Robert L. Barbieri, MD
Editor-in-Chief, OBG MANAGEMENT
Chief, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston
Kate Macy Ladd Professor of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston

Best prevention: Densitometry, drugs, determination

Ob/Gyns are well trained to care for more than 99% of women with osteopenia and osteoporosis. Yet most women at risk are not being diagnosed or treated. Since recent publication of randomized clinical trials, however, we have clearer direction on the decisive diagnosis and management questions.

Who should have a bone mass test?

Ob/Gyns know best

Solomon DH, Connelly MT, Rosen CJ, et al. Factors related to the use of bone densitometry: survey responses of 494 primary care physicians in New England. Osteoporosis Int. 2003;14:123–129.

Ob/Gyns were significantly more likely to order bone densitometry than internists and family physicians. However, any physician, including Ob/Gyns, who believed (mistakenly) that calcium-plus-vitamin D effectively treats osteoporosis or that osteoporosis should not be diagnosed by densitometry used screening less frequently than physicians without those beliefs.

Any woman should have bone density testing if it might influence her medical care. Osteoporosis is notoriously difficult to diagnose without densitometry.[1]

Besides identifying women at risk of fracture due to osteopenia or osteoporosis who are good candidates for drug therapy, testing can help motivate women to stop smoking, exercise, and take calcium and vitamin D to prevent bone loss. Just as women should know their weight, serum cholesterol, blood pressure, and mammographic findings, hypoestrogenic women should know their T-score.

The issue of relative costs and benefits of bone density testing is complex and con-

First-ever bone health advisory from US Surgeon General

Make use of prevention drugs

"If it's diagnosed in time, osteoporosis can be treated with new drugs that help prevent bone loss and rebuild bone before life-threatening fractures occur,"

said Richard H. Carmona, MD, MPH, in the first-ever Surgeon General's report on the nation's bone health.

The October 14 report urges physicians to look for red flags that may warrant bone density testing, and use the effective treatments now available, whenever indicated.

Test *any* woman over 50 who has *any* fracture

Bone density tests were recommended for anyone who suffers even a minor fracture after age 50, man or woman, and all women over age 65.

FREE POSTERS for your office encourage a bone-healthy lifestyle, including exams and bone density testing if prescribed. Patients can get a free full-color, 30-page magazine-style booklet, "The Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You."

Call 1-866-718-BONE
or visit www.surgeongeneral.gov.

Most women who suffer a low-trauma fracture have not had densitometry and are not taking a bone medication.

TABLE 1

Criteria, risk factors for densitometry

The National Osteoporosis Foundation, the North American Menopause Society, the American College of Obstetricians and Gynecologists, and the American Association of Clinical Endocrinologists concur on these criteria and risk factors for bone mineral density testing:

CRITERIA FOR SCREENING

Age 65 years or older

Age less than 65 years with risk factors (see below)

Low-trauma fracture

If densitometry results will influence use of drug treatment

Diseases and treatments associated with osteoporosis
(eg, rheumatoid diseases, chronic glucocorticoid therapy)

RISK FACTORS

Prior fracture

Diseases associated with osteoporosis

Body weight less than 127 pounds

Low-trauma fracture in a first-degree relative

Use of chronic glucocorticoid therapy

Cigarette smoking

TABLE 2

Rapid risk assessment: Test bone density if score is 9 or more

The Osteoporosis Risk Assessment Instrument advises testing all women age 65 or older, and menopausal women starting at age 55 who weigh less than 154 pounds and are not taking estrogen.

CRITERIA	POINTS
Age	
55-64	5
65-74	9
Older than 74	15
Weight	
Less than 60 kg (132 pounds)	9
60 to 70 kg (132 to 154 pounds)	3
Estrogen therapy	
Not currently using estrogen	2

Source: Cadarette SM, Jaglal SB, Kreiger N, McIsaac WJ, Darlington GA, Tu JV. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. CMAJ. 2000;162:1289–1294.

tinues to evolve. Although national organizations have guidelines **(TABLE 1)**, it is not clear if their sensitivity and specificity are optimal for identifying appropriate candidates for screening.

A reliable, quick tool identifies who to test

Cadarette SM, Jaglal SB, Murray TM, McIsaac WJ, Lawrence L, Brown JP. Evaluation of decision rules for referring women for bone density by dual-energy X-ray absorptiometry. JAMA. 2001;286:57–63.

A 3-item Osteoporosis Risk Assessment Instrument was more sensitive and specific in identifying screening candidates than the National Osteoporosis Foundation (NOF) criteria, according to an analysis of screening algorithms used in 2,365 menopausal women in the Canadian Multicentre Osteoporosis Study. A simple calculation based on age, weight, and estrogen use **(TABLE 2)** was clinically applicable.

In my practice, I focus on all women who have been hypoestrogenic for 12 to 24 months regardless of age, women with a previous low-trauma fracture, and women who weigh less than 132 pounds. Evidence is mounting that early treatment of bone loss is the best way to prevent future fracture. Well before osteoporosis is detected, significant structural integrity of the spine and hip has been lost.

It is my belief that guidelines will ultimately recommend bone mineral testing for all hypoestrogenic and menopausal women. This practice will help start pharmacologic therapy early in the disease, maximally protecting bone and reducing fracture risk. A large-scale randomized prospective trial of bone mineral density testing with long-term follow-up will be needed to crystallize this recommendation.

CONTINUED

When should treatment start?

Fracture begets fracture, treatment reduces risk

Delmas PD, Genant HK, Crans GG, Stock JL, Wong M, Siris E, Adachi JD. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. Bone. 2003;33:522–532.

Baseline fractures in 7,705 postmenopausal women were assessed by semiquantitative spinal radiographs.

In women with severe prevalent vertebral fractures (more than 40% loss of vertebral body height), risk of additional vertebral fractures over 3 years was 38% and risk of new nonvertebral fracture (wrist, hip) was 14%.

Treatment of severe prevalent vertebral fractures with raloxifene 60 mg daily reduced the risk of new vertebral fractures by 26% and new nonvertebral fractures by 47% over 3 years.

To prevent 1 new nonvertebral fracture, 10 patients needed to be treated; to prevent 1 additional nonvertebral fracture, 18 patients needed to be treated.

Many women with osteopenia should be on drug treatment.

Women who have already suffered a low-trauma fracture and women with osteoporosis have the greatest risk of fracture. The majority of women who suffer a low-trauma fracture have had neither a bone density measurement nor treatment with a bone medicine, many studies indicate. The Delmas study highlights the importance of prevalent vertebral fractures on the risk of subsequent fractures.

When to treat osteopenia. Many women with osteopenia should be on drug treatment, as should all women with osteoporosis, the NOF advises.

Although a woman with osteoporosis is more likely than a woman with osteopenia to suffer a fracture, the greatest absolute number of fractures occurs in osteopenic women, because that population is so large.

The NOF recommends starting treatment when the T–score measured by dual-energy X-ray absorptiometry (DXA) bone density testing is:

- less than –1.5 and the patient has 1 risk factor, or
- less than –2.0.[2]

This approach, it is hoped, will reduce progression to frank osteoporosis and reduce the number of fractures suffered by women with osteopenia.

What are the treatments for low bone mass?

Alendronate, risedronate, and raloxifene

The 3 most commonly used drugs for prevention and treatment of osteoporosis are: 2 bisphosphonates (alendronate and risedronate) and the selective estrogen receptor modulator raloxifene **(TABLE 3)**. All prevent fractures and cost about the same. Alendronate and risedronate are taken by mouth once weekly; raloxifene, daily. A raspberry-flavored liquid alendronate was recently added, for the 10% of women who prefer not to take pills.

Patients must be careful to take alendronate and risedronate in the fasting state and with sufficient water to ensure the pill enters the stomach, then continue to fast another 30 minutes for maximal absorption. The patient needs to remain erect to reduce risk of reflux and esophageal irritation.

CONTINUED

TABLE 3

Drugs for prevention and treatment of osteoporosis

CLASS, GENERIC NAME, AND INDICATION	BRAND NAME	DOSAGE		APPROXIMATE MONTHLY COST*
		DAILY	WEEKLY	
Estrogen for prevention of postmenopausal osteoporosis (loss of bone mass)				
Conjugated equine estrogen	Premarin	0.625 mg		$28
Calcitonin-salmon for prevention of progressive loss of bone mass in postmenopausal osteoporosis				
Calcitonin	Miacalcin	200 IU by nasal spray		$60
Bisphosphonates for treatment and prevention of osteoporosis in postmenopausal women				
Risedronate	Actonel		35 mg	$64
Alendronate	Fosamax		70 mg	$65
Selective estrogen receptor modulator for treatment and prevention of osteoporosis in postmenopausal women				
Raloxifene	Evista	60 mg		$71
Parathyroid hormone for treatment of postmenopausal women with osteoporosis who are at high risk for fracture				
Teriparatide-PTH 1-35	Forteo	20 µg by injection		$410

* Source: drugstore.com

Alendronate, risedronate, and raloxifene prevent fractures and cost about the same.

Teriparatide

Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87: 4528–4535.

Postmenopausal women with osteoporosis (n = 146) were randomized to receive either teriparatide injections (20 µg daily) plus placebo pills or alendronate 10 mg daily plus placebo injections for a median of 14 months. After 3 months of therapy, bone mineral density in the lumbar spine increased 12.2% and 5.6% in the teriparatide and alendronate groups, respectively. Teriparatide treatment resulted in fewer nonvertebral fractures than alendronate therapy.

Black DM, Greenspan SL, Ensrud KE, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003;349:1207–1215.

Postmenopausal women with osteoporosis (n = 238) were randomized to receive daily parathyroid hormone (PTH) (full length 1 to 84) injections (100 µg daily), alendronate 10 mg daily, or the combination. After 1 year, lumbar spine bone density as assessed by DXA increased 6.3%, 6.1%, and 4.6% in the PTH alone, PTH plus alendronate and alendronate-alone groups, respectively. In this study, PTH plus alendronate conferred no additional benefits over PTH alone.

Recombinant PTH 1-34 (teriparatide, Forteo) was approved in November 2002 for treatment of osteoporosis in postmenopausal women at high risk of fracture. It is very effective and likely superior to alendronate treatment. However, teriparatide, which is an injectable formulation, is expensive and this will likely limit

its use to complex cases.

Interestingly, the combination of PTH plus alendronate does not appear to be additive in the treatment of osteoporosis. Given current data, the bisphosphonates should not be combined with PTH.

How long should treatment continue?

This question can be answered from both scientific and practical clinical viewpoints.

The practical clinical problem is that when patients ask: "Doctor, how long do I need to take my bone medicine?" they are not emotionally prepared to hear, "Forever."

It is probably better to say that it's important to stay on treatment at least 1 to 2 years, and adhere closely to the regimen. When follow-up testing is obtained, the results can influence the next recommendation—which is likely to be that treatment should continue at least 1 or 2 more years. This pattern is more likely to ensure that the patient has high morale and follows the regimen.

Advise patients, "Stay on treatment for 1 to 2 years, then retest bone mass, then decide on further therapy."

Bone mass accrues as treatment continues

Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350:1189–1199.

In postmenopausal women with osteoporosis (n = 86) who were treated for 10 years with alendronate, 10 mg daily, hip and spinal bone density continued to increase throughout follow-up. Women who stopped therapy gradually lost bone density. After 10 years of alendronate, the increase in bone mineral density was 14% at the lumbar spine and 10% at the hip trochanter.

Studies have demonstrated that bone density continues to increase with up to 10 years of therapy with alendronate.

Alendronate halts bone loss after stopping estrogen

Ascott-Evans BH, Guanabens N, Kivinen S, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy. Arch Intern Med. 2003;163:789–794.

Postmenopausal women (n = 144) who had recently discontinued estrogen therapy were randomized to receive a placebo or alendronate, 10 mg daily. After 1 year, the alendronate group had a 2.3% increase in spinal bone density; the placebo group, a 3.2% decrease.

Once drug therapy stops, bone density begins to decrease—more rapidly after estrogen than after bisphosphonates. In women who stop estrogen, initiation of alendronate blocks bone loss that will otherwise occur. Therefore, women with osteopenia or osteoporosis who stop estrogen therapy should consider starting an alternative bone medicine.

How should you monitor treatment?

Nurses improve adherence

Clowes JA, Peel NFA, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab. 2004;89:1117–1123.

In this study, 75 postmenopausal women with osteopenia on raloxifene treatment were randomized to 3 different monitoring regimens: no monitoring, nurse interactions with the patient to ensure treatment compliance, or

monitoring of urinary markers of bone turnover.

The patients who had the best adherence to therapy had the greatest increase in bone mineral density.

Adherence increased by 57% in the nurse interaction group compared to no monitoring. Measuring urinary markers of bone turnover did not improve adherence or persistence with therapy compared to nurse interactions.

Nurse monitoring of treatment adherence appeared worthwhile, in this comparison of monitoring methods. In routine clinical practice, there is seldom a need to measure markers of bone turnover in women taking bisphosphonates.

Densitometry every 2 years

Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women. JAMA. 2003;289: 2525–2533.

A total of 373 women over age 65 were randomized to placebo, conjugated equine estrogen 0.625 mg daily, alendronate 10 mg daily, or both estrogen and alendronate. After 3 years, increases in spinal and hip bone density were greatest in the alendronate plus estrogen group. Alendronate alone was slightly better than estrogen alone in improving bone density at the hip. Alendronate and estrogen were similarly efficacious in improving spine bone density. All active regimens were superior to placebo.

In my practice, I measure bone density every other year to assess response to antiresorptive therapy. Since bone turnover is slow, more frequent measurements are seldom warranted. If bone density stabilizes or increases, I continue therapy.

If bone density decreases significantly on standard monotherapy, I would consider adding estrogen and repeating bone mineral testing in 1 year.

I would also check for secondary causes of bone disease by measuring serum thyroid-stimulating hormone, calcium, albumin, PTH and 25-hydroxyvitamin D.

Alternatively, a woman who has lost bone density on monotherapy can be referred to an endocrinologist. ■

Dr. Barbieri reports no financial relationships relevant to this article.

Disease toll

30 million
... American women have osteoporosis or osteopenia

Less than one-third
... of osteoporosis cases have been diagnosed

One-seventh
... of American women with osteoporosis receive treatment

50%
... of Caucasian women have osteopenia or osteoporosis by the end of the first postmenopausal decade

40%
... of women will eventually suffer a wrist, vertebral, or hip fracture

25%
... of women die within 1 year of a hip fracture

Dollar toll

$18 billion per year
... direct care cost for osteoporotic fractures

Sources: www.nof.org and www.surgeongeneral.gov

In patients who stop taking estrogen, consider an alternative bone medication.

REFERENCES

1. Chesnut CH. Osteoporosis: an under-diagnosed disease. JAMA. 2001;286:2865–2866.
2. Physicians Guide to Prevention and Treatment of Osteoporosis. Washington; DC; National Osteoporosis Foundation: 2003.