

Estrogen deficiency during menopause:

2. Low bone density in asymptomatic women without osteoporosis

CASE 2

Michael R. McClung, MD

Director, Oregon Osteoporosis Center
Assistant Director,
Department of Medical Education
Providence Portland Medical Center
Portland, Ore

James A. Simon, MD, Series Editor

Clinical Professor of Obstetrics and Gynecology
George Washington University School of Medicine
Washington, DC

Julie Fagan, MD, Education Reviewer

University of Wisconsin Medical School
Madison, Wis

A 58-year-old menopausal woman presented with concerns about osteoporosis. The patient recounted that a friend's recent diagnosis of osteopenia caused her to wonder about her own skeletal health. The patient had not experienced fractures and had no family history of osteoporosis. She did not exercise regularly and did not have a history of falls. Her dietary calcium intake was estimated to be 500 mg/d. Each day she took an additional 300 mg of calcium but did not take a multivitamin. She went through natural menopause at age 48 and took estrogen for 3 years to control hot flashes and vaginal dryness that did not recur when she discontinued therapy. She had no other recognized medical conditions.

On examination, the patient weighed 142 lb and was 66 in tall, her maximal adult height. Her physical examination was unremarkable, with no evidence of bone deformity or tenderness, muscle weakness, or neuromuscular impairment. Results of her recent blood count and routine serum chemistry tests (including serum calcium, creatinine, and alkaline phosphatase) were normal. Because of the patient's concern about her skeletal health, a bone density test was ordered. By dual-energy x-ray

Jointly sponsored by the University of Wisconsin Medical School and Dowden Health Media
Supported by an educational grant from Berlex, Inc.

Series learning objectives: After completing this series of case studies, the reader should be able to:

- Recognize the connection between estrogen deficiency and metabolic syndrome
- Regard HT as an option in patients with both vasomotor symptoms and features of the metabolic syndrome
- Screen for bone loss in patients without vasomotor symptoms or osteoporosis and determine fracture risk, if appropriate*
- Recognize when transdermal HT may be an alternative to nonhormonal agents used to prevent bone loss

* Learning objective addressed in this article

Intended audience: This educational activity has been developed for obstetricians and gynecologists.

Accreditation: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Wisconsin Medical School and Dowden Health Media. The University of Wisconsin Medical School is accredited by the ACCME to provide continuing medical education for physicians.

Credit designation: The University of Wisconsin Medical School designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

Disclosures: As a sponsor accredited by the ACCME, it is the policy of the University of Wisconsin Medical School to require disclosure of the existence of any significant financial interest or any other relationship that a faculty member or sponsor has with the manufacturer(s) of any commercial product(s) discussed in an educational program. The authors reported the following:

• **Michael R. McClung, MD**, is a consultant for Amgen Inc., Eli Lilly and Co., Merck and Co. Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Roche Diagnostics Corporation, and Sanofi-Aventis. He receives grants/research support from Amgen Inc., Eli Lilly and Co., Merck and Co. Inc., Novartis Pharmaceuticals Corporation, NPS Pharmaceuticals, Pfizer Inc., Roche Diagnostics Corporation, Sanofi-Aventis, and Wyeth.

• **James A. Simon, MD**, is a consultant for Abbott Laboratories, Barr Laboratories, Inc., Berlex Laboratories, BioSante, Endeavor, Galen, Lipocine, Merck and Co. Inc., Novavax, Inc., Pfizer Inc., Solvay Pharmaceuticals, Inc., TAP Pharmaceuticals Inc., and Wyeth. He receives grants/research support from Balance, Barr Laboratories, Inc., Bayer Corporation, Berlex Laboratories, Besins, BioSante, Bristol-Myers Squibb, Duramed Pharmaceuticals, Inc., Endeavor, Galen, Eli Lilly and Co., Merck and Co. Inc., National Institutes of Health, Novartis, Novavax, Inc., Organon/AKZO, Pfizer Inc., Pharmacia, Procter & Gamble Pharmaceuticals, Solvay Pharmaceuticals, Inc., TAP Pharmaceuticals Inc., 3M Pharmaceuticals, Watson Laboratories Inc., and Wyeth. He is on the speakers' bureau of Aventis Pharmaceuticals, Eli Lilly and Co., Merck and Co. Inc., Ortho-McNeil Pharmaceutical, Pfizer Inc., and Solvay Pharmaceuticals, Inc.

Note: In accordance with the ACCME Essential Areas and Policies regarding commercial support, the reader is advised that this continuing medical education activity may contain references to unlabeled or unapproved uses of drugs or devices.

Disclaimer: The opinions expressed herein are those of the authors and do not necessarily reflect those of the University of Wisconsin Medical School, Dowden Health Media, or Berlex Laboratories.

Release date: August 2005

Expiration date: August 2006

absorptiometry (DXA), the T-score value in the lumbar spine was -1.6 and in the total hip region, -1.4 . The patient was told that she had moderate osteopenia and was at increased risk for fracture. She responded to the diagnosis with questions about the severity of her bone problem and what steps could be taken to prevent osteoporosis.

■ FEATURES OF OSTEOPOROSIS

Osteoporosis is a disorder characterized by increased fracture risk due to impaired bone strength.¹ This usually is the result of bone loss that causes reduced bone mass and a destruction of bone tissue. Bone density remains quite stable in healthy premenopausal women, but bone loss ensues with the onset of estrogen deficiency.^{2,3} In the first few years after menopause, bone loss occurs as a result of cytokine-induced activation of osteoclastic bone resorption.⁴ The rates of loss are greatest during the first few years of estrogen deficiency but then slow to much lower levels (**TABLE 1**). Bone loss averages 1% to 2% per year in women who are within 5 years after menopause. Rates of loss of less than 1% per year are observed in women who are more than 5 years postmenopausal. At this rate, bone mineral density (BMD) changes of 1 T-score unit would occur over 10 to 15 years (1 T-score = 10% to 12% of peak bone mass).

Risk factors for more rapid bone loss include low body weight, extended bed rest, alcohol consumption, and smoking.⁵⁻⁷ Assays showing higher levels of biochemical markers of bone turnover are predictive of more rapid bone loss in certain patients.^{8,9} However, the variability of these assays limits their effectiveness in managing individual patients in clinical practice. In one widely quoted study, the average of 4 measurements of urinary N-telopeptide, a marker of bone resorption, was correlated with rates

TABLE 1

Rates of bone loss at the lumbar spine in healthy calcium-replete postmenopausal women

Reference	Years of \pm SD (Range)	Years since menopause \pm SD (Range)	Lumbar spine BMD # \pm SD [T-score \pm SD]	Years of follow-up	Decrease in BMD (%) \pm SD
<i>Less than 5 years since menopause</i>					
Mosekilde ¹	50 \pm 3	0.8 \pm 0.7	1.04 \pm 0.11 [-1 \pm 1.2]	5	4
McClung ²	51 \pm 0.4* (45 – 59)	2.3 \pm 0.4*	0.93 \pm 0.01*	3	3.5
Mortensen ³	51 \pm 4 (45 – 61)	3 \pm 1 (0.5 – 3)	0.96 \pm 0.11	2	4.3
Gallagher ⁴	53 \pm 3	2 \pm 1	[-0.5]	2	2.2 \pm 0.3
Nielsen ⁵	53 \pm 2 (40 – 65)	2.3 \pm 1.4	0.96 \pm 0.09*	2	3.2
<i>More than 5 years since menopause</i>					
Delmas ⁶	55 \pm 3 (45 – 60)	5 \pm 2 (2 – 8)	0.94 \pm 0.11 [-1.0 \pm 1.0]	2	0.8
PEPI ⁷	56 \pm (0.3*)	6 (6)	0.98 \pm 0.1*	3	1.8
McClung ⁸	54 \pm 3 (45 – 59)	6 \pm 6	0.95 \pm 0.11 [-0.9 \pm 1.0]	6	3.2
McClung ⁹	58 \pm 9	8 \pm 8	1.01 \pm 0.14	2	1.2 \pm 0.5

*Data are from placebo- or calcium-treated groups of large prospective clinical trials.

Variables expressed as mean \pm standard deviation (SD) when available except where marked as * =mean \pm SE # BMD in gm/cm²

REFERENCES

- Mosekilde L, Beck-Nielsen H, Sorensen OH, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women—result of the Danish Osteoporosis Prevention Study. *Maturitas*. 2000;36:181-193.
- McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. *Ann Intern Med*. 1998;128:253-261.
- Mortensen L, Charles P, Bekker PJ, et al. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab*. 1998;83:396-402.
- Gallagher JC, Baylink DJ, Freeman R, McClung M. Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies. *J Clin Endocrinol Metab*. 2001;86:4717-4726.
- Nielsen TF, Ravn P, Bagger YZ, et al. Pulsed estrogen therapy in prevention of postmenopausal osteoporosis. A 2-year randomized, double blind, placebo-controlled study. *Osteoporos Int*. 2004;15:168-174.
- Delmas P, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med*. 1997;337:1641-1647.
- The Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density. Results from the Postmenopausal Estrogen/Progestin Interventions Trial. *JAMA*. 1996;276:1389-1396.
- McClung M, Wasnich R, Hosking DJ, et al. Prevention of postmenopausal bone loss: Six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab*. 2004;89:4879-4885.
- McClung MR, Wasnich RD, Recker R, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res*. 2004;19:11-18.

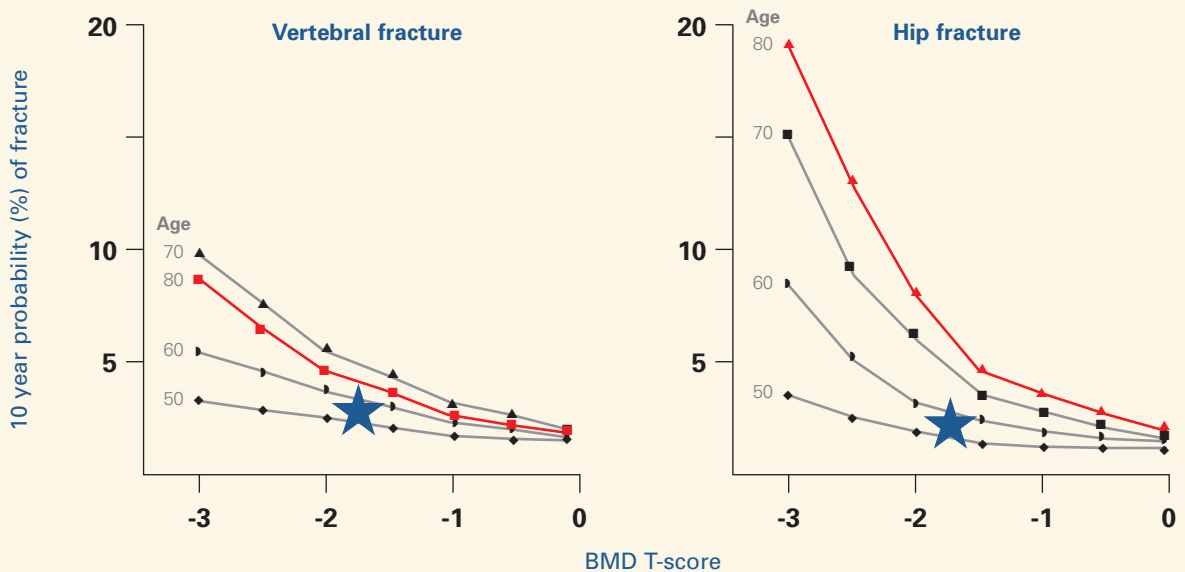
of bone loss in early postmenopausal women, but the value of any single test was not predictive of changes in bone density.⁸ With advancing age, bone loss progresses, the skeleton becomes less strong, and fractures of the spine and hip begin to increase in frequency.¹⁰

■ BONE DENSITY AND FRACTURE RISK

Bone mineral density-testing measures the amount of mineral in the skeleton but provides little information about bone structure or bone strength. At any age, women with low T-scores are at greater risk of fracture

FIGURE 1

Relationships between BMD T-scores and the 10-year probability of postmenopausal women of different ages experiencing a vertebral hip fracture



Stars represent the values of the patient discussed.

Adapted with permission from Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int.* 2001;12:989-995.

than women with higher values.¹¹ When BMD testing is adjusted for age, it is an important determinant of fracture risk in postmenopausal women. For each standard deviation (SD) decrease in age-adjusted bone density, fracture risk approximately doubles. This means that a woman with a Z-score of -1 (one standard deviation below age- and gender-matched controls) is twice as likely to have a fracture as a woman with average bone density for her age (Z-score = 0). However, when postmenopausal women are stratified by decades of age, important differences in the relationships between bone density and fracture risk are observed¹² (FIGURE 1). For any bone density value, younger women are at substantially lower risk for fracture than older women. Another major risk factor

for fractures in postmenopausal is a history of prior fragility fracture since menopause, and this risk is independent of BMD values.¹³ Therefore, if bone density testing is not adjusted for age and prior fracture history, the resulting T-score value tells us very little about bone strength and fracture risk.

Few studies have evaluated risk factors for fracture in women who are aged 50 to 60 years.¹⁴⁻¹⁶ Such a study would prove to be difficult since fracture rates, especially of the hip and spine, are very low in healthy young postmenopausal women, in spite of the bone loss that is already occurring. Fractures at sites other than the hip and spine occur more commonly in young postmenopausal women but are of much less clinical consequence. In a group of 87,594 women aged 50 to 64 years

(average age 57), the overall incidence of fracture was 8.4/1000 women-years, and the combined incidence of hip and spine fracture was 0.2% per year.¹⁴ In a cohort of 3068 perimenopausal women, risk factors for fracture included low bone density, history of previous fracture, maternal history of hip fracture, and having other medical problems.²⁴ Many commonly perceived risk factors, including age at menopause, years since menopause, calcium or caffeine intake, use of alcohol, smoking, and body size, were not predictive of fracture.

■ DIAGNOSING OSTEOPOROSIS

The diagnosis of osteoporosis in postmenopausal women is based solely on bone density values, although fracture risk is estimated on the basis of bone density and other clinical risk factors.¹⁷ A diagnostic threshold of 2.5 SDs below the average value in young women (T-score -2.5 or lower) now defines osteoporosis in postmenopausal women. This diagnostic threshold was chosen by a task force of the World Health Organization (WHO) based on epidemiological considerations, and it effectively identifies women at moderate to high fracture risk.¹⁸ However, many women whose bone density values do not meet the criteria for osteoporosis are at moderate or even high risk for fracture because of age, prior fracture, or other risks, and most fragility fractures occur in women whose BMD values are not consistent with osteoporosis.^{19,20}

The diagnosis of osteopenia, meaning low bone mass, was also defined by the WHO for epidemiological purposes and was not meant to be a clinical diagnosis. Osteopenia in postmenopausal women includes those with T-score values by DXA between -1 and -2.5 . In healthy young women, the normal range of bone density values (mean + 2 SDs) expressed

Recommendations for bone density testing

Based on evidence from prospective clinical trials, the United States Preventive Services Task Force has recommended that bone mineral density (BMD) be measured in all women 65 years of age and older.¹ They also recommend testing for women between ages 60 and 65 who have other risk factors for low bone density including low body weight and estrogen deficiency. Because of lack of evidence that bone density testing or treatment of young postmenopausal women is of value, they made no recommendations about bone density testing for postmenopausal women younger than age 60. The National Osteoporosis Foundation, in collaboration with organizations such as the American Academy of Orthopedic Surgeons, the American College of Obstetricians and Gynecologists, and The North American Menopause Society, have recommended that bone density testing be performed routinely in women 65 years of age and older and in younger postmenopausal women with important risk factors for low bone density, including being in the lowest quartile of body weight (less than 127 lb) and having a personal or family history of fragility fracture.^{2,3}

REFERENCES

1. US Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. *Ann Intern Med.* 2002;137:526-528.
2. National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis.* Washington, DC: 2003.
3. NAMS Board of Trustees and Editorial Board. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. *Menopause.* 2002;9:84-101.

as a T-score is -2 to $+2$. Thus, many women with osteopenia actually have low-normal bone density values.

The use of this diagnosis in bone density reports has resulted in substantial confusion, for it is a diagnosis with little clinical meaning. A diagnosis of osteopenia does not necessarily mean that bone loss has occurred, that bone strength is significantly impaired, that the patient is at high fracture risk, or that pharmacologic treatment is warranted.²¹ Both

a 52-year-old woman with a T-score of -1.2 and an 80-year-old woman with a T-score of -2.4 can be categorized as having osteopenia, but the risk of having any fracture varies by more than 4-fold between these 2 women, and the probability of having a hip fracture is about 15 times greater in the older woman.

The WHO criteria for postmenopausal osteoporosis do not apply to premenopausal women in whom the relationship between bone density and fracture risk has not been defined, and they apply only to measures made by DXA of the proximal femur and, in the United States, of the lumbar spine. T-scores derived from other bone-density testing devices (quantitative CT, ultrasonography) or in other skeletal sites, such as the finger or heel, do not have the same meaning in terms of age-related fracture risk as DXA results.²² However, some of these measurements have been shown to predict fracture risk. Additionally, the relationship between bone and fracture risk may be different in secondary causes of osteoporosis such as that associated with glucocorticoids.²³ As a result, the WHO criteria do not apply to those conditions.

■ PREVENTING BONE LOSS AND FRACTURES

The primary objective of treating patients with osteoporosis or those who are at risk for the disorder is to reduce the likelihood of fractures.²⁴ The means of accomplishing this objective include methods that preserve or improve bone strength and reduce the likelihood of falls and injuries that lead to fractures.

Calcium and Vitamin D

In elderly women with osteoporosis, very low calcium intake or malabsorption of calcium due to vitamin D deficiency or intestinal disease that results in secondary hyperparathyroidism and

accelerated bone loss is commonly observed.²⁵ In early menopausal women, the increased bone resorption that occurs with estrogen deficiency is not associated with increased levels of parathyroid hormone.²⁶ Thus, it is no surprise that increasing calcium intake has little effect on bone density values in early postmenopausal women except for those with marked calcium deficiency.²⁷ Recommending a total daily calcium intake of 1200 to 1500 mg daily and 400 to 800 units of vitamin D daily is appropriate to prevent significant calcium malabsorption. Calcium and vitamin D therapy protects older adults from fractures, but this effect has not been observed in younger postmenopausal women who have a lower fracture risk.^{28,29}

Exercise

Impact-loading exercise may have important effects on bone mass in growing animals and children.^{30, 31} The results of prospective exercise interventions on BMD values in postmenopausal women have been mixed, but even the most dramatic responses are quite small.³²⁻³⁴ In women beyond the menopausal transition, regular exercise may slow the rate of bone loss.³⁵

Pharmacologic agents

Three classes of drugs—estrogen, selective estrogen receptor modulators (SERMs), and bisphosphonates—are approved for the prevention of bone loss in postmenopausal women without osteoporosis (**TABLE 2**). By reducing bone turnover to levels seen in healthy premenopausal women, these agents prevent bone loss and preserve skeletal structure.³⁶ Estrogen therapy prevents bone loss in almost all women, even at lower dosages.³⁷⁻⁴⁰ No differences in effect are apparent between oral and transdermal estrogen preparations. Upon discontinuation of estrogen, the bone gains observed with therapy are quickly lost.⁴¹⁻⁴⁵

TABLE 2

Therapies approved for preventing bone loss in postmenopausal women without osteoporosis

Drug	Dosage	Contraindications or precautions	Side effects
Estrogen	Variable dosages and routes of administration	Unexplained uterine bleeding Known breast cancer Active or previous venous thrombosis	Breast tenderness Vaginal bleeding (with combined estrogen-progestin) Stroke Venous thrombosis
Raloxifene	60 mg daily	Active or previous venous thrombosis	Hot flushes Muscle cramps Venous thrombosis
Bisphosphonates			
Alendronate	5 mg daily or 35 mg once weekly	Hypocalcemia Inability to remain upright after dosing	Bone and muscle pain Abdominal pain
Risedronate	5 mg daily or 35 mg once weekly	Renal insufficiency	
Ibandronate	2.5 mg daily or 150 mg once monthly	Disorders of esophageal motility (alendronate)	

Raloxifene prevents bone loss, at least in older women with osteoporosis, and preliminary information suggests a reduced incidence of breast cancer in those adherent to this therapy.^{45,46} Because the skeletal effect of raloxifene is mediated by the estrogen receptor, it is anticipated that skeletal protection would wane quickly upon discontinuation.

In studies of 2 to 6 years' duration, bisphosphonates induce modest increases in bone density and preserve skeletal structure.^{5,47-50} Bone loss ensues upon discontinuation of bisphosphonate therapy, but the rapid "catch-up" loss observed with estrogen is not seen.^{44,51} There is little advantage in combining inhibitors of bone remodeling except possibly in the addition of a bisphosphonate when very low dosages of estrogen used to control menopausal symptoms are not effective in preventing bone loss or where vaginal estrogens are used primarily for

local symptoms and the impact of these estrogen dosages are not known.⁵²

Neither raloxifene nor bisphosphonates have been observed to reduce fracture risk in younger postmenopausal women without osteoporosis, although none of the studies have been large enough to evaluate the effect on fracture risk adequately. In perimenopausal women, estrogen therapy significantly reduced the incidence of wrist fractures by 57% (confidence interval, 15%-78%; $P = .01$).⁵³ The absolute risk reduction was 2.5% (from 3.9% in the control group to 1.4% in the treated group). No effect on the occurrence of other fractures was observed.

In the Women's Health Initiative studies, estrogen with or without progestin reduced the incidence of clinical fractures and fractures of both the hip and the spine in low-risk populations.^{54,55} The annualized incidence of spine and

hip fractures was reduced by about 5/10,000 women, resulting in number-needed-to-treat of about 2000 per year. Importantly, the frequency of experiencing a venous thrombotic event with hormone therapy was as great as was the likelihood of preventing a fracture of the hip or spine.⁵³ Since the risk of venous thrombosis with raloxifene is similar to that seen with estrogen, a similar risk/benefit ratio would be expected with that treatment of women at low risk for fracture.⁵⁶⁻⁵⁷

Even if these agents reduce fracture risk in younger postmenopausal women without osteoporosis to the same extent as seen in older women with osteoporosis, treatment would not be cost-effective unless there was very long-term residual skeletal protection upon discontinuation. Treatment with alendronate of postmenopausal women between the ages of 55 and 75 years who had BMD T-scores between -1.6 and -2.4 but no other risk factors was shown to be not cost-effective.⁵⁸

Fall prevention

Multifaceted fall prevention programs, which should include weight-bearing and resistance exercises, may be effective in reducing the incidence of falls by 30% in elderly adults, but they have not been demonstrated to reduce fracture risk.⁵⁹ Because the risk of falling and fractures is low in healthy young menopausal women, it is unlikely that exercise would reduce fracture risk. However, remaining physically active will help maintain muscle strength and balance and might be of benefit in reducing fracture risk in later life.

Overall, lifestyle factors have modest but important effects in preventing bone loss in healthy postmenopausal women. Bone loss can be effectively prevented with any of several pharmacologic agents; however, the clinical impact of fracture risk reduction in women at

low risk for fractures is small, and with some agents this benefit may be offset by important side effects.

DISCUSSION OF THE CASE

Although this patient does not meet the criteria for bone density testing, measurement of bone density was the only way to address her concerns about her bone health. The results, with values that are best described as being in the low-normal range for young women, are not unexpected for her age and do not imply that excessive or even significant bone loss has occurred. Given her age and lack of other risk factors, the patient's current risk of experiencing a fracture of the hip or spine is very low. Calculated from the data by Kanis, the probability that this patient will experience either a spine fracture or hip fracture over the next 10 years is about 4% (**FIGURE 1**). In the absence of osteoporosis, height loss, or clinical evidence of medical problems that adversely affect skeletal health, no further laboratory or imaging studies are warranted.

CASE RESOLUTION

After a discussion with the patient in which the physician reviewed the patient's risk factors, explained the meaning of her bone density test results, and discussed the treatment options, the patient was relieved to know that her current risk of experiencing a fracture was quite low. She understood that bone loss in women her age occurs very slowly and that general measures would be helpful in preventing bone loss. She increased her calcium intake to 1500 mg/d, began taking a multivitamin containing vitamin D, and began walking for exercise. Plans were made to re-evaluate her skeletal status,

including a repeat bone density study, in 2 or 3 years. If the patient had been very anxious about her skeletal health and not reassured by the information provided regarding her fracture risk, therapy with raloxifene or a bisphosphonate would have been considered in an effort to provide peace of mind and confidence in her daily routine if she had no residual menopausal symptoms. If she also suffered from persistent menopausal symptoms (ie hot flashes, night sweats, and vaginal dryness), in keeping with ACOG guidelines hormone therapy at the smallest effective dose for the shortest possible time might have been considered as well to provide symptom relief and prevent bone loss.⁶⁰

REFERENCES

1. NIH Consensus Development Panel on osteoporosis prevention, diagnosis and therapy. *JAMA*. 2001;285:785-795.
2. Pouilles JM, Tremollieres F, Ribot C. The effects of menopause on longitudinal bone loss from the spine. *Calcif Tissue Int*. 1993;52:340-343.
3. Recker R, Lappe J, Davies K, et al. Characterization of perimenopausal bone loss: a prospective study. *J Bone Miner Res*. 2000;5:1965-1973.
4. Jilka RL. Cytokines, bone remodeling, and estrogen deficiency: a 1998 update. *Bone*. 1998;23:75-81.
5. Sirola J, Kroger H, Honkanen R, et al. OSTPRE Study Group. Factors affecting bone loss around menopause in women without HRT: a prospective study. *Maturitas*. 2003;45:159-167.
6. Dawson-Hughes B, Krall EA, Harris S. Risk factors for bone loss in healthy postmenopausal women. *Osteoporos Int*. 1993;3(suppl 1):27-31.
7. Stepan JJ. Prediction of bone loss in postmenopausal women. *Osteoporos Int*. 2000;11(suppl 6):S45-S54.
8. Rosen CJ, Chesnut CH III, Mallinak NJ. The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation. *J Clin Endocrinol Metab*. 1997;82:1904-1910.
9. Garnero P, Sornay-Rendu E, Duboeuf F, et al. Markers of bone turnover predict postmenopausal forearm bone loss over 4 years: the OFELY study. *J Bone Miner Res*. 1999;14:1614-1621.
10. Cooper C. Epidemiology of osteoporosis. *Osteoporos Int*. 1999;9(suppl 2):S2-S8.
11. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996; 312:1254-1259.
12. Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int*. 2001;12:989-995.
13. Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15:721-727.
14. Siris ES, Brennan SK, Miller PD, et al. Predictive value of low BMD for 1-year fracture outcomes is similar for postmenopausal women ages 50-64 and 65 and older: results from the National Osteoporosis Risk Assessment (NORA). *J Bone Miner Res*. 2004;19:1215-1220.
15. Huopio J, Kroger H, Honkanen R, et al. Risk factors for perimenopausal fractures: a prospective study. *Osteoporos Int*. 2000;11:219-227.
16. Albrand G, Munoz F, Sornay-Rendu E, et al. Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: the OFELY study. *Bone*. 2003;32:78-85.
17. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int*. 2005;16:581-589.
18. Kanis JA, Gluer, CC. An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporos Int*. 2000;11:192-202.
19. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA*. 2001;286:2815-2822.
20. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab*. 2005;90:2787-2793.
21. McClung MR. Osteopenia: to treat or not to treat. *Ann Intern Med*. 2005;142:796-797.
22. Faulkner KG, von Stetten E, Miller P. Discordance in patient classification using T-scores. *J Clin Densitom*. 1999;2:343-350.
23. Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum*. 2003;48:3224-3229.
24. Delmas P. Treatment of postmenopausal osteoporosis. *Lancet*. 2002;359:2018-2026.
25. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalys II study. *Osteoporos Int*. 2002;13:257-264.
26. Nordin BE, Wishart JM, Clifton PM, et al. A longitudinal study of bone-related biochemical changes at the menopause. *Clin Endocrinol (Oxf)*. 2004;61:123-130.
27. Dawson-Hughes B, Dallal GE, Krall EA, et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med*. 1990;323:878-883.
28. Chapuy MC, Arlot ME, Delmas PD, et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ*. 1994;308:1081-1082.
29. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005;293:2257-2264.
30. Van Langendonck L, Claessens AL, Vlietinck R, et al. Influence of weight-bearing exercises on bone acquisition in prepubertal monozygotic female twins: a randomized controlled prospective study. *Calcif Tissue Int*. 2003;72:666-674.
31. Bass SL, Saxon L, Daly RM, et al. The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. *J Bone Miner Res*. 2002;17:2274-2280.
32. Going S, Lohman T, Houtkooper L, et al. Effects of exercise on bone mineral density in calcium-replete postmenopausal women with and without hormone replacement therapy. *Osteoporos Int*. 2003;14:637-643.
33. Chan K, Qin L, Lau M, et al. A randomized, prospective study of the effects of Tai Chi Chun exercise on bone mineral density in postmenopausal women. *Arch Phys Med Rehabil*. 2004;85:717-722.
34. Kemmler W, Lauber D, Weineck J, et al. Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women: results of the Erlangen Fitness Osteoporosis Prevention Study (EFOPS). *Arch Intern Med*. 2004;164:1084-1091.
35. Krall EA, Dawson-Hughes B. Walking is related to bone density and rates of bone loss. *Am J Med*. 1994;96:20-26.
36. Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. *J Bone Miner Res*. 2005;20:177-184.
37. Delmas PD, Confavreux E, Garnero P, et al. A combination of low doses of 17beta-estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. *Osteoporos Int*. 2000;11:177-187.

38. Lindsay R, Gallagher JC, Kleerekoper M, et al. Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporos Int*. 2005;16:372-379.
39. Delmas PD, Pornel B, Felsenberg D, et al. International Study Group. Three-year follow-up of the use of transdermal 17beta-estradiol matrix patches for the prevention of bone loss in early postmenopausal women. *Am J Obstet Gynecol*. 2001;184:32-40.
40. Warming L, Ravn P, Christiansen C. Levonorgestrel and 17beta-estradiol given transdermally for the prevention of postmenopausal osteoporosis. *Maturitas*. 2005;14:50:78-85.
41. Gallagher JC, Rapuri PB, Haynatzki G, et al. Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. *J Clin Endocrinol Metab*. 2002;87:4914-4923.
42. Greendale GA, et al. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med*. 2002;162:665-672.
43. Sornay-Rendu E, Garnero P, Munoz F, et al. Effect of withdrawal of hormone replacement therapy on bone mass and bone turnover: the OFELY study. *Bone*. 2003;33:159-66.
44. Dufresne TE, Chmielewski PA, Manhart MD, et al. Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional microcomputed tomography. *Calcif Tissue Int*. 2003;73:423-432.
45. Wasnich RD, Bagger YZ, Hosking DJ, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. *Menopause*. 2004;11:622-630.
46. The Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density. Results from the Postmenopausal Estrogen/Progestin Interventions Trial. *JAMA*. 1996;276:1389-1396.
47. Mortensen L, Charles P, Bekker PJ, et al. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab*. 1998;83:396-402.
48. Gallagher JC, Baylink DJ, Freeman R, McClung M. Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies. *J Clin Endocrinol Metab*. 2001;86:4717-4726.
49. McClung MR, Wasnich RD, Recker R, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res*. 2004;19:11-18.
50. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst*. 2004;96:1751-1761.
51. Ravn P, Weiss SR, Rodriguez-Portales JA, et al. Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. *J Clin Endocrinol Metab*. 2000;85:1492-1497.
52. Simon JA, Mack CJ. Treatment of osteoporosis: combination therapies. *Int J Fertil Womens Med*. 2003;48:127-131.
53. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. *Ann Intern Med*. 1998;128:253-261.
54. Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288:321-333.
55. Writing Group for the Women's Health Initiative. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The WHI randomized controlled trial. *JAMA*. 2004;291:1701-1712.
56. Grady D, Ettinger B, Moscarelli E, et al. Multiple Outcomes of Raloxifene Evaluations Investigators. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. *Obstet Gynecol*. 2004;10:837-844.
57. EVISTA US package insert, Eli Lilly & Co, Indianapolis, IN, 2003.
58. Schousboe JY, Nyman JA, Kane RL, et al. Cost effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med*. 2005;142:734-741.
59. Tinetti ME. Clinical practice. Preventing falls in elderly persons. *N Engl J Med*. 2003;348:42-49.
60. ACOG Practice Bulletin. Clinical management guidelines for obstetricians-gynecologists. 2004;103:203-216.

CME POSTTEST

To obtain 1 AMA category 1 credit for this course of study, circle the correct responses below and complete the CME credit application and program evaluation on page 12. Mail or fax pages 11 and 12 to: *Estrogen deficiency during menopause: Case 2*, University of Wisconsin Medical School Office of Continuing Medical Education, 2701 International Lane, Suite 208, Madison, WI 53074. Fax: 608.240.2151. No fee is required for this CME program. This test is valid through August 2006; no credit will be given after this date. You must correctly answer 7 of the 10 (70%) questions to receive credit.

1. **Bone density remains stable in healthy premenopausal women, but**
 - a. Diminishes with increasing levels of estrogen
 - b. Bone loss occurs as a result of cytokine-induced activation of osteoclastic bone resorption in early menopause
 - c. Is solely dependent on genetic factors
2. **In women who are within 5 years after menopause, bone loss averages**
 - a. 1% to 2% per year
 - b. 5% to 7% per year
 - c. More than 10% per year
3. **In postmenopausal women, osteoporosis is now defined by the World Health Organization (WHO) as**
 - a. A diagnostic threshold of 2.5 standard deviations below the average value in young women (T-score -2.5 or lower)
 - b. A T-score that is double the score for an older menopausal woman
 - c. Based on a combination of bone density values and fracture risk
4. **The United States Preventive Services Task Force has recommended that bone mineral density (BMD) be measured**
 - a. In all women beginning at menopause
 - b. Only in women aged 65 years and older who weigh less than 120 lb and have a history of fracture
 - c. In all women aged 65 years and older.
5. **The WHO criteria for postmenopausal osteoporosis apply only to**
 - a. Postmenopausal women in whom bone fracture risk has not been assessed
 - b. Measures made by DXA of the proximal femur and the lumbar spine
 - c. T-scores derived from CT scan or ultrasonography.
6. **Calcium and vitamin D therapy, which protects older adults from fractures, has been proven to be highly effective in younger postmenopausal women.**
 - a. True
 - b. False
7. **What 3 classes of drugs are approved for the prevention of bone loss in postmenopausal women without osteoporosis?**
 - a. Estrogen, selective estrogen receptor modulators, and bisphosphonates
 - b. Estrogen, selective estrogen receptor blockers, and calcium channel blockers
 - c. Estrogen, statins, and cathepsin K inhibitors
8. **The bone gains that were observed with therapy for osteoporosis are very quickly lost upon discontinuation of which agent(s)?**
 - a. Estrogen
 - b. Estrogen and raloxifene
 - c. Estrogen, raloxifene, and bisphosphonates
9. **Hot flushes, muscle cramps, and venous thrombosis are side effects of which therapy for preventing bone loss?**
 - a. Bisphosphonates
 - b. Estrogen
 - c. Raloxifene
10. **Results from the Women's Health Initiative found that estrogen with or without progestin reduced the incidence of clinical fractures and fractures of both hip and spine in low-risk populations.**
 - a. True
 - b. False

APPLICATION FOR CME CREDIT

To obtain 1 AMA category 1 credit for this course of study, complete the CME posttest on page 11, as well as the CME credit application and program evaluation on this page. Mail or fax both pages to the address below. No fee is required. This CME program is valid through August 2006; no credit will be given after this date.

Name _____

Specialty _____ Institution _____

Address _____

City _____ State _____ Zip _____

Telephone _____

Please check one: MD DO Other

I claim ____ credit(s) of category 1 AMA PRA credit (up to 1 credit).

Signature _____

PROGRAM EVALUATION

The University of Wisconsin Medical School values your opinion. Please check the box that best reflects your views on the following statements about this educational activity.

	Yes	No
1. Learning objectives were met.	<input type="checkbox"/>	<input type="checkbox"/>
2. Content was relevant to my practice.	<input type="checkbox"/>	<input type="checkbox"/>
3. Presentation was clear and organized.	<input type="checkbox"/>	<input type="checkbox"/>
4. Author demonstrated expertise in topic.	<input type="checkbox"/>	<input type="checkbox"/>
5. Content was fair, balanced, and free of commercial bias.	<input type="checkbox"/>	<input type="checkbox"/>

If no, please explain. _____

Estrogen deficiency during menopause: Case 2

University of Wisconsin Medical School
Office of Continuing Medical Education
2701 International Lane
Suite 208
Madison, WI 53074

Fax: **608.240.2151**