	1.2% ± 3.2%*	0.010	1.1% ± 3.0%
				Sedentary controls (n=20)	-0.002	-0.03 ± 1.9%	0.002	0.2% ± 1.9%
Dornemann et al. 1997 ^{84#}	6-month unblinded randomized controlled trial	Resistance exercises	35 premenopausal women ages 40-50. All participants took a 500 mg/day calcium supplement throughout the study.	Exercise group (n = 12, 6 dropouts)	0.020*	2.62%*	0.020 [†]	2.00% [†]
				Sedentary controls (n = 14, 3 dropouts)	0.022*	2.44%*	-0.008	-0.72%
Lohman et al. 1995 ⁸⁵	18-month unblinded randomized controlled trial	Weight-lifting	106 white premenopausal women ages 28-39. All participants took a 500 mg/day calcium supplement throughout study.	Exercise group (n=22, 37 dropouts)	-0.003	-0.32%	0.019 [†]	1.61% [†]
				Sedentary controls (n=34, 13 dropouts)	-0.015	-1.57%	-0.008	-0.65%

BMD, bone mineral density

BMD values extrapolated from 6-month follow-up data

* p < 0.05 for comparison of post-training value to pre-training value

[†] p < 0.05 for comparison of exercise group to control group

[‡] values were calculated if not reported in study

Table 3. Relationship between premenopausal and postmenopausal fracture

Study	Type	Participants	Outcome measures	Findings
Hosmer et al. 2002 ¹²¹	12-year prospective population-based cohort study	9086 ambulatory white women age 65 years and older.	Fractures that occurred after study enrollment.	Women with a history of premenopausal fracture were more likely to sustain a fracture during the study period than women without a history of fracture. Adjusted hazard ratio: 1.25; 95% CI, 1.03-1.50.
Wu et al. 2002 ¹²²	Cross-sectional	1284 women, at least 10 years postmenopausal, mean age $\pm$ SD: 73 ± 4 years.	Retrospective self-report of fracture	Women with a history of fractures between the ages of 20 and 50 years had 1.74 times the odds of sustaining a fracture after age 50 (OR, 1.74; 95% CI, 1.12-2.70). Fractures occurring before age 20 were not associated with increased odds of fracture after age 50 (OR, 1.01; CI 0.66-1.56)
Goulding et al. 1997 ¹²³	Cross-sectional	59 eumenorrheic premenopausal women, ages 40-55	DXA—BMD and BMC of LS	Women with a history of fractures had significantly lower BMD (6% less) than women who had never fractured.
Honkanen et al. 1997 ⁵	Retrospective population-based study	12,162 women ages 47-56 years in total study population.; 2412 women in BMD substudy with mean $\pm$ SD age 53.24 ± 2.80 years	Retrospective self-report of fracture DXA—BMD of LS and femoral neck	Women with a history of fractures between the ages of 20 and 34 were more likely to sustain a fracture between the ages of 35 and 57 than women without this history. (Hazard ratio 1.9; 95% CI, 1.6-2.3) An early premenopausal, low-energy wrist fracture was associated with 10.5% lower femoral BMD than for nonfractured women (p=0.026).
Torgerson et al. 1996 ¹²⁴	2-year prospective population-based cohort study	1857 perimenopausal women ages 47-51	Fractures that occurred after study enrollment	Women with a history of fracture, had 2 times the odds of sustaining a fracture during the study period (95% CI, 1.31-3.03). After adjusting for covariates, the OR of sustaining a fracture was 1.6 (95% CI, 1.16-2.34) for each SD reduction in BMD at the spine Family history of hip fracture (maternal grandmother) carried OR 3.7 (95% CI, 1.55-8.85). Postmenopausal or history of hysterectomy carried OR 1.98 (1.02-3.56).

DXA, dual x-ray absorptiometry
BMD, bone mineral density
BMC, bone mineral content

LS, lumbar spine
OR, odds ratio

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.

Arch Intern Med. 2004;164:603-614

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.¹ Vertebral fractures and distal forearm (Colles) fractures occur more commonly after menopause and are associated with a higher subsequent rate of hip fracture.²⁻⁴

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 Develop-

ment Panel on Osteoporosis Prevention, Diagnosis, and Therapy⁵ 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

From the Department of Family Medicine, Robert Wood Johnson Clinical Scholars Program (Dr Gourlay), and the Division of Endocrinology, Department of Internal Medicine (Dr Brown), University of North Carolina-Chapel Hill. The authors have no relevant financial interest in this article.

"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.⁶ 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.⁷

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.⁸ 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 meets World Health Organization criteria for osteoporosis.⁹ A T score between -2.5 and -1.0 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.⁸

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 ra-

diation 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.¹⁰ 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.⁸

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. Bonnicksen et al¹¹ 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.¹² 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 puberty¹³ and that the highest rates of calcium accrual may occur at a mean age of 12½ years in girls and 14 years in boys.¹⁴ 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.¹⁰ These periosteal changes could theoretically confer greater structural integrity and would not

Table 1. Prospective Studies of BMD in Premenopausal Women

Source	Length of Follow-up	Participants	Change in Femoral Neck BMD, Mean $\pm$ SD*		Change in Lumbar Spinal BMD, Mean $\pm$ SD*	
			g/cm ³ per Year	From Baseline per Year, %	g/cm ³ per Year	From Baseline per Year, %
Bainbridge et al. ²⁸ 2002	6 y	614 Women aged 24-44 y	-0.003†	-0.3†	Varied with time	
Hui et al. ³⁰ 2002	1-9 y (mean, 3.9 y)	130 Premenopausal white women aged 31-50 y	-0.00357 $\pm$ 0.0025†	-0.43†	-0.00209 $\pm$ 0.0050	-0.19
Salamone et al. ³¹ 1996	30 mo	290 Premenopausal white women aged 44-50 y				
		No menopausal symptoms	NA	NA	-0.0018	-0.17 $\pm$ 1.1
		$\geq$ 1 Menopausal symptom	NA	NA	-0.0050†	-0.50 $\pm$ 1.3†
Siemenda et al. ³² 1996	2-8 y	96 Premenopausal women aged 30-48 y	-0.0021 $\pm$ 0.013†	-0.25†	+0.0036 $\pm$ 0.012	+0.32

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.

be adequately detected by bone density measurements using DXA. One¹⁵ 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^{16,17} 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.^{18,19} The precise age at which peak bone mass occurs is unknown. Population-based, cross-sectional studies^{20,21} 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.²² 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.¹⁰

Multiple factors affect attainment of peak bone mass, including genetic background, nutritional influences, and activity level. Twin²³ and family²⁴ 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.²⁵⁻²⁷

Bone Mass in Premenopause

Sowers and Galuska²⁸ 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 studies²⁹⁻³² 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.³³⁻³⁶ Few studies have comprehensively examined predictors in younger patients. Moreira-Kulak et al³⁷ 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 al³⁸ 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 McColl³⁹ 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

Twin²³ and family²⁴ studies have shown that genetic factors play an important role in determining BMD. Candidate genes under study include vitamin D receptor (VDR) genes,⁴⁰⁻⁴⁵ the estrogen receptor gene,⁴⁶⁻⁴⁹ the collagen type 1 alpha 1 (COL1A1) gene,^{50,51} and genes that

regulate the growth hormone/insulin-like growth factor I axis.^{52,53} 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.⁵⁴⁻⁵⁶ 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.^{57,58} Asian Americans tend to have lower BMD values than whites, but they also have a lower rate of hip fracture.⁵⁹

Hormonal Factors

Endogenous Hormones. Bone loss can occur in the setting of prolonged amenorrhea and estrogen deficiency. Davies et al⁶⁰ 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 study⁶¹ 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 hypoeestrogenism, as evidenced by prolonged menstrual irregularity. Micklesfield et al⁶² 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,^{63,64} 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 al⁶⁵ examined OC use in 524 women aged 25 to 45 years participating in a multicenter, population-based cohort study, 454 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 study⁶⁶ 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^{67,68} involved small patient populations followed for as little as 6 months. A recent 3-year population-based cohort study⁶⁹ 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.^{70,71} 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 al⁷² 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 ($r=0.27$; $P<.05$).⁷² A cross-sectional study by Teegarden et al⁷³ 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 study⁶⁴ 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 al⁷⁴ 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 al⁷⁵ 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 radius⁷⁶ and hip⁷⁷ after 8 to 36 months of follow-up. A randomized clinical trial⁷⁸ 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 ± 4.7 kg vs a weight gain of 0.42 ± 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 al⁷⁹ 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 Keim⁸⁰ 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 study⁸¹ of 169 premenopausal women aged 29 to 46 years showed lower lumbar spinal BMD (-0.062 g/cm² 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 Cumming⁸² re-

Table 2. Physical Activity and BMD in Premenopausal Women

Source	Study Type	Exercise	Participants	Change in Femoral Neck BMD, Mean $\pm$ SD*		Change in Lumbar Spinal BMD, Mean $\pm$ SD*	
				g/cm ² per Year	From Baseline per Year, %	g/cm ² per Year	From Baseline per Year, %
Ito et al, ⁸¹ 2001	24-mo observational study	Volleyball	26 Premenopausal Asian women aged 42-49 y				
			Exercise group (n = 13)	NA	NA	0.001	0.05
			Sedentary controls (n = 13)	NA	NA	-0.011	-0.94
Goto et al, ⁸³ 2001	12-mo prospective cohort study	Walking	12 Premenopausal Asian women aged 35-42 y				
			Exercise group (n = 6)	0.022 $\pm$ 0.015†	2.67†	0.009 $\pm$ 0.015	0.90
			Sedentary controls (n = 6)	0.006 $\pm$ 0.014	-0.78	0.011 $\pm$ 0.027	1.06
Winters and Snow, ⁸⁴ 2000	18-mo nonrandomized controlled trial	Jumping and resistance exercises	49 Premenopausal women aged 30-45 y				
			Exercise group (n = 29)	0.008†	1.2 $\pm$ 3.2†	0.010	1.1 $\pm$ 3.0
			Sedentary controls (n = 20)	-0.002	-0.03 $\pm$ 1.9	0.002	0.2 $\pm$ 1.9
Domemann et al, ⁸⁵ 1997‡	6-mo unblinded randomized controlled trial	Resistance exercises	35 Premenopausal women aged 40-50 y; all participants took a calcium supplement (500 mg/d) throughout the study				
			Exercise group (n = 18; 6 dropouts)	0.020†	2.62†	0.020§	2.00§
			Sedentary controls (n = 17; 3 dropouts)	0.022†	2.44†	-0.008	-0.72
Lohman et al, ⁸⁶ 1995	18-mo unblinded randomized controlled trial	Weight lifting	106 White premenopausal women aged 28-39 y; all participants took a calcium supplement (500 mg/d) throughout the study				
			Exercise group (n = 59; 35 dropouts)	-0.003	-0.32	0.019§	1.61§
			Sedentary controls (n = 47; 13 dropouts)	-0.015	-1.57	-0.008	-0.65

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.

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 exer-

cisers and 70 controls). There were insufficient data to analyze the effect of nonimpact exercise on bone mass at the femoral neck.

Two studies^{83,84} published since the previously mentioned systematic review⁸² 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^{85,86} 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 studies⁸³⁻⁸⁷ 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.⁸⁸ In a cohort analysis of 130 women with AN recruited from the community, Grinspoon et al⁸⁹ found that 92% of participants met the World Health Organization criteria for osteopenia (BMD re-

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, hypoestrogenism, and possibly endogenous cortisol excess are mechanisms for accelerated bone loss in these patients. Bone loss has the potential to be most severe in chronic AN when onset of disease is before attainment of peak bone mass.⁹⁰

Other Diseases. A recent systematic review⁹¹ classified the following disease states as high risk (relative risk ≥ 2) for fracture related to bone mass loss in predominantly postmenopausal women: primary hyperparathyroidism, type 1 diabetes mellitus, AN, gastrectomy, 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, hyperprolactinemia⁹² and Sheehan syndrome). Diseases for which glucocorticoid therapy is commonly prescribed (eg, collagen vascular diseases⁹³ and cystic fibrosis⁹⁴) 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 intolerance⁹⁵ can affect bone health in part by altering calcium and vitamin D absorption and intake. A recent population-based study⁹⁶ 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 trial⁹⁷ 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-analysis⁹⁸ 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.^{99,100} 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,¹⁰¹ many patients taking chronic exogenous corticosteroids do not receive preventive therapy for bone loss.¹⁰²

Other Medications. Although long-term thyroid supplementation has been associated with significant osteopenia in cross-sectional studies,¹⁰³ a recent systematic review⁹¹ of cohort studies and case-control studies and a large cohort study³⁴ 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 analysis¹⁰⁴ did not show an association between use of anticonvulsant drugs and lower appendicular bone mass. A meta-

analysis¹⁰⁵ of 9 cross-sectional studies of long-term oral anticoagulant exposure found a modest negative association with bone density in the ultradistal radius but no significant association with bone density in the distal radius, spine, or hip.

Smoking

Two meta-analyses^{106,107} 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.^{108,109}

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.¹¹⁰ 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 al³⁸ found 15 patients (29%) with vertebral fractures and 12 with previous peripheral fractures.

Low bone mass has been associated with an increased incidence of stress fractures in female athletes¹¹¹ and military recruits.¹¹² Certain occupational groups, such as ballerinas, are at increased risk of delayed menarche and hypothalamic amenorrhea leading to osteopenia and stress fractures.¹¹³ A survey of 75 dancers found that 61% (n=46) reported a history of fracture, and 69%

Table 3. Relationship Between Premenopausal and Postmenopausal Fracture

Source	Study Type	Participants	Outcome Measures	Findings
Hosmer et al, ¹²² 2002	12-y prospective, population-based cohort study	9086 Ambulatory white women aged ≥ 65 y	Fractures that occurred after study enrollment	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)
Wu et al, ¹²³ 2002	Cross-sectional	1284 Women ≥ 10 y postmenopausal (mean $\pm$ SD age, 73 $\pm$ 4 y)	Retrospective self-report of fracture	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) Fractures occurring before age 20 y were not associated with increased odds of fracture after age 50 y (OR, 1.01; 95% CI, 0.66-1.56)
Goulding et al, ¹²⁴ 1997	Cross-sectional	59 Eumenorrheic premenopausal women aged 40-55 y	DXA, BMD, and BMC of LS	Women with a history of fractures had significantly lower BMD (6% less) than women who never had a fracture
Honkanen et al, ³ 1997	Retrospective, population-based study	12 162 Women aged 47-56 y in total study population; 2412 women in BMD substudy (mean $\pm$ SD age, 53.24 $\pm$ 2.80 y)	Retrospective self-report of fracture DXA, BMD of LS and femoral neck	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) An early premenopausal, low-energy wrist fracture was associated with 10.5% lower femoral BMD than for nonfractured women ($P = .03$)
Torgerson et al, ¹²⁵ 1996	2-y prospective, population-based cohort study	1857 Perimenopausal women aged 47-51 y	Fractures that occurred after study enrollment	Women with a history of fracture had 2 times the odds of sustaining a fracture during the study (95% CI, 1.31-3.03) After adjusting for covariates, the OR of sustaining a fracture was 1.6 (95% CI, 1.16-2.34) for each SD reduction in BMD at the spine Family history of hip fracture (maternal grandmother) carried an OR of 3.7 (95% CI, 1.55-8.85); postmenopausal status or history of hysterectomy carried an OR of 1.98 (95% CI, 1.02-3.56)

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; LS, lumbar spine; OR, odds ratio.

of the fractures described were stress fractures.¹¹⁴ Early stress fractures¹¹⁵ and vertebral fractures¹¹⁶ were documented in case series of patients with AN. A retrospective, population-based cohort study¹¹⁷ 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 study¹¹⁸ and with low body mass index due to pre-

sumed disordered eating in a cross-sectional study¹¹⁹ of 44 young women. A 24% prevalence of scoliosis was reported in an early study of young ballet dancers¹¹⁴; this value is substantially higher than the 2% prevalence of scoliosis reported in school-aged children and adolescents.^{120,121}

Late Clinical Outcomes

Retrospective data from postmenopausal studies^{3,122-125} suggest that fractures in early adulthood may predict fractures in the perimenopausal and postmenopausal period (**Table 3**). 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.¹²² 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 al³ found that a history of any fracture

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 for the prevention and treatment of corticosteroid-induced osteoporosis. This systematic review included 13 controlled clinical trials of 842 adults older than 18 years, most of whom were taking chronic corticosteroids for collagen vascular diseases (especially rheumatoid arthritis and lupus), asthma, or chronic obstructive pulmonary disease. The weighted mean difference in BMD between the treatment and placebo groups was 4.3% (95% CI, 2.7%-5.9%) at the lumbar spine and 2.1% (95% CI, 0.01%-3.8%) at the femoral neck. Efficacy regarding fracture prevention could not be determined. Currently, treatment trials are under way examining the efficacy of bisphosphonates in preventing or treating bone loss in premenopausal women with premature ovarian failure due to chemotherapy for breast cancer, in patients with cystic fibrosis, and in children with idiopathic juvenile osteoporosis.⁹⁷

A randomized controlled trial by Klibanski et al¹²⁷ (n=48) and a recent prospective cohort study by Golden et al¹²⁸ (n=50) showed that estrogen-progestin replacement therapy did not prevent progressive bone loss in premenopausal patients with AN. Raloxifene therapy was found to prevent gonadotropin-releasing hormone-agonist-related bone loss in a single-blind, random-

ized 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 Foundation¹³⁵ 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 perimenopausal 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 patients^{6,101,136,137}; 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

CONCLUSIONS

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 amenorrhea, 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.

Accepted for publication May 9, 2003.

We thank David Ontjes, MD, Russell Harris, MD, MPH, and Michael Pignone, MD, MPH, for their review of this manuscript and Jay Siwek, MD, for his editorial advice.

This study was supported by the Robert Wood Johnson Foundation, Princeton, NJ (Dr Gourlay) and by the University of North Carolina National Institutes of Health-sponsored Building Interdisciplinary Research Careers in Women's Health Program (Dr Brown).

Corresponding author: Margaret L. Gourlay, MD, Robert Wood Johnson Clinical Scholars Program, University of North Carolina—

Chapel Hill, 5034 Old Clinic Building, Campus Box 7105, Chapel Hill, NC 27599 (e-mail: margaret_gourlay@med.unc.edu).

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