Diagnosis and Treatment of Osteoporosis

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Osteoporosis affects approximately 8 million women and 2 million men in the United States. The associated fractures are a common and preventable cause of morbidity and mortality in up to 50 percent of older women. The U.S. Preventive Services Task Force recommends using dual energy x-ray absorptiometry to screen all women 65 years and older and women 60 to 64 years of age who have increased fracture risk. Some organizations recommend considering screening in all men 70 years and older. For persons with osteoporosis diagnosed by dual energy x-ray absorptiometry or previous fragility fracture, effective first-line treatment consists of fall prevention, adequate intake of calcium (at least 1,200 mg per day) and vitamin D (at least 700 to 800 IU per day), and treatment with a bisphosphonate. Raloxifene, calcitonin, teriparatide, or hormone therapy may be considered for certain subsets of patients. (*Am Fam Physician.* 2009;79(3):193-200, 201-202.

ILLUSTRATION BY JOHN W. KARAPELOU

▶ **See related editorial on page 189.**

▶ **Patient information:** A handout on osteoporosis, written by the authors of this article, is provided on page 201.

Approximately 8 million women and 2 million men in the United States have osteoporosis, and 34 million persons have osteopenia.[1] About one in two white women will experience an osteoporotic fracture in her lifetime.[2,3] Osteoporosis also occurs in older men, who have a higher mortality from hip fractures and a lower frequency of screening and treatment.[4,5] Overall, hip fractures cause an excess mortality of 10 to 20 percent at 12 months, and up to 25 percent of patients with hip fractures require long-term nursing home care.[2] In 2002, the cost of a hip fracture was estimated to be $34,000 to $43,000, with the annual cost of all osteoporotic fractures as high as $18 billion.[1]

Despite broadly accepted screening, diagnosis, and treatment guidelines, there is a large gap between knowledge and effective clinical practice. One study showed that only 49 percent of women were evaluated or treated in accordance with accepted guidelines.[5]

Definition

Osteoporosis is characterized by low bone mass and structural deterioration of bone tissue, leading to an increased risk of fractures. The World Health Organization (WHO) defines osteoporosis as a spinal or hip bone mineral density (BMD) of 2.5 standard deviations or more below the mean for healthy, young women (T-score of –2.5 or below) as measured by dual energy x-ray absorptiometry (DEXA).[6] Osteopenia is defined as a spinal or hip BMD between 1 and 2.5 standard deviations below the mean.[3,6]

Primary osteoporosis is the result of bone loss related to the decline in gonadal function associated with aging.[6] Selected factors that are associated with fracture or low BMD are listed in *Table 1*.[2,3] Secondary osteoporosis may result from chronic diseases, exposures, or nutritional deficiencies that adversely impact bone metabolism. Causes of secondary osteoporosis are listed in *Table 2*.[1,2,6,7]

Screening Recommendations for Practice

Published guidelines that address screening criteria vary because of gaps in evidence and differences in the way guidelines are formulated (i.e., evidence-based versus expert opinion). The U.S. Preventive Services Task

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Prevention of fractures and treatment of osteoporosis		
Older persons at risk of falls should consider exercise, physical therapy, home hazard assessment, and withdrawal of psychotropic medication to decrease fall risk.	B	26, 27
Daily vitamin D supplementation (at least 700 to 800 IU), with or without calcium, should be used to decrease fracture risk in persons 60 years and older.	B	15, 31
Bisphosphonates should be used to prevent osteoporotic fractures (see Table 5 for specific indications).	A	14, 16, 17, 21, 33, 34
Raloxifene (Evista) can be used to prevent vertebral fractures in postmenopausal women with osteoporosis, especially if at high risk of breast cancer.	A	22, 33, 34
Calcitonin (Miacalcin) can be used to prevent recurrent vertebral fractures in postmenopausal women.	B	23, 34
Teriparatide (Forteo) can be used to prevent vertebral and nonvertebral fractures in postmenopausal women with prior vertebral fractures.	A	24, 34
Screening		
The following populations should be screened for osteoporosis:		
All women 65 years and older	A	2, 3
Selected postmenopausal women and men 50 to 69 years of age with risk factors for fracture	C	2, 13
All men 70 years and older	C	2, 13

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

Force (USPSTF) guideline, based on a systematic review of the evidence, recommends screening DEXA in all women 65 years and older, as well as in women 60 to 64 years of age who have increased fracture risk. The USPSTF states that the evidence is insufficient to recommend for or against screening in postmenopausal women younger than 60 years.[3] The National Osteoporosis Foundation (NOF), which receives substantial support from the pharmaceutical industry, developed a guideline using an expert panel that recommends screening in women 65 years and older, men 70 years and older, adults with a fracture, and selected postmenopausal women and men with clinical risk factors for fracture *(Table 1[2,3])*.[2]

Table 1. Selected Factors Associated with Fracture or Low Bone Mineral Density in Postmenopausal Women

Increasing age	Excessive alcohol (> 2 drinks per day), caffeine, and tobacco use
Low body weight (< 127 lb [58 kg])	History of falls
Personal history of fracture	Low level of physical activity
Family history of osteoporotic fracture	Low calcium or vitamin D intake
Not using hormone therapy	Use of certain medications or presence of certain medical conditions (Table 2)
White or Asian race	

Information from references 2 and 3.

It is reasonable to clinically assess age and risk factors when deciding which women to screen. Validated clinical rules, such as the Simple Calculated Osteoporosis Risk Estimation (SCORE) tool, may be considered as well. The SCORE tool is a six-item instrument with a sensitivity of 91 percent and a specificity of 40 percent. It is used to predict which women may benefit from DEXA screening.[8] This calculator may be found at http://osteoed.org/tools.php.

The USPSTF found that, for women 55 to 59 years of age, the number needed to screen (NNS) over five years was more than 4,000 to prevent one hip fracture and 1,300 to prevent one vertebral fracture. The NNS to prevent one hip fracture over five years declines with age, to 1,856 for women 60 to 64 years of age, 731 for women 65 to 69 years of age, and 143 for women 75 to 79 years of age.[9]

Diagnosis

Osteoporosis is diagnosed clinically or radiographically. Osteoporosis may present with low-impact fractures (occurring from a fall at or below standing height) or fragility fractures (occurring spontaneously).[7] Osteoporosis is most commonly diagnosed with a T-score of −2.5 or below as determined by central DEXA scan of the total hip, femoral neck, or lumbar spine.[2,3,6] Quantitative computed tomography can be

Table 2. Causes of Secondary Osteoporosis

Cause	Examples	Cause	Examples
Chronic medical and systemic diseases	Amyloidosis	Medication	Anticonvulsants (e.g., phenobarbital, phenytoin [Dilantin])
	Ankylosing spondylitis		Drugs causing hypogonadism (e.g., parenteral progesterone, methotrexate, gonadotropin-releasing hormone agonists)
	Chronic obstructive pulmonary disease		Glucocorticoids
	Human immunodeficiency virus or acquired immunodeficiency syndrome		Heparin (long-term)
	Inflammatory bowel diseases		Immunosuppressants (e.g., cyclosporine [Sandimmune], tacrolimus [Prograf])
	Liver disease (severe)		Lithium
	Multiple myeloma		Thyroid hormone excess
	Renal insufficiency or renal failure	Nutrition	Alcohol (> 2 drinks per day)
	Rheumatoid arthritis		Anorexia nervosa
	Systemic lupus erythematosus		Celiac disease
Endocrine and metabolic disorders	Athletic amenorrhea		Gastric bypass or gastrectomy
	Cushing syndrome		Vitamin D deficiency
	Diabetes mellitus, type 1		
	Hemochromatosis		
	Hyperadrenocorticism		
	Hyperparathyroidism (primary)		
	Hyperthyroidism		
	Hypogonadism (primary and secondary)		
	Hypophosphatasia		

Information from references 1, 2, 6, and 7.

used to assess BMD, but is limited by radiation exposure and cost. Quantitative calcaneal ultrasonography and peripheral DEXA, which measures BMD in the heel, finger, and forearm, are more portable and less costly than central DEXA and can effectively predict fracture risk. Their results, however, do not correlate well enough with central DEXA to be used diagnostically, and they have not been shown to be useful in monitoring treatment over time.[10] Biochemical markers of bone turnover in the serum or urine are not currently recommended for diagnosis.[6,11]

Evaluating for Suspected Secondary Osteoporosis

The number of postmenopausal women with osteoporosis from a secondary cause is unknown, but thought to be low. A careful history and physical examination may identify common causes of secondary osteoporosis. If clinical evaluation does not raise suspicion of a secondary cause, there is currently little evidence to warrant additional testing in postmenopausal women.[12]

In contrast, approximately 50 percent of pre- and perimenopausal women with osteoporosis have an associated underlying cause.[12] There are no evidence-based guidelines to direct the evaluation of a suspected secondary cause of osteoporosis.[11,12] In pre- and perimenopausal women, a basic laboratory evaluation should be considered if there is no clear etiology evident by history and physical examination *(Table 3[7])*.

Screening and Diagnosis of Osteoporosis in Men

In the United States, one in eight men will have an osteoporotic fracture in his lifetime, accounting for 30 percent of hip fractures and 18 percent of the total annual cost of osteoporosis.[1,4] Men have nearly twice the mortality from hip fractures compared with women.[1,4,13] Because data on the screening, diagnosis, and treatment of osteoporosis in men are limited, most published recommendations are based on expert opinion.[7,12] The NOF and the International Society for Clinical Densitometry recommend screening all men 70 years and older and men 50 to 69 years of age with risk factors (the USPSTF guidelines do not address screening in men).[2,13] Based on a recent systematic review, the American College of Physicians also recommends that older men be periodically assessed for risk of osteoporosis and have DEXA performed if at increased risk.[14] The validity of using a T-score of −2.5 or below as the diagnostic criterion for osteoporosis in men is unclear, but this is a commonly used standard.[12,13] Approximately 50 percent of men with osteoporosis have a secondary cause and warrant additional evaluation, along with a careful history and physical examination.[7,12] In addition to treating any underlying cause, interventions

Table 3. Evaluation for Suspected Secondary Osteoporosis in Selected Patients

Test	*Possible etiology*
Initial screening tests	
Chemistry panel	
Alkaline phosphatase	High levels in Paget disease, immobilization
Calcium	Low levels in vitamin D deficiency, malabsorption
	High levels in hyperparathyroidism
Liver or kidney function	Liver or kidney disease
Complete blood count	Bone marrow malignancy, malabsorption
Thyroid-stimulating hormone	Hyperthyroidism
Total testosterone (men)	Hypogonadism
25-hydroxyvitamin D (men)	Vitamin D deficiency
Additional tests (based on level of severity of osteoporosis or clinical suspicion of underlying disease)	
Estradiol (pre- or perimenopausal women)	Hypogonadism
Intact parathyroid hormone	Hyperparathyroidism
Serum protein electrophoresis	Multiple myeloma
25-hydroxyvitamin D (women)	Vitamin D deficiency

Adapted with permission from Mauck KF, Clarke BL. Diagnosis, screening, prevention, and treatment of osteoporosis. Mayo Clin Proc. *2006;81(5):665.*

Table 4. Therapy Outcomes for Postmenopausal Women with Osteoporosis

Therapy	*Number needed to treat to decrease the risk of fracture*
Hip fracture	
Vitamin D (700 to 800 IU per day)[15]	45 for 2 to 5 years*
Alendronate (Fosamax)[16]	91 for 3 years†
Risedronate (Actonel)[17]	77 for 3 years*
Zoledronic acid (Reclast)[18]	91 for 3 years*
Hormone therapy[19]	385 for 5 years*
Vertebral fracture	
Alendronate[16]	37 for 3 years†
Ibandronate (Boniva)[20]	20 for 3 years†
Risedronate[21]	15 for 3 years‡
Zoledronic acid[18]	13 for 3 years*
Raloxifene (Evista)[22]	29 for 3 years*
Calcitonin (Miacalcin)[23]	10 for 5 years†
Teriparatide (Forteo)[24]	11 for 1.5 years†

NOTE: *There were differences in the study populations (age, T-scores, and presence or absence of previous vertebral fractures) in these studies.*

**—This study included women with and without a previous vertebral fracture (primary and secondary prevention).*

†*—This study included only women who had a previous vertebral fracture (secondary prevention).*

‡*—This study included only women who did not have a previous vertebral fracture (primary prevention).*

Information from references 15 through 24.

proposed by experts are similar to those for women, as discussed below.

Indications for Treatment

Recommendations about which persons with osteoporosis should receive treatment vary.[2,6] The NOF recommends treatment of postmenopausal women and men with a personal history of hip or vertebral fracture, T-score of –2.5 or below, or low bone mass (T-score between –1 and –2.5) and a 10-year probability of hip fracture of at least 3 percent or any major fracture of at least 20 percent.[2] The 10-year probability of fracture is calculated using the WHO fracture risk assessment tool (http://osteoed.org/tools.php). The WHO recommendations are less specific, and they differ from those of the NOF. The WHO recommends treating persons with or at risk of osteoporosis.[6] *Table 4* summarizes the effectiveness of different pharmacologic approaches to treatment.[15-24] *Table 5* summarizes prescribing and cost information for medications approved by the U.S. Food and Drug Administration (FDA).[25]

Nonpharmacologic Treatment

FALL PREVENTION

A multifactorial approach that addresses vision deficits, balance and gait abnormalities, cognitive impairment, and dizziness is the cornerstone of fall prevention. Improving lighting; removing loose rugs; and adding grab bars near bathtubs, toilets, and stairways can enhance safety.[26] Formal home safety evaluations and physical therapy treatments are beneficial.[27] Eliminating medications that can affect alertness and balance is critical.[26,27] The use of hip protectors is no longer considered effective.[28,29]

CALCIUM

The results of studies examining the effectiveness of calcium on fracture risk are mixed, but one subgroup from a recent meta-analysis showed decreased fracture rates in older women with 80 percent or greater adherence

to calcium supplementation.[30] A daily intake of at least 1,200 mg of calcium is recommended for all women with osteoporosis.[2,12] A detailed list of dietary sources of calcium can be found at http://www.nos.org.uk, under "Building Healthy Bones."

Most postmenopausal women consume inadequate amounts of dietary calcium; therefore, supplementation is needed. For optimal absorption, a single dose of calcium supplement should contain 500 mg or less of elemental calcium, necessitating multiple daily doses. Calcium carbonate is the least expensive, requires acid for absorption, and should be taken with meals. Calcium citrate is more expensive and does not need to be taken with meals. All calcium supplements may cause constipation and gastrointestinal upset.[7] The absorption of numerous medications, most notably levothyroxine, fluoroquinolones, tetracycline, phenytoin (Dilantin), angiotensin-converting enzyme inhibitors, iron, and bisphosphonates, can be significantly decreased when given with calcium. These medications should be given several hours before or after calcium supplements.[7]

VITAMIN D

The NOF recommends 800 to 1,000 IU of vitamin D daily for persons 50 years and older.[2] Daily intake of at least 700 to 800 IU of vitamin D is shown to prevent hip fractures in older persons,[31] with a number needed to treat (NNT) of 45 over two to five years of treatment.[15] Because it is difficult to consume this amount of dietary vitamin D, supplementation is important.

For patients with documented vitamin D deficiency, oral ergocalciferol (vitamin D_2) in a dosage of 50,000 IU weekly for eight weeks is usually an effective treatment. This should be followed by a maintenance dosage of 50,000 IU every two to four weeks or oral cholecalciferol (vitamin D_3) in a dosage of 1,000 IU once daily. The goal of treatment is a sustained serum 25-hydroxyvitamin D level greater than 30 ng per mL (74 nmol per L).[32] Measurement of serum levels following treatment is important because of the possible risk of vitamin D toxicity, but the optimal interval for testing is not known. Multiple alternative strategies for treating vitamin D deficiency exist.[32]

Table 5. Medications Approved by the U.S. Food and Drug Administration for Osteoporosis

Indication	*Medication*	*Typical dosage*	*Route*	*Fracture type*	*Monthly cost**
Prevention	Estrogen†, with or without progesterone	0.625 mg daily	Oral	Hip, vertebral, nonvertebral	With progesterone: $40 Without progesterone: $47
Prevention and treatment	Alendronate (Fosamax)	70 mg weekly	Oral	Hip, vertebral, nonvertebral	Tablet: $87, $77 (generic) Solution: $96
	Ibandronate (Boniva)	150 mg monthly	Oral	Vertebral	$100
	Risedronate (Actonel)	35 mg weekly	Oral	Hip, vertebral, nonvertebral	$92
	Raloxifene (Evista)	60 mg daily	Oral	Vertebral	$108
Treatment	Ibandronate	3 mg every three months for four doses	Intravenous	Increases bone mineral density, but fracture end point not evaluated	$162‡
	Zoledronic acid (Reclast)	5 mg annually for three doses	Intravenous	Hip, vertebral, nonvertebral	$104
	Calcitonin (Miacalcin)	200 IU daily	Nasal	Vertebral	$126
	Teriparatide (Forteo)	20 mcg daily up to two years	Subcutaneous	Vertebral, nonvertebral	$675

**— Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in* Red Book. *Montvale, NJ: Medical Economics Data; 2008. Cost to the patient will be higher, depending on prescription filling fee. Costs are for brand name drugs only, unless otherwise indicated.*

†—Hormone therapy is only appropriate in women with significant vasomotor symptoms for whom benefit outweighs risk.

‡—Cost per 3-mg dose (given once every three months).

Information from reference 25.

Pharmacologic Treatment

BISPHOSPHONATES

Oral bisphosphonates inhibit osteoclastic activity and are potent antiresorptive agents. Randomized clinical trials demonstrate a reduction of vertebral and hip fractures with alendronate (Fosamax)[16,33,34] and risedronate (Actonel).[17,21,33,34] Alendronate and risedronate have also demonstrated effectiveness in men[35,36] and in glucocorticoid-induced osteoporosis.[37,38] Both daily and intermittent uses of ibandronate (Boniva) have demonstrated antifracture effectiveness at the spine only.[20,34] As age increases, the NNT to prevent all types of fractures decreases.[9]

Weekly and monthly dosing make taking bisphosphonates easier. Nevertheless, nonadherence is problematic and is associated with worse outcomes.[39] Oral bisphosphonates must be taken with a full glass of water. A 30- to 60-minute wait is required before reclining or consuming other medications, beverages, or food to lower the risk of upper gastrointestinal adverse effects.

The optimal length of oral bisphosphonate therapy is unknown. A recent study found that women who take alendronate for five years followed by five years of placebo have no increase in the incidence of nonvertebral or hip fractures compared with women who take alendronate for 10 years. There is, however, an increase in vertebral fractures.[40] This suggests that relatively low-risk women (i.e., no personal history of vertebral fractures and only modestly reduced T-score) may consider an interruption in bisphosphonate treatment.

The intravenous bisphosphonates currently approved by the FDA for the treatment of postmenopausal osteoporosis are zoledronic acid (Reclast), given 5 mg yearly (shown to decrease vertebral and hip fractures),[18,34] and ibandronate, given 3 mg every three months (shown only to increase BMD in the intravenous form; the oral form has been shown to decrease vertebral fractures).[41] Although the cost of these medications is high, use may prove to be an attractive strategy for high-risk patients who are unable to tolerate or are noncompliant with oral therapy, or those currently hospitalized for hip fracture.

Recent concerns have been raised about the association of bisphosphonates with osteonecrosis of the jaw. To date, this rare complication is most often associated with the frequent infusion of intravenous bisphosphonates in patients with cancer.[42]

RALOXIFENE

Raloxifene (Evista), a selective estrogen receptor modulator, is approved for the treatment of postmenopausal osteoporosis. Raloxifene has estrogen agonist activity on the bones and lipids, and an estrogen antagonist effect on the breast and uterus. Raloxifene is effective for reducing the incidence of vertebral fractures, but effectiveness at the hip has not been shown.[22,33,34] Raloxifene is commonly associated with increased vasomotor symptoms. Although raloxifene increases the risk of venous thromboembolism, it is indicated to decrease the risk of invasive breast cancer in postmenopausal women with osteoporosis. Perhaps it may be best used in postmenopausal women with osteoporosis who are unable to tolerate bisphosphonates, have no vasomotor symptoms or history of venous thromboembolism, and have a high breast cancer risk score.

CALCITONIN

Calcitonin nasal spray (Miacalcin) is an antiresorptive agent approved for the treatment of postmenopausal osteoporosis at a dosage of 200 IU in alternating nostrils each day. It is shown to decrease the occurrence of vertebral compression fractures, but not nonvertebral or hip fractures.[23,34] Although calcitonin has modest analgesic properties in the setting of acute and chronic vertebral compression fracture,[43] it is not considered first-line treatment for osteoporosis because more effective medications are available.[7]

TERIPARATIDE

Teriparatide (Forteo) is a recombinant human parathyroid hormone with potent bone anabolic activity. In a dosage of 20 mcg per day given subcutaneously for up to two years, teriparatide decreases vertebral and nonvertebral fractures.[24,34] Adverse effects may include orthostatic hypotension, transient hypercalcemia, nausea, arthralgia, and leg cramps. Increased risk of osteosarcoma is seen in rats exposed to high doses. Consequently, teriparatide is contraindicated in patients with risk of osteosarcoma, such as those with Paget disease, previous skeletal radiation, or unexplained elevation of alkaline phosphatase level. Teriparatide is approved for the treatment of postmenopausal women with severe bone loss, men with osteoporosis who have a high risk of fractures, and persons who have not improved on bisphosphonate therapy. One study suggests that it is advisable to follow teriparatide therapy with bisphosphonate therapy to maintain BMD gained.[44]

HORMONE THERAPY

The Women's Health Initiative confirmed that estrogen, with or without progesterone, slightly reduced the risk of hip and vertebral fractures, but found that this benefit did not outweigh the increased risk of stroke, venous

thromboembolism, coronary heart disease, and breast cancer, even for women at high risk of fractures.[19] Lower doses of conjugated equine estrogens and estradiol have been shown to improve BMD, but the reduced risk of fracture has not been demonstrated[45] and the safety is unknown. The FDA recommends hormone therapy for osteoporosis only in women with moderate or severe vasomotor symptoms, using the lowest effective dose for the shortest time.

COMBINATION THERAPY

Bisphosphonates do not have additive effects on BMD when used concomitantly with parathyroid hormone,[44] but they do have additive effects on BMD when combined with hormone therapy.[45,46] Antifracture effectiveness of these combinations has not been shown. Although research continues, there is currently a limited role for combination therapy beyond subspecialty consultation or clinical trials.

Treatment Follow-Up

There is no clear evidence to guide follow-up recommendations once the diagnosis of osteoporosis is made and treatment is initiated. It is reasonable to assess response to therapy at least once, after no less than 24 months. More frequent testing might be appropriate in the setting of accelerated bone loss, such as the chronic administration of glucocorticoids. Successful treatment is best determined by lack of fracture, but the surrogate outcome of stability or increase in BMD suggests treatment effectiveness. A decrease in BMD suggests noncompliance, inadequate calcium and vitamin D supplementation, an unidentified secondary cause of osteoporosis, or treatment failure.

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