Diagnosis, Screening, Prevention, and Treatment of Osteoporosis

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Osteoporosis is the most common bone disease in humans and affects both men and women. The clinical and public health implications of the disease are substantial because of the mortality, morbidity, and cost of medical care associated with osteoporotic fractures. Osteoporosis is diagnosed on the basis of a low-impact or fragility fracture or low bone mineral density, which was best assessed by central dual-energy x-ray absorptiometry. Both nonpharmacological therapy (calcium and vitamin D supplementation, weight-bearing exercise, and fall prevention) and pharmacological treatments (antiresorptive and anabolic agents) may be helpful in the prevention and treatment of osteoporosis. Therefore, clinicians need to be vigilant in instituting primary prevention measures for those at high risk for osteoporosis and in instituting treatment for patients diagnosed as having the disease either by screening or a history of fracture. This article provides an overview of the diagnosis, screening, prevention, and treatment of osteoporosis.

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BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; FDA = Food and Drug Administration; ICSI = Institute for Clinical Systems Improvement; NOF = National Osteoporosis Foundation

Osteoporosis is the most common bone disease in humans and affects both men and women, usually during or beyond the seventh decade of life. Among US women older than 50 years, 13% to18% meet current diagnostic criteria for osteoporosis, and an additional 37% to 50% meet criteria for osteopenia. For men of the same age, 3% to 6% meet criteria for osteoporosis, and 28% to 47% meet criteria for osteopenia.[1] Osteoporosis has clinical and public health implications because of the mortality, morbidity, and cost of medical care associated with osteoporotic fractures. Elderly persons constitute the fastest-growing age group in the world, and the annual number of osteoporotic fractures is predicted to increase considerably with the continued aging of this population in future decades. In the United States, about 1.5 million fractures are attributed to osteoporosis each year. Of this total, approximately half are vertebral fractures and one fifth each are hip, wrist, and other fractures,[2] Although therapy that can reduce the risk of osteoporotic fractures is available, osteoporosis often remains undiagnosed until a fracture occurs. In addition, patients with osteoporosis-related fractures often are not evaluated or treated for osteoporosis and sustain additional fractures. Therefore, clinicians need to be vigilant in instituting primary prevention measures for those at high risk for osteoporosis and in instituting treatment for patients diagnosed with the disease either by screening or a history of fracture. This article provides an overview of the diagnosis, screening, prevention, and treatment of osteoporosis.

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A question-and-answer section appears at the end of this article.

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DEFINITION

Osteoporosis is a chronic, progressive disease characterized by low bone mass, microarchitectural bone deterioration, and decreased bone strength that lead to increased bone fragility and a consequent increase in fracture risk.[3] Osteoporosis may be classified as either primary or secondary. Primary osteoporosis is bone loss associated with the aging process in both women and men and with the loss of gonadal function in men. In primary osteoporosis, the rate of activation of skeletal bone remodeling units is normal, but the filling of bone resorption pits is incomplete. Secondary osteoporosis is bone loss caused by a variety of chronic medical conditions, medications, and nutritional deficiencies. In most types of secondary osteoporosis, the rate of activation of skeletal bone remodeling units is increased at least initially, such that an increased proportion of the skeleton is undergoing remodeling at any one time. Some common secondary causes of osteoporosis and disease processes associated with the disorder are outlined in Table 1.

DIAGNOSIS

Before 1994, the diagnosis of osteoporosis required evidence of a fragility fracture. In 1994, the World Health Organization established operational definitions of osteoporosis and osteopenia in postmenopausal white women based on bone mineral density (BMD) (Table 2) to help researchers and clinicians classify degrees of bone loss. Expert opinion, based on literature review, suggests that the current World Health Organization definition of osteoporosis in postmenopausal white women can be applied to men as well.[5] In current clinical practice, osteoporosis is diagnosed on the basis of either a health outcome (low-impact or fragility fracture) or an intermediate outcome (low BMD). A low-impact fracture is one that occurs after a fall from standing height or less; a fragility fracture occurs spontaneously or with no trauma (cough, sneeze, sudden movement).

TABLE 1. **Common Secondary Causes of Disease Processes Associated With Osteoporosis***

Endocrine disorders
Cushing syndrome
Hypogonadism
Hyperthyroidism
Primary hyperparathyroidism
Rheumatologic disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Ankylosing spondylitis
Juvenile polyarticular arthritis
Malignancy
Multiple myeloma
Pharmacotherapy
Glucocorticoid excess
L-thyroxine overreplacement
Anticonvulsants (phenytoin or phenobarbital)
Lithium, aluminum
Cytotoxic drugs, immunosuppressants (cyclosporine A, tacrolimus)
Heparin (long-term)
Drugs causing hypogonadism (aromatase inhibitors, methotrexate, antimetabolite chemotherapy, depo-medroxyprogesterone acetate, and gonadotropin-releasing hormone agonists such as buserelin, leuprolide, and nafarelin)
Gastrointestinal disease
Chronic liver disease (especially primary biliary cirrhosis and primary sclerosing cholangitis)
Inflammatory bowel disease (particularly Crohn disease)
Celiac disease
Gastric bypass or gastrectomy
Renal insufficiency or failure
Miscellaneous causes
Vitamin D deficiency of any cause
Alcohol abuse
Anorexia nervosa, malnutrition
Movement disorders (Parkinson disease)
Amyloidosis
Acquired immunodeficiency syndrome, human immunodeficiency virus
Chronic obstructive pulmonary disease
Cerebrovascular accident
Multiple sclerosis
Prolonged bed rest or wheelchair bound from any cause

*For a more extensive list of causes, see Annotation Appendix A of the Institute for Clinical Systems Improvement guidelines.[4]

TABLE 2. **World Health Organization Definitions of Osteopenia and Osteoporosis in White Women[3]***

Normal	Hip BMD >1.0 SD below the young adult female reference mean† (T score above –1.0)
Osteopenia	Hip BMD between 1.0 and 2.5 SDs below the young adult female reference mean† (T score between –1.0 and –2.5)
Osteoporosis	Hip BMD ≥2.5 SDs below the young adult female reference mean† (T score at or below –2.5)
Severe osteoporosis or established osteoporosis	Hip BMD ≥2.5 SDs below the young adult female reference mean† in the presence of 1 or more fragility fractures

*Based on hip bone mineral density (BMD) measurements assessed with dual-energy x-ray absorptiometry.

†The young adult female reference mean is determined with use of the mean hip BMD from the National Health and Nutrition Examination Survey reference database of women aged 20-29 years.

Although multiple technologies are available for measurement of BMD, central dual-energy x-ray absorptiometry (DXA) of the hip (femoral neck or total hip) is the gold standard for diagnosing osteopenia or osteoporosis.[5,6] However, many experts, including the International Society for Clinical Densitometry, recommend using the lowest central DXA T score of posteroanterior lumbar spine, femoral neck, or total hip (or the 33% distal radius of the nondominant forearm, if measured) to make the diagnosis.[7] Dual-energy x-ray absorptiometric measurements of BMD at other sites (including the trochanter, Ward triangle, lateral lumbar spine, other forearm regions, heel, or total body) or with other technologies (calcaneal ultrasonography, peripheral DXA, quantitative computed tomography, single- or dual-photon radionuclide absorptiometry, or magnetic resonance imaging) may be useful for assessing risk of fracture, but they are not recommended for use in diagnosing osteoporosis.[6,7] If DXA measurements at different sites are considerably disparate, most clinicians would use the lowest BMD measurement.

Dual-energy x-ray absorptiometric measurement of bone density is noninvasive, accurate, reproducible, and predictive of short- and long-term fracture risk. The results are reported as a density measurement in gm/cm^2, in addition to T and Z scores. T scores represent the number of SDs from the mean bone density values in normal sex-matched young adults. The T score is used to make a diagnosis of normal bone density, osteoporosis, or osteopenia in postmenopausal women and in men age 50 years and older. Z scores represent the number of SDs from the normal mean value for age- and sex-matched control subjects. A Z score of –1.0 or lower (many experts suggest using a Z score of –2.0 or lower) may suggest the presence of a secondary cause of osteoporosis, although no definitive data support this hypothesis. Z scores are used preferentially to assess bone loss in premenopausal females and in men younger than age 50 years. A Z score of –2.0 or lower is defined as "below the expected range for age"; a Z score above –2.0 is "within the expected range for age."[7]

ROLE OF SCREENING

Osteoporosis is a disease in which screening of asymptomatic individuals may be beneficial because it has a long preclinical course before the onset of fracture and because of the availability of both a reliable test to establish the diagnosis and treatments that have been shown to reduce the risk of fractures. General consensus exists regarding the recommendation that osteoporosis screening with BMD measurements should be individualized, but how this individualized approach to screening should be achieved remains controversial.

TABLE 3. **National Osteoporosis Foundation Recommendations for Bone Mineral Density Measurements in Postmenopausal White Women[8]***

All women ≥65 y, regardless of additional risk factors
All postmenopausal women ≤65 y who have 1 or more additional risk factors (see below) for osteoporosis (other than being white, postmenopausal, and female)
Postmenopausal women of any age who present with fractures (to confirm diagnosis and determine disease severity)
Major risk factors
Personal history of fracture as an adult
History of fragility fracture in a first-degree relative
Low body weight (<127 lb)
Current smoking
Current or previous use of oral corticosteroid therapy for >3 mo
Additional risk factors
Impaired vision
Estrogen deficiency at an early age (<45 y)
Dementia
Poor health, frailty
Recent falls
Low calcium intake (lifelong)
Low physical activity
Alcohol in amounts of >2 drinks per day

*Criteria recommended for white postmenopausal women do not necessarily apply to women of other races, to premenopausal women, or to men.

Many national and organizational guidelines and systematic reviews have attempted to outline clinical criteria for screening individuals for osteoporosis. Disagreement among the published guidelines reflects, at least in part, variances in expert opinion and gaps in the available evidence to support these recommendations. Most guidelines recommend using risk factor assessment to help select patients for bone density testing, but because of inadequate data, no consensus exists about which risk factors are most important to consider. Several groups have suggested guidelines for BMD testing in postmenopausal women, the population group for which the most evidence is available.

In the United States, a commonly accepted guideline is that of the National Osteoporosis Foundation (NOF)[8] (Table 3). However, use of this guideline may result in more frequent testing because the risk factors listed are so common in this population. The US Preventive Services Task Force has also made recommendations regarding osteoporosis screening in postmenopausal women[9] (Table 4). These guidelines are conservative and formulated from evidence-based literature review. Unfortunately, they may not be useful clinically because they do not clearly address which postmenopausal women who are younger than 65 years should be tested and do not recommend screening any postmenopausal women younger than age 60 for any reason, even though women between menopause and age 60 experience rapid early postmenopausal bone loss.

TABLE 4. **Summary of US Preventive Services Task Force Recommendations for Osteoporosis Screening in Postmenopausal Women[9]**

All women ≥65 y
Women ≥60 y who are at increased risk for osteoporotic fractures. Exact risk factors are difficult to specify on the basis of available evidence. Body weight <70 kg is the single best predictor. Current nonuse of estrogen therapy is also predictive. Some evidence supports the use of individual risk factors (smoking, family history, alcohol or caffeine use, sedentary lifestyle, and low calcium and vitamin D intake) as a basis for identifying high risk in women <65 y
No studies have evaluated the optimal intervals for repeated screening. Because of limitations in the precision of testing, a minimum of 2 y is generally needed to reliably detect a major change in bone density. However, longer intervals may be adequate for repeated screening. The yield of screening is higher in older women. No data are available that indicate the appropriate age at which to stop screening

Although the NOF and US Preventive Services Task Force guidelines provide recommendations for postmenopausal women, they offer no recommendations for premenopausal women or for men. The Institute for Clinical Systems Improvement (ICSI) guidelines provide a reasonable (evidence- and expert opinion–based) summary of who should be screened according to pretest probability of fracture based on risk factors.[4] These guidelines may help clinicians determine which patients should undergo BMD testing. The ICSI guidelines incorporate the NOF recommendations in addition to recommendations for men and both premenopausal and postmenopausal women. Measurement of BMD is recommended for patients at high risk for future fractures, as outlined in Table 5.

TABLE 5. **ICSI Guidelines for BMD Testing in High-Risk Individuals***

1. Men or women with previous fragility fracture (spontaneous fracture or fracture after a fall from standing height or less)
2. Men or women currently or previously treated with >3 mo of glucocorticoid therapy at a dosage of ≥5 mg/d of prednisone
3. Men or women with radiographic osteopenia or vertebral fracture documented radiographically
4. All women >65 y
5. Postmenopausal women <65 y with at least 1 of the following additional risk factors
Low body weight (<127 lb or BMI ≤20)
Family history of fracture (any fracture in a first-degree relative that occurred after age 45 y)
Current smoker (>1 pack/d)
Not using HRT
Menopause before age 40 (surgical or natural)
Taking HRT for >10-15 y
6. Men or women with a chronic disease known to be associated with bone loss*
7. Premenopausal women with amenorrhea for >1 y
8. Men with hypogonadism for >5 y
9. Men or women with prolonged immobilization (bed rest or wheel chair bound for >1 year)
10. Men or women who have received solid organ or allogenic bone marrow transplants

*The most common causes are outlined in Table 1; for a more extensive list, see Annotation Appendix A of the ICSI guidelines.[4] BMD = bone mineral density; BMI = body mass index; HRT = hormone replacement therapy; ICSI = Institute for Clinical Systems Improvement.

How often should screening BMD testing be repeated? The US Preventive Services Task Force addressed this issue and reported no evidence for or against repeated screening.[10] However, estimations can be made based on the age-specific prevalence of osteoporosis and the precision of the bone density test used. In clinical practice, BMD is often measured at 2- to 3-year intervals for recently postmenopausal women because this age group has a higher rate of bone loss, at 5-year intervals for younger postmenopausal women after the immediate postmenopausal bone loss has stabilized, and at 2- to 5-year intervals for older women. No data support an appropriate age at which to stop screening.

Clinical guidelines help guide practice but should not replace clinical judgment and patient preferences. The final decision about when and how often to perform BMD testing is ultimately at the discretion of the physician and the patient.

LABORATORY TESTING FOR SECONDARY CAUSES

Among men, 30% to 60% of osteoporosis cases are associated with secondary causes (most commonly hypogonadism, glucocorticoid use, and alcoholism); among perimenopausal women, more than 50% of cases are associated with secondary causes (most commonly hypoestrogenemia, glucocorticoid use, thyroid hormone excess, and anticonvulsant therapy). The prevalence of secondary conditions is thought to be lower in postmenopausal women, but the actual proportion is unknown.[10]

General consensus exists among osteoporosis specialists that a minimum screening laboratory profile should be considered for all patients who are diagnosed as having osteoporosis. However, no consensus exists regarding which tests should be done. Many experts have also suggested that patients who have osteoporosis and a Z score of less than –1.0 (some suggest using a Z score of less than –2.0) should have more extensive laboratory screening for secondary causes of osteoporosis. A diagnosis of osteoporosis in men should also prompt a thorough work-up for secondary causes regardless of their Z score because about half will have an identifiable cause for the bone loss. The ICSI guidelines provide recommendations regarding laboratory testing in patients with newly diagnosed osteoporosis[4] (Table 6).

TABLE 6. **ICSI Guidelines for Laboratory Testing in Patients With Newly Diagnosed Osteoporosis[4]***

Laboratory test	Rationale
Z score above –1.0 (patients less likely to have secondary causes of osteoporosis)	
Serum creatinine	Renal failure is associated with secondary hyperparathyroidism
Liver function tests	Intrinsic liver diseases and cholestatic disorders are associated with multifactorial causes of increased risk of osteoporosis
Serum calcium	Increased in patients with hyperparathyroidism and decreased in those with malabsorption or vitamin D deficiency
Alkaline phosphatase	Increased in patients with Paget disease of bone, prolonged immobilization, acute fractures, and other bone diseases
Serum phosphorus	Decreased in patients with osteomalacia
Thyroid studies (thyrotropin and thyroxine)	Hyperthyroidism-associated bone loss
Sedimentation rate or C-reactive protein	May indicate an inflammatory process or monoclonal gammopathy associated with bone loss)
Complete blood cell count	To evaluate for bone marrow malignancy, infiltrative processes (anemia, low WBC, or low platelets), or malabsorption (anemia, microcytosis, or macrocytosis)
Urinary calcium excretion	24-hour urinary calcium excretion on a high calcium intake diet screens for malabsorption and hypercalciuria—a correctable cause of bone loss; low 24-hour urinary calcium excretion suggests vitamin D deficiency, osteomalacia, or malabsorption due to small bowel disease such as celiac sprue
Serum 25-hydroxyvitamin D	To identify vitamin D deficiency
Serum intact (whole-molecule) PTH	Screening for hyperparathyroidism
Z score below –1.0 or premature osteoporotic fracture (patients at higher risk of having secondary causes of osteoporosis)	
All the above tests plus the following additional tests	
Serum testosterone (total and free)	Screening for hypogonadism in men; if abnormal, LH, FSH, and prolactin measurements may be indicated to determine the cause of the hypogonadism
Serum estradiol	Screening for hypogonadism in premenopausal or perimenopausal women; if abnormal, LH, FSH, and prolactin measurements may be indicated to determine the cause of the hypogonadism
Tissue transglutaminase antibodies	If gluten enteropathy is suspected clinically
24-hour urinary free cortisol and overnight dexamethasone suppression test	If hypercortisolemia is suspected
Serum and urine protein electrophoresis with immunoelectrophoresis as indicated	If monoclonal gammopathy is suspected

*FSH = follicle-stimulating hormone; ICSI = Institute for Clinical Systems Improvement; LH = luteinizing hormone; PTH = parathyroid hormone; WBC = white blood cell count.

The cost-effectiveness of testing for secondary causes of osteoporosis is unknown because cost-effectiveness analyses have yet to be performed. In a chart review study, Tannenbaum et al[11] examined this issue in perimenopausal and postmenopausal women and found that a testing strategy consisting of 24-hour urinary calcium, serum calcium, and serum parathyroid hormone determinations in all women and serum thyrotropin measurements in women receiving thyroid replacement therapy would be sufficient to diagnose secondary causes of osteoporosis in 86% of women; adding 25-hydroxyvitamin D would diagnose secondary causes in up to 98%. However, this study was observational and small. More recently, in a secondary analysis of data collected as part of the Fracture Intervention Trial that included 15,316 postmenopausal women, Jamal et al[12] reported that the prevalence of abnormal test results in postmenopausal women with and without osteoporosis was similar, with the exception of low thyrotropin. These authors concluded that routine laboratory testing (other than thyrotropin measurements) in otherwise healthy women with osteoporosis was not useful.

Clearly, more research is needed in this area, especially in premenopausal and perimenopausal women and in men because the prevalence of secondary causes of osteoporosis in these groups is high. Until more cost-effectiveness data are available, it is reasonable to follow the strategy outlined in the ICSI guidelines (Table 6) for premenopausal or perimenopausal women, for postmenopausal women with comorbidities, and for men. For otherwise healthy postmenopausal women who have no clinical history or physical examination finding suggestive of a secondary cause of osteoporosis, it may be reasonable to only obtain a serum thyrotropin level.

Importantly, the aforementioned recommendations should be used only to direct testing for individuals who are asymptomatic or do not have clinical evidence of secondary osteoporosis on history and physical examination. If a specific secondary cause of osteoporosis is suspected on the basis of the history and physical examination findings, further directed testing is indicated.

NONPHARMACOLOGICAL THERAPY FOR PREVENTION AND TREATMENT OF BONE LOSS

Calcium and Vitamin D

Calcium absorption normally decreases with advancing age. In addition, aging is associated with decreasing serum 1,25-dihydroxyvitamin D levels, less sun exposure, and reduced skin capacity for vitamin D production. Supplementation of calcium and vitamin D should be considered in all elderly patients if dietary intake and sun exposure are inadequate to meet recommended targets.

Calcium supplementation may prevent bone loss or even mildly increase BMD,[13,14] and some data suggest that it may minimally reduce fracture risk.[15] However, for patients with osteoporosis, calcium supplementation should be used as an adjunct to other pharmacological interventions rather than as monotherapy. The National Institutes of Health consensus conference guidelines[16] suggest that women should optimize their elemental calcium intake to 1000 mg/d until menopause and increase it to 1500 mg/d thereafter. Men should optimize their elemental calcium intake to 1000 mg/d until age 65, then increase it to 1500 mg/d.

The preferred source of calcium is foods such as dairy products. Some dietary sources of calcium include yogurt (400 mg per cup), milk (300 mg per cup), calcium-enriched orange juice (300 mg per cup), cheese (150-180 mg/oz), and canned salmon with bones (180 mg per 3 oz). Calcium supplements are an alternative means by which optimal calcium intake can be reached in those who cannot meet this need by diet alone. Numerous calcium supplements are available in a variety of salts that can be used to supplement dietary calcium intake. The most commonly used calcium supplements are calcium carbonate or calcium citrate. Factors to consider in selecting an agent include absorption, convenience, and cost. Calcium absorption is generally maximal at individual doses of 500 mg of elemental calcium. Calcium carbonate contains 40% elemental calcium, requires stomach acid for digestion and absorption, and is the least expensive option. It should be taken with meals in doses of no more than 500 mg of elemental calcium at a time. Calcium citrate contains 21% elemental calcium, does not require stomach acid for digestion, and is more bioavailable but is more expensive than calcium carbonate. Calcium citrate can be taken with or without food in doses of no more than 500 mg of elemental calcium at a time. Calcium citrate is the preferred calcium supplement for patients who are hypochlorhydric or achlorhydric (including those taking gastric acid–inhibiting drugs) and for patients with a history of kidney stones. The most common adverse effects of all calcium supplements are constipation, bloating, and gas; however, these adverse effects may be less frequent with calcium citrate. Patients taking medications whose absorption may be impaired by calcium (ie, levothyroxine, fluoroquinolones, angiotensin-converting enzyme inhibitors) should also be advised to avoid taking calcium supplements within several hours of taking these medications.

Vitamin D supplementation may prevent bone loss or mildly increase BMD[17] and modestly reduces vertebral and nonvertebral fracture risk in vitamin D–deficient individuals.[15,18] A recent meta-analysis concluded that oral vitamin D supplementation of 700 to 800 IU/d appears to reduce the risk of hip and nonvertebral fractures in ambulatory or

institutionalized elderly persons, whereas a dose of 400 IU/d was insufficient for fracture prevention.[19] Sufficient vitamin D intake is necessary to maintain circulating serum levels of 1,25-dihydroxyvitamin D adequate to stimulate calcium absorption; therefore, a combination supplement containing both calcium and vitamin D is preferred if dietary intake is inadequate. Dietary sources of vitamin D include vitamin D–fortified milk or orange juice (400 IU per quart) and cereals (40-50 IU per serving), egg yolks, saltwater fish, and liver. Some calcium supplements and most multivitamin tablets also contain vitamin D. An intake of 400 to 600 IU of vitamin D per day is recommended by the National Academy of Sciences for all adults older than age 50. The NOF recommends 800 IU/d for those at risk of deficiency, such as elderly, chronically ill, housebound, or institutionalized individuals.

Weight-Bearing Exercise

Weight-bearing exercise appears to be effective in maintaining or increasing bone density at the lumbar spine and hip in postmenopausal women, but currently, no evidence suggests that it decreases fractures.[20] Recommendations include weight-bearing exercise in the form of walking, mild- to moderate-impact aerobics, and resistance exercises as tolerated. Regular exercise also increases muscle mass and strength, improves balance and coordination, and has been shown to reduce the risk of falls by about 25% in frail elderly persons.[21]

Fall Prevention

Randomized clinical trials have supported the value of assessing risk factors for falls in elderly patients and making appropriate interventions for those at high risk.[22] Risk factors include visual impairment, cognitive impairment, poor balance or gait, neuromuscular and musculoskeletal disabilities, muscle weakness, postural hypotension, multiple medications, and environmental hazards. Interventions for modifiable risk factors should include physical therapy to improve strength and balance, gait aids if needed, prevention or treatment of hypotension, and avoidance of medications that may potentially alter mental status or gait stability. Elimination of environmental hazards in the home is also helpful in preventing falls. This includes recommending shoes with nonskid soles, placing nonslip mats under area rugs, removing any nonessential throw rugs in the home or clutter on the floors, and installing grab bars in the tub, shower, and toilet areas, sturdy stairway railings, and night-lights. In a recent meta-analysis, vitamin D supplementation was reported to reduce the risk of falls among ambulatory or institutionalized older individuals with stable health by more than 20%.[23]

PHARMACOLOGICAL INTERVENTIONS FOR PREVENTION AND TREATMENT OF BONE LOSS

Treatment thresholds for osteoporosis are not the same as diagnostic thresholds, although some experts have recommended that they should be. In the United States, most experts agree on the treatment thresholds outlined by the NOF,[24] which recommends that the following individuals be considered for pharmacological intervention: (1) patients with a BMD T score below –2.0, (2) patients with a BMD T score below –1.5 if additional risk factors are present (previous fracture as an adult, history of fragility fracture in a first-degree relative, body weight <57 kg, current smoking, use of oral corticosteroid therapy for >3 months), and (3) any patient with a previous vertebral or hip fracture.

Pharmacological interventions with Food and Drug Administration (FDA) approval for treatment of osteoporosis should be recommended first. These include the oral bisphosphonates (alendronate, risedronate, and ibandronate), raloxifene, nasal calcitonin, and teriparatide. The FDA has withdrawn approval of estrogen or hormone therapy for treatment of osteoporosis but has continued approval of their use for osteoporosis prevention in selected postmenopausal women.

The primary goal of pharmacological therapy in patients with osteoporosis is to reduce the risk of future fracture, not just increase bone density. Currently, the pharmacological agents available for treatment of osteoporosis fall into 1 of 2 categories: antiresorptive agents or anabolic agents. All the currently available drugs except teriparatide are antiresorptive agents. These agents reduce bone resorption more than promote bone formation and thereby suppress bone turnover and loss, whereas anabolic agents stimulate bone formation more than reduce bone resorption. Table 7 summarizes the currently available FDA-approved medications for the prevention and/or treatment of osteoporosis.

No head-to-head clinical trials have compared the fracture efficacy of the antiresorptive agents, and only a few head-to-head clinical trials have compared the bone density effects of these agents. Most studies with fracture end points have involved postmenopausal women. In short-term clinical trials, alendronate increased BMD more than did raloxifene or calcitonin and produced a slightly greater increase than risedronate. Evidence from the current literature suggests that the antiresorptive therapies (including bisphosphonates, raloxifene, calcitonin, and estrogen) reduce vertebral fracture risk by 30% to 50%. Hip fracture reduction has been shown consistently with only some of the oral bisphosphonates (alendronate and risedronate) and with hormone therapy.[25] However, because the efficacy of the oral bisphosphonates in reducing hip fracture risk has

TABLE 7. **Agents Currently Approved by the Food and Drug Administration for Prevention and Treatment of Osteoporosis**

Drug/dose	Cost*	Indications
Alendronate		
P: 5 mg/d; 35 mg/wk	$72	P, T: Postmenopausal women with osteoporosis
T: 10 mg/d; 70 mg/wk		T: Men with osteoporosis
		Glucocorticoid-induced osteoporosis (women or men)
Risedronate		
P, T: 5 mg/d; 35 mg/wk	$71	P, T: Postmenopausal women with osteoporosis
		Glucocorticoid-induced osteoporosis (women or men)
Ibandronate		
P, T: 2.5 mg/d; 150 mg/mo	$76	P, T: Postmenopausal women with osteoporosis
Raloxifene		
P, T: 60 mg/d	$85	P, T: Postmenopausal women with osteoporosis
Calcitonin nasal spray		
T: 200 IU/d	$93	T: Postmenopausal women with osteoporosis
Estrogen		
P: Multiple formulations	$32-$41	P: Postmenopausal women with osteoporosis
Teriparatide		
T: 20 μg/d injection	$590	T: Postmenopausal women with osteoporosis
		Men with primary or hypogonadal osteoporosis

*Approximate monthly cost from www.drugstore.com (accessed August 1, 2005). P = prevention; T = treatment.

been shown in osteoporotic patients or subgroups of osteoporotic patients in these trials, many experts suggest that oral bisphosphonates be considered as first-line therapy for patients with established osteoporosis (those with T scores lower than –2.5 and prevalent vertebral fractures).

Bisphosphonates

Bisphosphonates block bone resorption by inhibiting osteoclast activity and are currently the most potent oral antiresorptive agents available for prevention or treatment of osteoporosis. Only 3 bisphosphonates are currently FDA-approved for osteoporosis treatment and prevention: alendronate, risedronate, and ibandronate. The recommended doses and FDA indications for use are summarized in Table 7. Intravenous bisphosphonates, including pamidronate and zoledronic acid, are not FDA-approved for prevention or treatment of osteoporosis but are occasionally used off-label for patients who cannot tolerate oral bisphosphonates. Strong clinical trial evidence supports the use of alendronate, risedronate, and ibandronate for preventing fractures in women with postmenopausal osteoporosis or osteopenia.[26,27] These agents have been shown to reduce vertebral and hip fractures by 50% to 60% in postmenopausal women.[28-30] Clinical trial evidence also supports the use of alendronate for preventing fractures in men with osteoporosis.[31]

For all oral bisphosphonates, patients should be instructed to take each tablet with 6 to 8 ounces of plain water first thing in the morning and at least 30 minutes before ingesting the first meal, beverage, or medication of the day. Patients should not recline for at least 30 minutes (60 minutes with ibandronate) to reduce the potential for esophageal injury. If symptoms of esophageal disease (difficult or painful swallowing, retrosternal pain, new or worsening heartburn) or severe musculoskeletal pain develops, discontinuation may be appropriate. Rarely, patients may develop jaw osteonecrosis or eye inflammation with oral or intravenous bisphosphonates. However, if one oral bisphosphonate is not tolerated, occasionally an alternative oral bisphosphonate is. Oral bisphosphonates are contraindicated in patients with hypocalcemia, hypersensitivity to bisphosphonates, renal insufficiency (creatinine clearance <30-35 mL/min), or esophageal irritation or stricture. Oral bisphosphonates should be used cautiously in patients who have difficulty swallowing or severe gastroesophageal reflux and those who have undergone gastric bypass or are receiving long-term anticoagulant therapy.

Raloxifene

Raloxifene is a selective estrogen receptor modulator that is approved for both the prevention and the treatment of postmenopausal osteoporosis at a dose of 60 mg/d. It has been shown to decrease vertebral fractures by about 50%, but because of inadequately powered trials, no evidence is currently available on hip fracture reduction.[26,32]

Raloxifene selectively interacts with estrogen receptors, exerting an estrogen agonist effect in some areas (bone and lipid metabolism) while acting as an estrogen antagonist in others (breast and uterus). Because of this selective effect on estrogen receptors, raloxifene potentially has the added benefits of breast cancer risk reduction and cardiovascular disease prevention, although this has not yet been shown

definitively in clinical trials. Raloxifene decreases total and low-density lipoprotein cholesterol but has no effect on high-density lipoprotein cholesterol. Common adverse effects include increased risk of venous thromboembolism and increased vasomotor symptoms. Raloxifene is contraindicated in patients with a history of venous thromboembolic events and should not be recommended for premenopausal women or women concurrently using estrogen replacement therapy. Although clinical trial evidence suggests that raloxifene may reduce breast cancer risk, its use in breast cancer patients is not recommended at this time.

Calcitonin

Salmon calcitonin nasal spray is FDA-approved for the treatment of osteoporosis at a dose of 200 IU in alternating nostrils each day. It inhibits bone resorption by osteoclasts, thereby preventing bone loss and vertebral fractures, but it has not been shown to reduce nonvertebral or hip fractures.[33,34] This drug may also decrease the pain associated with acute or subacute vertebral fractures. There are no contraindications to calcitonin use other than hypersensitivity to the drug; common adverse effects include nasal symptoms and rhinitis in about 12% of patients. Because of the availability of other medications that have better efficacy in fracture reduction, calcitonin is not considered first-line treatment for osteoporosis.

Estrogen / Hormone therapy

The role of hormone therapy in the prevention and treatment of osteoporosis remains controversial. The US National Institutes of Health–funded Women's Health Initiative trial showed that estrogen alone,[35] or in combination with progesterone,[36] decreased bone turnover, bone loss, and fractures. Combination hormone therapy is associated with a mildly increased absolute risk of serious adverse events, including coronary heart disease, stroke, venous thromboembolism, and breast cancer[36]; estrogen therapy alone also has been shown to be associated with an increased risk of stroke and venous thromboembolism but does not appear to be associated with an increase in coronary heart disease or invasive breast cancer.[35] In the United States, hormone therapy is approved only for the prevention, not treatment, of osteoporosis. The revised FDA guidelines recommend that approved nonestrogen products be considered for prevention of osteoporosis; however, if hormone therapy is used, it is recommended in doses as low as possible for as short a time as possible. Nevertheless, some experts believe that estrogen therapy is still the first-line therapy for osteoporosis prevention in younger women with surgical menopause who have no contraindications to its use. In addition, some experts advocate the short-term use (5-7 years) of combination hormone therapy in the immediate postmenopausal years for the prevention of osteoporosis (and often for the treatment of hot flashes) in women who have no contraindications to its use.

Teriparatide

Recombinant human parathyroid hormone analogues are potent bone anabolic agents that increase bone turnover (formation more than resorption). Teriparatide is the first anabolic drug approved for treatment of osteoporosis. It is FDA-approved for the treatment of osteoporosis in postmenopausal patients with severe bone loss who are at high risk for fracture[37] and for the treatment of hypogonadal or primary osteoporosis in men at high risk for fracture.[38] This drug increases bone density, thereby reducing vertebral fractures by 65% and nonvertebral fractures by 53%. The reduction in vertebral fracture risk continues for at least 18 months after therapy is discontinued.[39] Teriparatide may potentially be used in combination or in sequence with antiresorptive agents but is not yet approved for such use (see Combination Therapy section).

Teriparatide is given as a once-daily 20-μg subcutaneous injection for a maximum duration of 2 years. Adverse effects include light-headedness, dizziness, nausea, arthralgias, leg cramps, and occasionally a postinjection increase in serum calcium level. The risk of postinjection hypercalcemia is insufficient to warrant monitoring of serum calcium levels during treatment. A "black box warning" indicates that teriparatide produced an increased incidence of osteosarcoma in rats and that it should not be used in patients with a history of bone malignancy, Paget disease of bone, unexplained hypercalcemia, or skeletal radiation exposure or those younger than 18 years. Its use is best reserved for men or postmenopausal women with severe bone loss and preexisting osteoporotic fractures. Teriparatide should also be considered for individuals at high risk for fractures (T scores less than –3.5), even in the absence of preexisting fracture. In addition, teriparatide is an alternative for patients who are unable to tolerate oral bisphosphonates.

Combination Therapy

To date, no studies of combination therapy have had sufficient power to assess its effects on fracture outcomes. However, risedronate and alendronate, as well as calcitonin, have been shown to have an additive effect of increasing BMD when combined with hormone replacement therapy.[40] Teriparatide used in combination with alendronate has been reported to be less effective in increasing bone density than teriparatide alone in postmenopausal women[41] and in men.[38] Combination treatment with raloxifene and teriparatide may enhance the bone-forming ef-

fects of teriparatide in postmenopausal women,[42] and previous treatment with raloxifene does not blunt the expected teriparatide-induced BMD increases when these agents are used in sequence.[43] However, previous treatment with alendronate does prevent the expected teriparatide-induced BMD increase, particularly in the first 6 months.[43] For now, combination therapy is reserved for patients who have severe osteoporosis and should be initiated and monitored by a bone specialist.

FOLLOW-UP TESTING AFTER PHARMACOLOGICAL INTERVENTION

The need for routine follow-up BMD testing to monitor the effect of pharmacological intervention is still controversial. Serial measurements of BMD or markers of bone turnover are potentially useful methods to monitor response to therapy.

Specific evidence addressing the most efficient use of BMD measurements for monitoring treatment is lacking. Many experts have advocated a role for serial BMD measurements in monitoring the effects of therapy. If follow-up BMD testing is done, the results should be interpreted cautiously. Central DXA, although one of the most precise measurements used in medical practice, is still limited by the calculated precision of the machine and the expertise of the technician performing the test (coefficient of variation is between 1% and 2%, depending on the machine). Follow-up BMD testing should be performed on the same machine, preferably by the same technologist, to achieve the lowest precision error and greatest accuracy in documenting true change. An antiresorptive agent will generally affect trabecular bone (spine) earlier and to a greater degree than cortical bone (hip). Therefore, considerable improvement of BMD at the lumbar spine can be expected earlier than at the hip. Lack of bone-density response at the hip should not be interpreted as treatment failure if the repeat testing is done within 2 years. Stability or an increase in BMD indicates successful therapy.

In normal circumstances, bone is lost from the lumbar spine at a rate of approximately1% per year during late postmenopause. With treatment, bone loss should be notably decreased. However, the DXA machine is not precise enough to detect such small differences in BMD after a short interval. Therefore, a period of at least 2 years is usually needed to ensure that the change in BMD seen on DXA is true change and not just due to random variations in measurement. In general, repeated BMD testing to monitor treatment in a patient with normal rates of bone loss is recommended after a period of 2 to 5 years. An exception to this strategy would be patients who are at high risk for accelerated bone loss (bone lost at a higher rate than usual) such as patients taking corticosteroids or suppressive doses of thyroid hormone, women in early menopause who are not taking hormone replacement therapy, and women who have recently stopped hormone replacement therapy. In such patients, follow-up DXA may be indicated at an earlier interval (6-12 months). Medicare provides coverage for BMD evaluation with central DXA every 2 years to monitor osteoporosis therapy or for screening of patients with risk factors for osteoporosis and includes a provision for BMD testing at an earlier interval when "medically necessary." Patients in whom bone density declines considerably during therapy may require further evaluation. This decline may be due to treatment failure, but other considerations include noncompliance, inadequate calcium or vitamin D intake, or a secondary cause of osteoporosis.

Biochemical markers of bone turnover have also been advocated for monitoring response to therapy. Many experts believe that the markers of bone turnover may offer additional value in assessing the effectiveness of drug therapy because the effects of most osteoporosis therapies on bone markers are rapid (3-6 months) compared to BMD, in which 1 to 2 years may be necessary to determine the effect of treatment. Markers of bone turnover typically are separated into those associated with bone formation vs those associated with bone resorption. Markers of bone formation include bone alkaline phosphatase, osteocalcin, and the type I collagen propeptides. Markers of bone resorption include urinary calcium, tartrate-resistant acid phosphatase, bone sialoprotein, type I collagen cross-linked telopeptides, and pyridinium derivatives. Currently, however, the daily and seasonal fluctuations in these markers, in addition to intraindividual variation, have limited their clinical use. Because no single marker is accurate enough to reliably identify nonresponders to treatment and further research is necessary to clarify which markers should be used and when, routine measurement of markers of bone turnover is not recommended for monitoring response to osteoporosis treatment at this time.

SUMMARY

Osteoporosis is an important growing public health concern that is underrecognized, undertreated, and largely preventable. Most patients at high risk for fractures do not receive adequate evaluation or treatment for prevention of future fractures. More concerning is that most patients who are diagnosed as having fragility or low-impact fractures are not being evaluated or treated for osteoporosis. In fact, a recent review of the literature concluded that treatment rates for osteoporosis were low across all populations, but men and patients treated by generalists are at an especially high risk of not receiving treatment.[44] Many factors likely contrib-

ute to these poor statistics and have not been well defined in the literature. Intuitively, however, generalists have a major role in educating patients about osteoporosis, assessing their risk for the disease, facilitating screening, and administering treatment. This concise review provides a straightforward and useful approach to these issues for practicing clinicians.

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Questions About Osteoporosis

1. Which *one* of the following statements regarding calcium supplementation is *false*?
   a. Calcium absorption is limited to about 500 mg of elemental calcium at a time
   b. A 500-mg tablet of calcium carbonate contains 500 mg of elemental calcium
   c. After menopause, calcium intake should be at least 1500 mg of elemental calcium daily
   d. Calcium citrate is the preferred supplement for patients who are taking acid suppression therapy
   e. Adequate calcium intake is a necessary adjunct to all osteoporosis pharmacotherapy

2. In which *one* of the following situations would BMD testing *not* be necessary?
   a. All women older than 65 years
   b. A 65-year-old man taking hormone therapy for metastatic prostate cancer for the past 5 years
   c. A 56-year-old moderately obese but otherwise healthy recently postmenopausal (<5 years) woman who is taking hormone replacement therapy, is a nonsmoker, and has no personal or family history of fracture
   d. A 38-year-old woman who received a kidney transplant 3 years ago from a living related donor
   e. A 45-year-old man with severe multiple sclerosis who has been wheelchair-bound for the past 10 years

3. Which *one* of the following statements regarding BMD testing is *false*?
   a. T scores represent the number of SDs from normal sex-matched young adult mean bone density values
   b. Z scores represent the number of SDs from normal mean bone density values for age- and sex-matched control subjects
   c. A Z score of –1.0 or lower may suggest the presence of a secondary cause of osteoporosis
   d. A peripheral DXA T score of –2.5 or lower is diagnostic of osteoporosis
   e. The central DXA T score at the femoral neck or hip is the gold standard for diagnosing osteopenia or osteoporosis

4. In which *one* of the following should pharmacological treatment of osteoporosis be *recommended* based on the NOF guidelines?
   a. A 75-year-old woman with a femoral neck T score of –1.5 and no additional osteoporosis risk factors
   b. All postmenopausal women with a T score of –1.5 or lower, regardless of risk factors
   c. A 45-year-old woman with an ankle fracture after a skiing accident
   d. A postmenopausal woman with a recent hip fracture caused by a fall from standing height
   e. A 68-year-old woman with "osteopenia" noted on a recent x-ray of the hand

5. Which *one* of the following statements regarding the currently available FDA-approved medications for osteoporosis is *true*?
   a. All available FDA-approved medications for osteoporosis have equal antifracture efficacy
   b. Combination therapy with alendronate and teriparatide provides improvements in bone density above and beyond what can be achieved by teriparatide alone
   c. Bisphosphonates have been shown to decrease the incidence of vertebral fractures but not hip fractures
   d. Bisphosphonates are currently the most potent oral antiresorptive agents available for the prevention or treament of osteoporosis
   e. Estrogen replacement therapy was recently shown to have antifracture efficacy in the Women's Health Initiative trial and therefore is now approved by the FDA as an effective treatment for postmenopausal osteoporosis

Correct answers:
1. *b*, 2. *c*, 3. *d*, 4. *d*, 5. *d*