

## In the Clinic

# Osteoporosis

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**CME Objective:** To review current evidence for the prevention, diagnosis, and treatment of osteoporosis.

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Osteoporosis is a skeletal disorder characterized by compromised bone strength that predisposes a person to an increased risk for fracture (1). Bone strength is determined by properties that include bone mineral density (BMD), bone geometry (size and shape of bone), degree of mineralization, microarchitecture, and bone turnover. It is a common disease with serious clinical consequences. In the United States, about 44 million people have osteoporosis or osteopenia (low bone mass) that could lead to low-trauma fractures. About 50% of white women and 20% of men will have an osteoporosis-related fracture in their lifetimes. Fractures of the hip and spine may be disabling and are associated with mortality rates that are about 20% greater than that of an age-matched population. A fragility fracture (i.e., a nontraumatic fracture or one that occurs with low trauma, such as a fall from the standing position) of any type is a sentinel event that increases the risk for future fractures. To reduce the burden of osteoporotic fractures, high-risk patients must be identified, evaluated for factors contributing to skeletal fragility, and treated to reduce fracture risk. Pharmacologic agents can reduce the risk for fracture in appropriately selected patients, with a generally favorable safety profile.

## Screening and Prevention

### Who should be screened for osteoporosis?

All patients should be evaluated for factors contributing to skeletal health. Those with clinical risk factors for osteoporosis or fracture (see the Box: Clinical Risk Factors for Osteoporosis and Low-Trauma Fracture) may benefit from further evaluation that includes BMD testing.

The National Osteoporosis Foundation (NOF) has developed evidence-based guidelines (2), which are virtually identical to those of the International Society for Clinical Densitometry (ISCD) (3), for selecting patients to have a BMD test (see the Box: Indications for Bone Mineral Density Testing).

Other organizations have published variations of these recommendations. For example, the US Preventive Services Task Force has determined that all women aged 65 years and older and women younger than 65 who have a 10-year probability of major osteoporotic fracture  $\geq$  9.3% should have a screening BMD test (4). The American College of Physicians (ACP) guidelines recommend that “older men” and men “who are at increased risk for osteoporosis and are candidates for drug therapy” have a BMD test (5). As with all clinical tests, BMD should only be measured

if the results might influence clinical decisions or recommendations for treatment.

### How should screening be done, and how are the results interpreted?

Bone mineral density measured with dual-energy x-ray absorptiometry (DXA) is used to screen for and diagnose osteoporosis, assess fracture risk, and monitor changes in BMD over time. The World Health Organization (WHO) has developed a freely available, computer-based fracture risk assessment tool, FRAX (6), that can be used with or without BMD, to estimate the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, forearm) in untreated men and women between the ages of 40 and 90. The items used for the calculation are readily available from routine clinical care and are listed in the Box: FRAX Tool.

Expression of fracture risk as a 10-year probability provides greater clinical utility than relative risk, because relative risk is dependent on the risk for the comparator population as well as the patient's risk. In addition, the limited number of easily obtainable clinical risk factors used is more practical than the numerous published clinical risk factors.

#### Clinical Risk Factors for Osteoporosis and Low-Trauma Fracture

- Advanced age
- Female sex
- Estrogen deficiency (any cause after puberty)
- History of fracture as an adult
- History of fragility fracture in first-degree relative
- History of glucocorticoid use for more than 3 months
- Current cigarette smoking
- Low body weight (<127 lbs)
- Poor health/frailty
- White race
- Asian race
- Low calcium intake
- Alcoholism
- Inadequate physical activity
- Dementia; cognitive impairment
- Recurrent falls
- Impaired neuromuscular function and other parameters of immobility
- Impaired eyesight despite optimal correction
- Residence in a nursing home
- Long-term heparin therapy
- Anticonvulsant therapy
- Aromatase-inhibitor therapy
- Androgen-deprivation therapy

The interpretation of DXA results and categorization of patients as having osteopenia or osteoporosis are listed in the Box: Classification of Bone Mineral Density by Dual-Energy X-Ray Absorptiometry.

### What lifestyle measures are recommended for prevention?

Regular physical activity and good nutrition, with particular regard to adequate intake of calcium and vitamin D, can help to optimize peak bone mass and reduce the subsequent rate of bone loss. Encourage resistance exercise, recognizing the need to adjust exercise programs according to a patient's concurrent problems. Avoidance of smoking and moderate alcohol consumption should be recommended, and counseling or behavioral modification programs for these problems should be considered when appropriate. In addition to the skeletal benefits, regular physical activity can improve cardiovascular fitness, assist with weight control, and provide an enhanced sense of well-being. Excessive exercise may be harmful to skeletal health, as seen in adolescents and young adults with poor nutrition and hormonal abnormalities associated with the female-athlete triad (eating disorder, amenorrhea, osteoporosis). If possible, exposure to medications known to have harmful skeletal effects (e.g., glucocorticoids, aromatase inhibitors, androgen-deprivation therapy, and anticonvulsants) should be minimized or avoided. For frail, elderly patients, the importance of fall prevention by means including modifying the home environment; leg-strengthening exercises; balance training; and avoiding drugs that may cause sedation, hypotension, or dizziness should be emphasized.

*Weight-bearing exercise maintains bone strength by stimulating bone formation (7). Observational, retrospective, and prospective randomized trials have shown an association between exercise and bone accretion during growth as well as with maintenance of bone mass in adulthood, with particular benefit from high-impact*

*exercise. A simple jumping exercise (10 minutes, 3 times a week for 7 months) in a randomized, controlled trial (RCT) done in 121 ten-year-old boys augmented total body bone mineral content (8), which was sustained even after a further 7 months of "de-training." Another RCT conducted in prepubescent children showed that a 7-month exercise program that included jumping was better than a program that included stretching in improving bone mass at the hip and spine (9). Weight-bearing exercise has been associated with a small but significant BMD increase in meta-analyses of 25 studies in premenopausal and postmenopausal women (10) and 8 studies in men (11).*

### What is the role of calcium and vitamin D in the prevention of osteoporosis?

Calcium and vitamin D are essential nutrients for the accrual of bone during childhood and adolescence and the maintenance of bone mass in adulthood. Inadequacy can result in rickets in children and osteomalacia or osteoporosis in adults. The NOF recommends a daily calcium intake of at least 1200 mg with diet plus supplements, if needed, for postmenopausal women and men age 50 years and older, with a tolerable upper limit for daily calcium intake set at 2500 mg (2). Excessive calcium intake may be associated with increased risk for hypercalciuria and nephrolithiasis. In patients with malabsorption due to intestinal disease, bariatric surgery, or achlorhydria (which affects absorption of calcium carbonate, predominantly in the fasting state), consider increasing the oral dose of calcium to 2000 mg/d. Because of the high prevalence of reduced gastric acidity that is either endogenous or due to medications (e.g., proton-pump inhibitors), calcium carbonate is best taken with meals to optimize absorption. Calcium citrate, which is well-absorbed regardless of gastric acidity, may be taken with or without food. Measurement of the 24-hour urinary calcium may be helpful in monitoring therapy, noting that <50 to

### Indications for Bone Mineral Density Testing

- Women aged 65 years and older and men aged 70 and older, regardless of clinical risk factors
  - Younger postmenopausal women and men aged 50 to 69 about whom you have concern based on the clinical risk profile
  - Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk, such as low body weight, prior low-trauma fracture, or high-risk medication\*
  - Adults who have a fracture after age 50
  - Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose  $\geq$  5 mg prednisone or equivalent for  $\geq$  3 months) associated with low bone mass or bone loss
  - Anyone being considered for pharmacologic therapy for osteoporosis
  - Anyone being treated for osteoporosis, to monitor treatment effect
  - Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
  - Postmenopausal women discontinuing estrogen should be considered for bone density testing
- \*High-risk medications include long-term glucocorticoids, anticonvulsants, aromatase inhibitors, and androgen-deprivation therapy.

### FRAX Tool

- Clinical items used by the FRAX tool to estimate 10-year risk for major osteoporotic fracture (hip, clinical spine, proximal humerus, distal forearm) and hip fracture:
- Age
  - Sex
  - Height
  - Weight
  - Ethnicity (for US calculator only: caucasian, black, Hispanic, or Asian)
  - Optional item: femoral neck bone mineral density (g/cm<sup>2</sup>)
- Yes/no responses to each of the following:
- Previous fracture
  - Parent with hip fracture
  - Current smoking
  - Glucocorticoid use
  - Rheumatoid arthritis
  - Secondary osteoporosis
  - Three or more units of alcohol per day
- Calculator freely available at [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX).

### Classification of Bone Mineral Density by Dual-Energy X-Ray Absorptiometry

In postmenopausal women and men aged 50 and older—apply the WHO diagnostic criteria

- Normal: T-score  $-0.1$  or above
- Low bone mass (osteopenia): T-score below  $-1.0$  and above  $-2.5$
- Osteoporosis: T-score  $-2.5$  or below
- Severe osteoporosis: T-score  $-2.5$  or below and personal history of fragility fracture

In premenopausal women and men under age 50—do not apply the WHO diagnostic criteria

- Z-scores, not T-scores, are preferred
- Z-score of  $-2.0$  or lower is defined as “below the expected range for age”
- Z-score above  $-2.0$  is “within the expected range for age”

In children (males and females less than age 20)—do not apply the WHO diagnostic criteria

- Use Z-scores, not T-scores
- If the Z-score is below  $-2.0$ , use such terminology as “low bone density for chronological age” or “below the expected range for age”
- There are no densitometric criteria for diagnosing osteoporosis in children

WHO = World Health Organization.

100 mg/24 h suggests calcium malabsorption, assuming adequate intake and normal renal function.

The blood level of serum 25-hydroxyvitamin D necessary for optimum skeletal health, and the dose of vitamin D required to achieve it, is not known. Many experts believe that the minimum desirable serum level of 25-hydroxyvitamin D is about 75 nmol/L (30 ng/mL), requiring an average daily intake of at least 800 to 1000 IU in older men and women (12). The NOF recommends an intake of vitamin D3 800 to 1000 IU/d for all adults age 50 years and older; doses over 2000 IU/d may be necessary and safe for some patients. Vitamin D toxicity with hypercalcemia is rare and probably requires a daily dose in excess of 40,000 IU (13). Food products fortified with vitamin D, together with modest exposure to sunlight, can be suggested. Chronically ill, elderly persons who cannot get out during the day are particularly susceptible to vitamin D deficiency; therefore, oral supplementation is an acceptable alternative.

*Although it is often difficult to distinguish the effects of calcium and vitamin D in clinical trials, many studies suggest that the typical intake of both is suboptimum. A meta-analysis of 15 randomized clinical trials in postmenopausal women, representing 1806 participants, showed that calcium was more effective than placebo at reducing rates of bone loss after 2 or more years of treatment with a pooled difference in percentage change from baseline of 2.05% (95% CI, 0.24 to 3.86) for total body BMD, 1.66% (CI, 0.92 to 2.39) for the lumbar spine at 2 years, 1.60% (CI, 0.78 to 2.41) for the hip, and 1.91% (CI, 0.33 to 3.50) for the distal radius (14).*

*An 18-month prospective randomized trial in 3270 healthy ambulatory elderly women (mean age, 84 years), not selected according to baseline fracture risk, showed that supplementation with vitamin D3 (cholecalciferol) and calcium improved BMD at the proximal femur by 7.3% compared with placebo ( $P < 0.001$ ), reducing the risk for hip fracture by 43% ( $P < 0.043$ ) and nonvertebral fractures by 32% ( $P < 0.015$ ) (15). A similar effect was observed in a 3-year trial of 176 men and 213 women aged 65 or older who were*

*randomly assigned to vitamin D3 supplementation on BMD in men and women aged 65 years and older (16).*

### When should pharmacologic treatment be considered for prevention?

In the early postmenopausal years, bone remodeling accelerates in women due to estrogen deficiency, sometimes resulting in rapid bone loss. This is particularly troublesome when baseline BMD is low, which is often due to low peak bone mass. Under these circumstances, early intervention with pharmacologic agents may prevent or reverse bone loss, maintain trabecular microarchitecture, and ultimately reduce fracture risk. The ACP recommends consideration of pharmacologic treatment “for men and women who are at risk for developing osteoporosis” (17). Drugs that are approved for the prevention of postmenopausal osteoporosis (Table 1) have been shown in RCTs to stabilize or increase BMD in early postmenopausal women who do not have osteoporosis. This has been demonstrated with alendronate (18), risedronate (19), ibandronate (20), raloxifene (21), and estrogen (22). In RCTs for osteoporosis prevention, fracture reduction benefit has not been shown with risedronate, ibandronate, or raloxifene; however, a post hoc subgroup analysis of the Fracture Intervention Trial showed that alendronate was effective in reducing the risk for vertebral fractures in women with a femoral neck T-score between  $-1.6$  and  $-2.5$  (23). The Women’s Health Initiative trial showed that estrogen alone (24) or combined with progesterone (22) reduced fractures in women not specifically selected to be at increased risk for osteoporosis. The decision to begin pharmacologic therapy for prevention of osteoporosis should be based on consideration of the balance between the expected benefit and potential risks of each pharmacologic agent (Table 1) for each patient.

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**Table 1. Pharmacologic Agents for Management of Osteoporosis**

<i>Agent</i>	<i>Mechanism of Action</i>	<i>Dosage</i>	<i>Benefits</i>	<i>Side Effects</i>	<i>Notes</i>
Raloxifene	Selective estrogen-receptor modulator; suppressive effects on osteoclast and bone resorption; estrogen antagonist in uterine and breast tissues	60 mg/d	Increases bone mass; decreases vertebral fractures; reduces risk for invasive breast cancer	Increased thromboembolic risk; increased vasomotor symptoms; increased risk for fatal stroke	Does not need to be given with progesterone. Not recommended for premenopausal women or women concurrently using estrogen replacement. FDA-approved indications: prevention and treatment of osteoporosis in postmenopausal women. No evidence for reduction of hip or nonvertebral fracture risk.
Oral bisphosphonates (alendronate, risedronate, ibandronate). Note that a recently approved novel formulation of risedronate 35 mg/wk, with an enteric coating and a chelating agent, is approved for treatment of postmenopausal osteoporosis only; must be taken immediately after breakfast.	↓ bone resorption by attenuating osteoclast activity	10 mg/d or 70 mg/wk for treatment or 5 mg/d for prevention (alendronate); 150 mg/mo (ibandronate); 5 mg/d, 35 mg/wk, or 150 mg/mo (risedronate)	Increases bone mass; decreases vertebral fractures; decreases in hip and nonvertebral fractures with alendronate and risedronate	May cause esophageal irritation	Should not be taken with food. Instruct patient to take first thing in the morning with 6–8 oz water and not to recline or ingest anything else for at least 30 min (alendronate, risedronate) or 60 min (ibandronate). Do not use in patients with chronic kidney disease (creatinine clearance <35 mL/min [alendronate] or < 30 mL/min [risedronate, ibandronate]). FDA-approved indications: prevention and treatment of osteoporosis in postmenopausal women (alendronate, risedronate, ibandronate), treatment of osteoporosis in men (alendronate, risedronate), prevention (risedronate) and treatment (alendronate, risedronate) of glucocorticoid-induced osteoporosis in women or men. No evidence for reduction of hip or nonvertebral fracture risk for ibandronate.
Denosumab	↓ bone resorption by attenuating osteoclast formation, activity, and survival	60 mg/d SQ every 6 mo	Increases bone mass; decreases vertebral, hip, and nonvertebral fracture rates	Increased risk for cellulitis, eczema, and flatulence in the phase 3 pivotal fracture trial	No restrictions in dosing according to renal function. FDA-approved indication: treatment of osteoporosis in postmenopausal women at high fracture risk.
IV bisphosphonates (zoledronate, ibandronate)	↓ bone resorption by attenuating osteoclast activity	5 mg IV over no less than 15 min once every 12 mo for treatment or once every 24 mo for prevention (zoledronate); 3 mg IV over 15–30 sec every 3 mo	Increases bone mass; decreases vertebral fracture, hip fracture, and other nonvertebral fracture rates	Flu-like symptoms after first dose	FDA-approved for prevention (zoledronate) and treatment (zoledronate, ibandronate) of postmenopausal osteoporosis, to increase bone mass in men with osteoporosis (zoledronate), and treatment of osteoporosis in men (zoledronate), and prevention (zoledronate) and treatment (zoledronate) of glucocorticoid-induced osteoporosis in women and men.
Calcitonin	↓ bone resorption by attenuating osteoclast activity	Nasal spray: 200 IU/d	Slight increases in bone mass; decreases vertebral fracture rates	Rhinitis, irritation of nasal mucosa	May be beneficial in decreasing pain associated with acute or subacute vertebral fracture. Because of availability of medications with better efficacy in fracture reduction, calcitonin is not considered first-line treatment for osteoporosis. FDA-approved indications: treatment of osteoporosis in women who are at least 5-years postmenopausal. No evidence for reduction of hip or nonvertebral fracture risk.
Teriparatide	Stimulates bone formation	20 µg/d SQ	Increases bone mass; decreases vertebral and nonvertebral fracture rates	Dizziness, nausea	Maximum lifetime duration 2 years. Contraindicated in patients with baseline risk for osteosarcoma, including those with Paget disease of bone, unexplained elevation of AKP, open epiphyses, or history of skeletal radiation. FDA-approved indications: high risk for fracture with postmenopausal osteoporosis, men with primary or hypogonadal osteoporosis, and men and women with sustained systemic glucocorticoid therapy.

AKP = alkaline phosphatase; FDA = U.S. Food and Drug Administration; IU = international units; IV = intravenous; SQ = subcutaneous.

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**Screening and Prevention...** A healthy lifestyle, good nutrition, and avoidance of medications known to be harmful to bone are fundamental components of prevention of osteoporosis. Pharmacologic therapy to reduce fracture risk is indicated in patients with osteopenia who are at high fracture risk and should be considered in patients without osteopenia who are anticipated to have rapid bone loss that could soon result in osteoporosis and high fracture risk.

## CLINICAL BOTTOM LINE

## Diagnosis and Evaluation

### How should osteoporosis be diagnosed?

Osteoporosis may be diagnosed in postmenopausal women and men 50 years and older when the lowest T-score of the lumbar spine, femoral neck, total hip, or 33% (one third) radius (a region of interest in the distal radius that is defined by each DXA manufacturer) is  $-2.5$  or less according to WHO criteria. This cut-off was selected because it identifies approximately 30% of postmenopausal women as having osteoporosis by measurement of BMD at the lumbar spine, hip, and forearm, which approximates the lifetime risk for fracture at these skeletal sites. The T-score is the standard deviation (SD) difference between the BMD of the patient and a sex-matched, young-adult, white reference population. A presumptive diagnosis of osteoporosis may also be made in the presence of a fragility (low-trauma) fracture, regardless of BMD. In premenopausal women and men younger than 50 years, Z-scores (the SD difference between the patient's BMD and an age-, sex- and ethnicity-matched reference population)—not T-scores—should be used, and the WHO diagnostic criteria should not be applied.

*Based on a meta-analysis of 229 studies that compared osteoporosis screening with 2 widely accepted screening methods, the predictive value of a 1-SD decrease in BMD for fracture is similar to that of a 1-SD increase in blood pressure for predicting risk for stroke or a 1-SD increase in serum cholesterol concentration for predicting coronary artery disease (25). A cost-effectiveness analysis has*

*reported that universal bone densitometry testing combined with alendronate therapy for patients found to have osteoporosis is highly cost-effective for women aged 65 years and older and may be cost-saving for ambulatory women aged 85 years and older (whether living independently or residing in nursing homes) (26).*

### What should the initial evaluation of a patient newly diagnosed with osteoporosis include?

The evaluation of a patient with osteoporosis begins with a focused medical history and physical examination (see the Box: Potentially Helpful Findings on Physical Examination for Osteoporosis).

The medical history should include information about diet, lifestyle, medications, family history, falls, fractures, and a focused review of systems. Height should be measured with a wall-mounted stadiometer. Particular attention is given to signs that may indicate a cause of osteoporosis (e.g., signs of hyperthyroidism), complications (e.g., kyphosis), or the risk for falls (e.g., evaluation of gait and balance). Appropriate laboratory studies (Table 2) should be done to determine whether clinically relevant contributing factors are present (e.g., malabsorption) and to identify potential safety concerns that could influence the treatment decisions (e.g., hypocalcemia). Imaging studies may be helpful in carefully selected patients. For example, spine imaging may diagnose previously unrecognized vertebral fractures in patients with height loss or kyphosis; a nuclear bone scan or an

x-ray may detect Paget disease of bone in a patient with unexplained elevation of serum alkaline phosphatase levels; and a barium swallow may detect an esophageal stricture in a patient with swallowing difficulties and may influence choices for treatment.

*Although there is no established consensus on the optimum laboratory testing for patients with low BMD, panels of experts have recommended various combinations of tests. In a cross-sectional study of 664 women seen at an osteoporosis and metabolic bone disease specialty clinic, those without known secondary causes were screened with extensive laboratory testing. It was found that 32% had previously unknown contributing factors, and a strategy of measuring 24-hour urinary calcium, serum calcium, serum parathyroid hormone, and serum thyroid-stimulating hormone in women receiving thyroid replacement identified 85% at an estimated cost of \$75 per patient (27).*

### When should consultation be considered in evaluation?

Consider referral to a physician with expertise in osteoporosis and metabolic bone disease when secondary causes of osteoporosis are suspected or when clinical and laboratory data are discordant. Consider referral to a gastroenterologist for small bowel biopsy when celiac disease is suspected. Consider referral to an oncologist when laboratory findings suggest multiple myeloma or other forms of cancer. Referral to an appropriate osteoporosis specialist should be

### Potentially Helpful Findings on Physical Examination for Osteoporosis

Loss of height may be associated with vertebral fracture  
Low body weight is an independent risk factor for fracture  
Weight loss may be due to hyperthyroidism or malnutrition  
Fast heart rate may be due to hyperthyroidism or anemia  
Fast respiratory rate may be due to asthma  
Kyphosis may be the result of vertebral fractures or upper back muscle weakness  
Poor gait, muscle strength, balance may increase the risk for falls and fractures  
Paralysis or immobility may result in bone loss, increased risk for falls, or both  
Joint laxity could be due to the Marfan syndrome, osteogenesis imperfecta, or the Ehlers-Danlos syndrome  
Inflammatory arthritis is associated with osteoporosis and the use of glucocorticoids  
Osteoarthritis or lower limb injury may result in decreased load-bearing and bone loss  
Blue sclera, poor tooth development, hearing loss, and fracture deformities are associated with osteogenesis imperfecta  
Poor dental hygiene is a risk factor for osteonecrosis of the jaw with bisphosphonate therapy  
Thyromegaly, thyroid nodules, and proptosis suggest hyperthyroidism  
Urticaria pigmentosa suggests systemic mastocytosis  
Kyphosis or shortened distance between lowest ribs and iliac crest suggests vertebral fractures  
Abdominal tenderness may be due to inflammatory bowel disease  
Stretch marks, buffalo hump, and bruising suggest glucocorticoid excess  
Signs of venous thrombosis suggest that treatment with estrogen or raloxifene may be contraindicated  
Small testicles in men suggest hypogonadism

considered when a patient with normal BMD sustains a nontraumatic fracture; when recurrent fractures or continued bone loss occurs in a patient receiving therapy without obvious treatable causes of bone loss; when osteoporosis is unexpectedly severe or has unusual features; or when a patient has a condition that complicates management (e.g., renal failure, hyperparathyroidism, or malabsorption) (28).

**Diagnosis...** Most patients with osteoporosis and low BMD can be evaluated and treated by a primary care physician. Essential laboratory tests for the initial evaluation of all patients with osteoporosis include a complete blood count; measurement of serum calcium, phosphorus, creatinine, aspartate and alanine transaminase, alkaline phosphatase, and thyroid-stimulating hormone and 24-hour urinary calcium levels; and testosterone in men with osteoporosis. Additional tests may be appropriate depending on clinical circumstances. The decision to refer to an osteoporosis specialist is determined by the level of expertise and comfort of the referring physician in evaluating complex or unusual diagnostic issues.

### CLINICAL BOTTOM LINE

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**Table 2. Laboratory Evaluation for Secondary Causes of Osteoporosis\***

<i>Essential tests</i>	<i>Comments/Disorder Detected</i>
Complete blood count	Cancer
Serum calcium	High in hyperparathyroidism
Serum phosphorus	Low with osteomalacia
Serum creatinine	High with chronic kidney disease
Serum thyroid-stimulating hormone	Low in hyperthyroidism
Serum liver enzymes	High with chronic liver disease
Serum alkaline phosphatase	High with chronic liver disease and Paget disease of bone, low with hypophosphatasia
Serum total/free testosterone in men	Hypogonadism
24-hour urinary calcium	Low (< 50–100 mg/24 h) with calcium malabsorption, high (> 250 mg/24 h in women or >300 mg/24 h in men) with excessive calcium absorption or renal calcium leak
<i>Optional tests according to clinical circumstance</i>	
Serum 25-hydroxyvitamin D	Vitamin D deficiency/insufficiency
Serum parathyroid hormone in patients with high serum calcium	Hyperparathyroidism
Serum/urine protein electrophoresis, kappa/lambda light chains	Multiple myeloma in elderly patients
Serum celiac antibodies (antigliadin, endomysial, tissue transglutaminase) when malabsorption is suspected	Celiac disease (small bowel biopsy needed to confirm diagnosis)
24-hour urinary free cortisol or overnight dexamethasone suppression test if hypercortisolism is suspected	The Cushing syndrome
Serum tryptase	Systemic mastocytosis

\*Tests not listed may be indicated according to clinical circumstances.

## Treatment

### What are the goals of treatment?

The goal of treatment is to reduce the risk for fractures. Fractures occur when a force applied to a bone exceeds its strength; fracture risk is reduced by improving bone strength and preventing falls. Bone strength cannot be directly measured in vivo; therefore, surrogate markers of bone strength, such as BMD and markers of bone turnover, are used to assess skeletal health at baseline and to monitor for effectiveness of treatment (discussed below). BMD is typically measured about 1 to 2 years after starting therapy, with the goal of maintaining or increasing BMD. Essential care for skeletal health includes regular physical activity and adequate intake of calcium and vitamin D. Pharmacologic agents have been proven to reduce fracture risk. Fall risk can be assessed through simple office tests, such as observing how easily the patient rises from a chair and moves to the examination table, and whether he or she is able to walk a straight line or balance on 1 foot. Periodic reevaluation of the risk for falls is appropriate because

risk may increase with advancing age. Reduction in fall risk with such measures as quadriceps strengthening and balance training is important in osteoporosis treatment, especially in frail, elderly patients.

### What lifestyle measures are recommended?

Encourage smoking cessation and reduced alcohol use, which may require counseling or behavioral modification programs. Encourage regular weight-bearing and muscle-strengthening exercise, recognizing the need to adjust exercise programs in patients with concurrent disease. For frail, elderly patients, emphasize the importance of prevention of falls, best accomplished by evaluating home safety, minimizing use of mind-altering medications (e.g., sedatives, hypnotics, and narcotic analgesics), and leg-strengthening exercises.

### How much calcium and vitamin D are recommended?

The NOF treatment recommendations include a recommendation for adequate calcium and vitamin D

19. Cranney A, Tugwell P, Adachi J, et al. Meta-analysis of risendronate for the treatment of postmenopausal osteoporosis. *Endocr Rev.* 2002;23:517-23.
20. 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.
21. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev.* 2002;23:524-28.
22. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290:1729-38.

intake in postmenopausal women and men age 50 and older, regardless of whether osteoporosis is present. Suggest oral calcium supplements (e.g., calcium carbonate or calcium citrate) to patients whose daily dietary calcium intake is less than 1200 mg. Advise the patient that calcium carbonate supplements should be taken with meals to ensure the presence of stomach acid, which enhances absorption. Calcium citrate may be taken with or without meals. Since a reduction in stomach acid will also decrease absorption of calcium carbonate formulations; consider advising all elderly patients and those receiving acid-suppression therapy to take calcium citrate rather than other calcium formulations. Recommend an intake of vitamin D3, 800 to 1000 IU/d, for all adults age 50 and older; doses over 2000 IU/d may be necessary and safe for some patients. The effectiveness of vitamin D intake is assessed by measurement of the serum 25-hydroxyvitamin level, not by the dose that is taken. Since it requires at least 3 months to achieve a new steady state after changing the vitamin D dose, it is prudent to wait at least that amount of time before measuring the serum 25-hydroxyvitamin D level. Suggest using fortified food products and moderate exposure to sunlight, keeping in mind that sunblock that prevents tanning and burning also reduces vitamin D production in the skin.

*A large RCT of more than 36 000 healthy postmenopausal women reported that calcium and vitamin D supplementation increased BMD at the hip but did not significantly reduce the risk for hip fracture (29); however, the dose of vitamin D (400 IU) was suboptimum and adherence to therapy was poor (59% at the end of the study). The study found that among women who were adherent to therapy (i.e., took at least 80% of study medication), even with the suboptimum dose of vitamin D, there was a significant 29% reduction in hip fracture risk. Most major modern trials of antiresorptive therapies (such as bisphosphonates, discussed below) have provided basal calcium intake*

*for all participants; thus, the efficacy of all currently available antiresorptive agents has been shown only in women who maintain adequate calcium intake. Histamine-2 receptor antagonists and proton-pump inhibitors may decrease calcium bioavailability (30).*

### What pharmacologic interventions are effective for treatment, and how should they be chosen?

The NOF has established indications for initiation of pharmacologic therapy to reduce the risk for fracture as assessed by BMD testing, history of spine or hip fracture, and use of FRAX in patients with osteopenia. The ACP recommends offering pharmacologic treatment to “men and women who have known osteoporosis and to those who have experienced fragility fractures” (17). Pharmacologic agents proven to reduce fracture risk in patients with osteoporosis are listed in Table 1; in addition, estrogen with or without medroxyprogesterone also improves BMD and reduces the risk for fracture in postmenopausal women (24, 31); however, estrogen is not approved for treatment of osteoporosis due to evidence that the risks outweigh the benefits, even in women at high risk for fracture (22). Drug selection should be based on all available clinical information, including estimation of fracture risk, comorbid conditions, patient preferences, efficacy, safety, expectations of adherence to therapy, and affordability (32–44). Effective communication of risk and shared decision making allow the patient to fully participate in treatment decisions (45). In addition to pharmacologic therapy, measures should be taken to ensure adequate intake of calcium and vitamin D; limit exposure to medications known to have harmful skeletal effects; and reduce the risk for falls, especially in frail elderly patients (see section on falls).

The oral bisphosphonates alendronate, risedronate, and ibandronate are each first-line therapy for the treatment of osteoporosis for many

23. Quandt SA, Thompson DE, Schneider DL, et al. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of -1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. *Mayo Clin Proc.* 2005;80:343-49.
24. Anderson GL, Lian M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291:1701-12.
25. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ.* 1996;312:1254-59.
26. Schousboe JT, Ensrud KE, Nyman JA, et al. Universal bone densitometry screening combined with alendronate therapy for those diagnosed with osteoporosis is highly cost-effective for elderly women. *J Am Geriatr Soc.* 2005;53:1697-704.
27. Tannenbaum C, Clark J, Schwartzman K, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *J Clin Endocrinol Metab.* 2003;87:4431-37.
28. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis: executive summary of recommendations. *Endocr Pract.* 2010;16:1016-19.
29. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006;354:669-83.

30. Graziani G, Como G, Badalamenti S, et al. Effect of gastric acid secretion on intestinal phosphate and calcium absorption in normal subjects. *Nephrol Dial Transplant*. 1995;10:1376-80.
31. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288:321-33.
32. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med*. 1995;333:1437-43.
33. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535-41.
34. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures - Results from the fracture intervention trial. *JAMA*. 1998;280:2077-82.
35. McClung MR, Geusens P, Miller PD, et al. Effect of risendronate on the risk of hip fracture in elderly women. *N Engl J Med*. 2001;344:333-40.
36. Reginster J-Y, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risendronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int*. 2000;11:83-91.

patients due to proven efficacy, generally favorable safety profiles, and low cost (particularly with generic alendronate). Instruct patients to take oral bisphosphonates on an empty stomach with 8 oz of water, without any food or other medications to maximize absorption and to remain upright for at least 30 minutes (60 minutes with ibandronate) to reduce risk for esophageal injury. A newly approved formulation of weekly risendronate is taken immediately after breakfast, thereby avoiding the inconvenience of the pre- and postdose fasting required with other oral bisphosphonates. Do not use these agents in patients with hypocalcemia, renal insufficiency (creatinine clearance <30 to 35 mL/min), or esophageal stricture, and use cautiously in those with difficulty swallowing, severe gastroesophageal reflux, gastric bypass, or disorders treated with long-term anticoagulation. Patients with a remote history of peptic ulcer disease or gastroesophageal reflux that is well controlled with medications are often able to take oral bisphosphonates without difficulty. Discontinue if symptoms of esophageal irritation (retrosternal pain, significantly worsened reflux symptoms) or severe musculoskeletal pain develops. Consider referral to an appropriate specialist if symptoms persist despite discontinuation. An association of bisphosphonates with osteonecrosis of the jaw (46) and atypical femur fractures (47) has been reported, without clear evidence of a causal relationship. In part because of these safety concerns, the concept of a "drug holiday" after long-term bisphosphonate therapy has been raised. A drug holiday can be considered in patients treated with bisphosphonates, but not other osteoporosis medications, because of their long skeletal half-life and evidence of persistence of effect in some patients for a period after discontinuation (48). There are no clinical practice guidelines for starting or ending a drug holiday. Potential candidates are patients who should not have been treated in the first place and those who have

been treated for at least 5 years and are no longer at sufficiently high fracture risk to justify continuing treatment.

Injectable denosumab, ibandronate, or zoledronate are useful for treatment of osteoporosis when oral bisphosphonates are ineffective (e.g., significant decrease in BMD, failure to suppress bone turnover markers), contraindicated (e.g., esophageal stricture, achalasia), associated with gastrointestinal intolerance (e.g., heartburn, abdominal pain), likely to be poorly absorbed (e.g., uncontrolled celiac disease, inflammatory bowel disease), or if the patient is unable to remain upright for 30 to 60 minutes after dosing (Table 1). The most common adverse reaction with intravenous bisphosphonates is an acute-phase reaction, usually consisting of mild, transient, flu-like symptoms, particularly after the first injection. Denosumab has been associated with a small but significant increased risk for adverse dermatologic events, such as eczema and serious cellulitis. Intravenous bisphosphonates should not be given to patients with severely impaired renal function, although there are no such restrictions with denosumab.

Consider raloxifene therapy for treatment of postmenopausal osteoporosis, particularly in early postmenopausal women at high risk for breast cancer (raloxifene reduces the risk for invasive breast cancer), no history of thromboembolic disease, low risk for stroke, low risk for hip fracture, and few or no problems with hot flashes. Do not use raloxifene in patients who are at high risk for stroke or have a history of thromboembolic events, premenopausal women, or women receiving concurrent estrogen therapy.

Nasal salmon calcitonin is approved for the treatment of osteoporosis in women who are at least 5 years postmenopausal and are not able to take other U.S. Food and Drug Administration (FDA)-approved agents. It is administered as a nasal spray at a

dose of 200 IU daily, using alternating nostrils. The only contraindication to calcitonin is hypersensitivity to the drug. Do not use as a first-line treatment for osteoporosis because other available medications have better efficacy in fracture reduction.

Consider prescribing teriparatide (synthetic recombinant parathyroid [PTH] 1-34) for treatment of patients at high risk for fracture, defined by the FDA as having a history of osteoporotic fracture, multiple risk factors for fracture, or failure of or intolerance to other available osteoporosis therapy. It is used at a dose of 20 µg, injected subcutaneously, once daily for 18 to 24 months for patients at high risk for fracture. Intermittent PTH injections directly stimulate bone formation. Teriparatide is the only osteoanabolic agent approved for the treatment of osteoporosis. It has been associated with an increased risk for osteosarcoma in rats given very large doses, but no such increased risk has been reported in humans treated according FDA recommendations.

### How should patients be monitored?

Serial BMD measurements by DXA can be used to monitor for response to therapy. It is appropriate to measure BMD 12 to 24 months after initiating or changing therapy and periodically thereafter. Consider testing more frequently (e.g., every 6 months until stable) in conditions associated with rapid bone loss, such as glucocorticoid therapy. In untreated patients, significant bone loss may influence a decision to initiate treatment (e.g., treatment is indicated if a recalculation of fracture risk with FRAX shows values that exceed the intervention thresholds or if the T-score goes to -2.5 or below). In treated patients, an increase or stability in BMD is considered an acceptable response to therapy that is associated with a reduction in fracture risk. A significant loss of BMD usually

represents nonresponse or a suboptimum response to therapy, suggesting the need for reevaluation of treatment and evaluation for secondary causes of osteoporosis. Always compare BMD (g/cm<sup>2</sup>), not T-score or Z-score when assessing changes in BMD. In order to determine whether an apparent change in BMD is statistically significant, the DXA facility must calculate the precision error and least significant change according to established guidelines (3).

Consider serial measurement of a bone turnover marker to evaluate efficacy of drug therapy. Bone resorption markers include urine and serum N-telopeptide, serum C-telopeptide, urine pyridinoline, and urine deoxypyridinoline, urine hydroxyproline; bone formation markers include serum osteocalcin, serum bone-specific alkaline phosphatase, and serum procollagen type 1 N-terminal propeptide. Bone turnover markers are biochemical byproducts of bone remodeling that provide some insight into the dynamic process of bone resorption and formation. In clinical trials, antiresorptive therapy is associated with a reduction in bone turnover markers and anabolic therapy is associated with an increase in bone turnover markers. However, due to “coupling” of resorption and formation due to “crosstalk” between osteoclasts and osteoblasts, markers of bone resorption and formation usually change in the same direction. Expert consensus suggests that markers of bone turnover provide potentially useful information to supplement follow-up BMD measurement, and the NOF suggests measurement of a bone turnover marker as a method for monitoring the effects of therapy (2). One way to use a bone marker to monitor therapy is to measure it at baseline before therapy and repeat about 3 months later, obtaining the specimen under identical circumstances each time. A significant decrease in a bone turnover marker

37. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *Vertebral Efficacy With Risedronate Therapy VERT. Study Group. JAMA.* 1999;282:1344-52.
38. Chesnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res.* 2004;19:1241-49.
39. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007;356:1809-22.
40. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* 2007;357:1799-809.
41. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361:756-65.
42. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene - Results from a 3-year randomized clinical trial. *JAMA.* 1999;282:637-45.

with antiresorptive therapy or a significant increase in a bone turnover marker with anabolic therapy is suggestive of a beneficial effect of therapy and predictive of a subsequent BMD response. There is high preanalytic and analytic variability with bone markers, so that the change must often be large to be considered significant (e.g., the least significant change for urinary N-telopeptide is about 40%).

If measurement of BMD or a bone turnover marker does not show the expected response, then evaluation for contributing factors should be considered and corrected if possible (49). It should be determined whether the patient is taking medication regularly and correctly (which is particularly important with the oral bisphosphonates) and whether calcium and vitamin D intake is sufficient. Examples of diseases, conditions, and medications that may result in a suboptimum response to therapy include malabsorption, immobilization, and glucocorticoid therapy. When the factors responsible for poor response cannot be corrected, a change may be necessary (e.g., changing an oral bisphosphonate to an injectable antiresorptive agent, or switching from an antiresorptive agent to teriparatide).

### When should consultation be considered for management?

After the diagnosis of osteoporosis is made, consider consultation if special expertise is needed for management of associated disorders. These may include hyperparathyroidism, hyperthyroidism, vitamin D deficiency or osteomalacia, hypocalciuria unresponsive to oral calcium supplementation, hypercalciuria, Cushing syndrome, glucocorticoid-induced osteoporosis, hypopituitarism, or hypogonadism in males. Elevated alkaline phosphatase levels or markedly elevated bone turnover markers suggest an underlying metabolic bone disease, such as Paget disease of bone, metastatic disease, or recent fracture, that would benefit from expert consultation.

Consider consultation with an osteoporosis specialist when routine therapy is not possible or effective, including significant bone loss after 1 to 2 years of drug therapy, when combination therapy for osteoporosis is being considered, or when the standard therapies have not been tolerated. Consultation is also required to manage patients with fractures, including vertebroplasty or kyphoplasty for painful acute spinal fractures resistant to medical therapy, or an orthopedist when surgery may be required.

43. Chesnut CH, III, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med.* 2000;109:267-76.
44. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-41.
45. Lewiecki EM. Risk communication and shared decision making in the care of patients with osteoporosis. *J Clin Densitom.* 2010;13:335-45.
46. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007;22:1479-89.
47. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2010;25:2267-94.

**Treatment...** Patients at high risk for fracture, identified by BMD testing and clinical risk factors, are most likely to benefit from medication to reduce fracture risk. The NOF suggests treating postmenopausal women and men 50 years and older who have a T-score of  $-2.5$  or less at the lumbar spine or femoral neck, those who have had a hip or vertebral fracture, and those with a T-score between  $-1.0$  and  $-2.5$  who have a 10-year FRAX probability of major osteoporotic fracture  $\geq 20\%$  or a 10-year probability of hip fracture  $\geq 3\%$ . The selection of the best drug for the patient should be individualized according to clinical circumstances and considering factors that include the magnitude of fracture risk, comorbid conditions, and patient preference. All patients should be counseled on the importance of a healthy lifestyle and adequate intake of calcium and vitamin D. Monitoring for treatment effect with BMD testing and/or bone turnover markers assures that the patient is responding to therapy. Patients with suboptimum response should be evaluated for factors contributing to poor skeletal health and considered for a change in therapy.

### CLINICAL BOTTOM LINE

### What should patients be taught?

Patients should be informed about the association between low BMD and fracture risk. They should understand the importance of adequate calcium and vitamin D intake, as the maximum beneficial effects of all drugs for osteoporosis are seen in calcium- and vitamin D-replete persons. The role of weight-bearing exercise in maintaining bone mass should be explained. Patients should be told of the importance of avoiding or changing certain habits that may detrimentally affect bone mass, such as smoking and excess alcohol consumption. The benefit and potential risks of pharmacologic agents for the prevention and treatment of osteoporosis should be discussed. In patients treated with oral bisphosphonates, precise dosing instructions need to be followed.

### How can falls and bone fractures be prevented?

Risk factor modification is a key element in successful management

of patients with osteoporosis. Home safety evaluations, which can be done by occupational therapists or home health care services, may be helpful to assess for potential physical or structural problems that might cause falls. Concerns, such as slippery floors and impeded pathways, should also be identified and corrected.

*Falls in the elderly can be reduced with a comprehensive fall-reduction program, including home safety evaluations, exercises that improve strength and balance, and reduction in the use of drugs that impair cognitive abilities (50). Sources of patient education may include one-on-one instruction; community resources; consultation with nutritionists, physical therapists, and exercise physiologists; handouts; and the Internet. After starting therapy, patient education through regular contact with a health care professional has been shown to improve adherence to therapy and be associated with a greater increase in BMD compared with no monitoring (51).*

**Patient Education...** A well-informed patient is best equipped to make appropriate decisions on lifestyle and nutrition to optimize skeletal health. Understanding the consequences of osteoporosis and the balance of benefits and risks of pharmacologic therapy may lead to improved clinical outcomes.

## CLINICAL BOTTOM LINE

### What measures do U.S. stakeholders use to evaluate the quality of osteoporosis care?

The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of performance measures developed and maintained by the National Committee for Quality Assurance (NCQA), an independent 501(c)(3) nonprofit organization. HEDIS measures are widely used in managed care and by the Centers for Medicare & Medicaid Services to improve health care quality in the United States. The HEDIS measures for osteoporosis

are the number of Medicare women aged 65 years and older who report ever having a BMD test for osteoporosis (“testing rate”) and the percentage of women aged 67 years and older who had a BMD test or prescription for a drug to treat or prevent osteoporosis within 6 months of a fracture. (“treatment rate”). The NCQA reported an osteoporosis testing rate of 68.0% and a treatment rate of 20.7% for 2009 (52), suggesting that there is much room for improvement in reducing the burden of osteoporotic fractures.

## Practice Improvement

48. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296:2927-38.
49. Lewiecki EM. Nonresponders to osteoporosis therapy. *J Clin Densitom*. 2003;6:307-14.
50. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2009;CD007146.
51. Clowes JA, Peel NF, 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;89:1117-23.]
52. National Committee for Quality Assurance. The state of health care quality. Accessed at [www.ncqa.org/portals/0/state%20of%20health%20care/2010/SOHC%202010%20-%20Full2.pdf](http://www.ncqa.org/portals/0/state%20of%20health%20care/2010/SOHC%202010%20-%20Full2.pdf) on 7 March 2011.

53. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.
54. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2008.

### What do professional organizations recommend regarding care?

Osteoporosis is diagnosed according to WHO criteria (53) based on BMD measurement by DXA using quality standards established by the ISCD (3). A T-score of  $-2.5$  or less at the lumbar spine, femoral neck, total hip, or 33% radius (if measured) in a postmenopausal woman or man aged 50 years or older is consistent with a diagnosis of osteoporosis. The 10-year probability of hip fracture and major osteoporotic fracture can be estimated using the WHO fracture risk algorithm, FRAX (6), with input that includes the patient's age, sex, height, weight, information on 7 clinical risk factors for fracture, and

femoral neck BMD, if available. Evidence-based treatment recommendations have been developed for the United States by the NOF (54). Treatment with pharmacologic agents should be considered in a postmenopausal woman or man aged 50 years and older with a T-score of  $-2.5$  or less at the femoral neck or lumbar spine, a history of fracture of the hip or spine, or a T-score between  $-1.0$  and  $-2.5$  with a FRAX 10-year probability of hip fracture that is 3% or greater or a 10-year probability of major osteoporotic fracture that is 20% or greater. Treatment decisions for individual patients should be based on all available clinical information in addition to clinical practice guidelines.

**Practice Improvement...** Despite the availability of excellent clinical tools to assess fracture risk and widely available drugs to reduce fracture risk, osteoporosis remains underdiagnosed and undertreated. Familiarity with clinical practice guidelines for the evaluation and treatment of osteoporosis can lead to improved clinical outcomes with reduced burden of osteoporotic fractures.

### CLINICAL BOTTOM LINE

## In the Clinic Tool Kit

### Osteoporosis

#### PIER Module

<http://pier.acponline.org/physicians/diseases/d297/d297.html>

PIER module on osteoporosis. PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

#### Patient Information

<http://pier.acponline.org/physicians/diseases/d297/d297-pi.html>

Patient information that appears on the following page for duplication and distribution to patients.

[www.effectivehealthcare.abrg.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=92](http://www.effectivehealthcare.abrg.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=92)

A consumer guide for postmenopausal women from the Agency for Healthcare Research and Quality, released in 2008.

#### Clinical Guidelines

[www.annals.org/content/149/6/404.full](http://www.annals.org/content/149/6/404.full)

Clinical practice guideline for the pharmacologic treatment of low BMD or osteoporosis to prevent fractures from the ACP.

[www.aace.com/sites/default/files/OsteoGuidelines2010.pdf](http://www.aace.com/sites/default/files/OsteoGuidelines2010.pdf)

Clinical practice guideline for the diagnosis and treatment of postmenopausal osteoporosis from the American Association of Clinical Endocrinologists.

#### Diagnostic Tests and Criteria/Quality-of-Care Guidelines

[www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteors.htm](http://www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteors.htm)

Recommendations for screening for osteoporosis in postmenopausal women, from the US Preventive Services Task Force.

[www.qualitymeasures.abrg.gov/search/search.aspx?term=osteoporosis](http://www.qualitymeasures.abrg.gov/search/search.aspx?term=osteoporosis)

Guidelines available from the National Quality Measures Clearinghouse.

In the Clinic

# THINGS YOU SHOULD KNOW ABOUT OSTEOPOROSIS

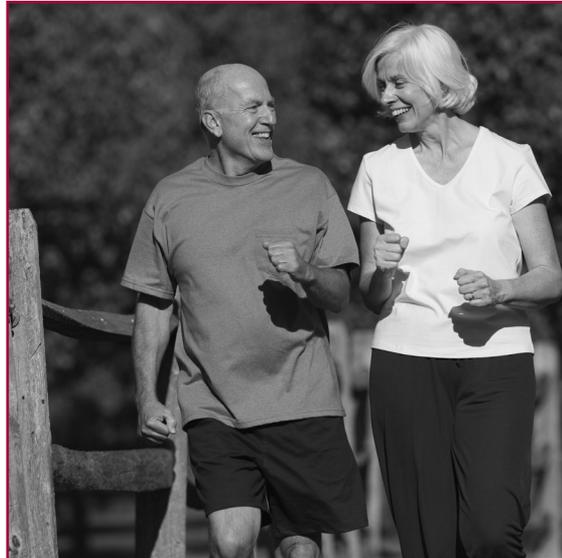
In the Clinic  
Annals of Internal Medicine

## What is osteoporosis?

- Osteoporosis is a disease that makes bones weak and susceptible to fractures (broken), even when there has been no trauma or only a low level of trauma that would not cause a normal bone to break.
- Osteoporosis can be diagnosed before a fracture occurs with a bone mineral density (BMD) test using dual-energy x-ray absorptiometry (DXA).
- If a low-trauma fracture occurs in a postmenopausal woman or a man aged 50 or older, a presumptive diagnosis of osteoporosis may be made regardless of BMD.

## Why is it important?

- About 44 million Americans have osteoporosis or low bone mass (osteopenia) that could lead to low-trauma fractures.
- A 50-year-old white woman has a 50% chance of having an osteoporotic fracture in her remaining lifetime, and a man the same age has about a 20% chance.
- The risk for osteoporotic fractures is high in whites, low in blacks, and intermediate in Hispanics and Asians, although individuals of any ethnicity can develop osteoporosis and have fractures.
- Osteoporotic fractures can result in chronic pain, disability, loss of independence, and increased risk for death.



## How is it treated?

- All adults should take care to be physically active and maintain an adequate amount of calcium and vitamin D.
- A daily intake of about 1200 mg calcium in the diet plus supplements, if needed, and vitamin D 800 to 1000 IU is recommended.
- In the frail elderly, fall prevention measures include an evaluation of the home to look for ways to reduce the risk for falls, leg-strengthening exercises, and balance training.
- Medications are helpful to reduce fracture risk when it is high.

## For More Information

[www.nof.org](http://www.nof.org)  
National Osteoporosis Foundation: information, education, and support for people with osteoporosis in the United States.

[www.iof.org](http://www.iof.org)  
International Osteoporosis Foundation: information and education on osteoporosis from a worldwide perspective.

[www.iscd.org](http://www.iscd.org)  
International Society for Clinical Densitometry: information on the role of high quality BMD testing in the care of people with osteoporosis.

**ACP**  
AMERICAN COLLEGE OF PHYSICIANS  
INTERNAL MEDICINE | *Doctors for Adults*®

1. A 72-year-old man is evaluated for a 2-week history of low back pain. The patient has a history of alcoholism but stopped drinking alcohol 10 years ago. He also has stage 3 chronic kidney disease and a 50-pack-year smoking history. Current medications are hydrochlorothiazide, ramipril, and a multivitamin.

On physical examination, vital signs are normal. Lumbar lordosis, decreased mobility and spasm of the paravertebral muscles, and tenderness to palpation at L4-L5 are noted. Neurologic screening examination findings are normal.

Laboratory studies showed the following: calcium, 9.0 mg/dL (2.25 mmol/L), creatinine, 2.1 mg/dL (185.6 μmol/L), phosphorus, 3.2 mg/dL (1.0 mmol/L), parathyroid hormone, 50 pg/mL (50 ng/L), testosterone, 400 ng/dL (13.9 nmol/L), 25-hydroxy vitamin D, 34 ng/mL (85 nmol/L), estimated glomerular filtration rate, 40 mL/min/1.73 m<sup>2</sup>.

A radiograph of the lumbosacral spine shows a compression fracture of L4. A dual-energy x-ray absorptiometry scan shows a T-score of -3.0 in the lumbosacral spine and -3.2 in the left hip.

Which of the following is the best treatment for this patient?

- A. Alendronate
- B. Calcitonin
- C. Teriparatide
- D. Testosterone

2. A 58-year-old man is evaluated for possible osteoporosis. He recently underwent removal of a 1.6-cm nonfunctioning pituitary adenoma and was placed on levothyroxine therapy.

On physical examination, vital signs are normal. Examination of the neck reveals no palpable goiter. The testes are small and soft. Laboratory studies showed the following: follicle-stimulating hormone, <1.0 mU/mL (1.0 U/L), luteinizing hormone, <1.0 mU/mL (1.0 U/L), testosterone, 50 ng/dL (1.7 nmol/L),

thyroxine (t<sub>4</sub>), free, 1.2 ng/dL (15.5 pmol/L). A dual-energy x-ray absorptiometry scan shows T-scores of -2.5 in the left hip and -2.6 in the lumbar spine.

In addition to calcium and vitamin D supplementation, which of the following is the most appropriate initial treatment for this patient?

- A. Bromocriptine
- B. Calcitonin
- C. Decreased dosage of levothyroxine
- D. Testosterone

3. A 62-year-old woman is evaluated during a follow-up visit for hypertension. She has no complaints and is monogamous with her husband of 35 years. Her only current medication is hydrochlorothiazide. On physical examination, blood pressure is 136/72 mm Hg and weight is 62 kg (136 lb). Physical examination is normal. Total cholesterol is 188 mg/dL (4.87 mmol/L) and HDL cholesterol is 54 mg/dL (1.40 mmol/L). She received an influenza vaccination 3 months ago and a herpes zoster vaccination 1 year ago. Her last Pap smear was 14 months ago and it was normal, as were the previous three annual Pap smears.

Which of the following is the most appropriate health maintenance option for this patient?

- A. Abdominal ultrasonography
- B. Dual-energy x-ray absorptiometry
- C. Pap smear
- D. Pneumococcal vaccine

4. A 70-year-old woman is evaluated for worsening gastroesophageal reflux disease with heartburn. She first noticed this symptom 1 month ago when she began taking alendronate, 70 mg orally once weekly, for osteoporosis. Current medications are alendronate, calcium, and ergocalciferol.

A dual-energy x-ray absorptiometry scan reveals a T-score of -3.0 in the lumbar spine and -2.5 in the left hip.

After the alendronate is discontinued, which of the following is now the most appropriate treatment for this patient?

- A. Calcitonin
- B. Intravenous ibandronate
- C. Intravenous zoledronate
- D. Raloxifene

5. A 72-year-old woman comes to the office for a follow-up evaluation of osteoporosis. She has a history of vertebral compression fractures. For the past 5 years, the patient has been taking oral formulations of elemental calcium, 1500 mg/d; ergocalciferol, 800 U/d; and alendronate, 70 mg once weekly. She is adherent to her therapy.

On physical examination, the patient appears frail. Vital signs are normal, and BMI is 19. There is obvious kyphosis. Mild tenderness in the region of the prior compression fractures is noted.

Laboratory studies showed the following: calcium, 9.5 mg/dL (2.4 mmol/L), phosphorus, 3.8 mg/dL (1.2 mmol/L), parathyroid hormone, 33 pg/mL (33 ng/L), thyroid-stimulating hormone, 1.8 μU/mL (1.8 mU/L), 25-hydroxy vitamin D, 35 ng/mL (87 nmol/L), urine calcium, 315 mg/24 h (7.9 mmol/24 h). Results of a bone mineral density study show T-scores of -3.8 in the spine and -3.7 in the hip, compared with scores obtained 3 years ago of -3.4 and -3.3, respectively.

Which of the following is the best next step in management?

- A. Add teriparatide
- B. Change to high-dose ergocalciferol
- C. Discontinue the alendronate and start teriparatide
- D. Substitute intravenous zoledronate for the alendronate

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at [http://www.acponline.org/products\\_services/mksap/15/?pr31](http://www.acponline.org/products_services/mksap/15/?pr31)). Go to [www.annals.org/intheclinic/](http://www.annals.org/intheclinic/) to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.