Bone Health and Osteoporosis

Beatrice C. Lupsa, MD*, Karl Insogna, MD

KEYWORDS

• Osteoporosis • Menopause • Fracture • Bone loss • Bone mineral density • DXA • Calcium • Vitamin D

KEY POINTS

- Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue leading to an increased risk of fragility fractures.
- Central dual-energy X-ray absorptiometry measurements are the gold standard for determining bone mineral density.
- A well-balanced diet containing adequate amounts of calcium and vitamin D, exercise, and smoking cessation are important to maintaining bone health as women age.
- Pharmacologic agents should be recommended in patients at high risk for fracture.

INTRODUCTION

Osteoporosis is the most common skeletal disease in humans. It is characterized by low bone mass and microarchitectural deterioration of the bone tissue, leading to decreased bone strength and increased risk of low-energy fractures, or so-called fragility fractures. Osteoporosis affects a large number of people of both sexes and all races and its prevalence increases with age. Osteoporosis is a risk factor for fracture just as hypertension is for stroke. The most common osteoporotic-related fractures are those of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist).

This article focuses on postmenopausal bone health and osteoporosis. It provides guidance for providers of health care to women on proper screening, identification of secondary causes, and appropriate treatment of osteoporosis.

PATHOPHYSIOLOGY

The skeleton is one of the largest organ systems in the body. It consists of a mineralized matrix with a small but highly active cellular fraction. Bone is formed by

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Department of Internal Medicine, Yale Bone Center, Yale University School of Medicine, New Haven, CT, USA
* Corresponding author. 333 Cedar Street, FMP 107, P.O. Box 208020, New Haven, CT 06519.
E-mail address: beatrice.lupsa@yale.edu

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osteoblasts, which are derived from marrow mesenchymal cells. Osteoblasts are also important for initiating resorption. Along with the osteocytes, they release receptor activator of nuclear factor kappa B ligand (RANKL) which is essential for osteoclastogenesis. In addition to RANKL, osteoblasts produce an inhibitor of osteoclastogenesis called osteoprotegerin (OPG). OPG is a soluble receptor for RANKL that binds this ligand and prevents interaction of RANKL with its cognate receptor, receptor activator of nuclear factor kappa B. Osteoclasts are derived from hematopoietic progenitors and are highly specialized cells involved in bone resorption. The principal stimulator of osteoclast formation is RANKL.

The osteoblasts and osteoclasts are involved in bone remodeling, which is a dynamic process by which old bone is removed from the skeleton and new bone is added. Remodeling can be activated by both systemic and local factors. Changes in mechanical force can activate remodeling to improve skeletal strength and to remove and repair the bone that has undergone microdamage. Systemic hormones influencing bone remodeling include parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, calcitonin, growth hormone, glucocorticoids, thyroid hormones, gonadal hormones, and cytokines. Usually this cycle is tightly coupled and the amount of new bone formed by osteoblasts is equal to the amount resorbed by osteoclasts. Bone loss occurs when this balance is altered, resulting in greater bone removal than replacement. This imbalance occurs with menopause and advanced age.[1]

During the menopausal transition, serum estradiol levels decrease by 85% to 90% and serum estrone decreases by 65% to 75% relative to premenopausal values. With the onset of menopause and the decrease in estrogen levels, the rate of bone remodeling increases by 2-fold to 4-fold. There is a greater increase in bone resorption, resulting in an imbalance in bone remodeling. The imbalance in bone resorption leads to an accelerated phase of bone loss and an efflux of skeletal-derived calcium to the extracellular fluid. These changes lead to a negative total body calcium balance, which further aggravates the skeletal losses.[2]

At menopause, women undergo rapid trabecular bone loss, which usually continues for 5 to 8 years after the cessation of menses. Initially, about 20% to 30% of the trabecular bone and 5% to 10% of the cortical bone is lost. About 8 to 10 years after menopause, a second phase of bone loss becomes predominant in which both trabecular and cortical bone are lost at equal rates. The loss of bone tissue leads to deterioration in skeletal microarchitecture and an increase in fracture risk. Later in the course of menopause, age-related bone loss and accompanying changes in the material properties of bone exacerbate the bone loss associated with estrogen deficiency.

At the cellular level the increased number and activity of osteoclasts disrupts trabecular connectivity and increases cortical porosity. Resorption pits created as part of an accelerated bone remodeling cycle are incompletely filled because osteoblastic new bone formation does not keep pace with rates of bone resorption. Reduced bone density and bone quality compromise the mechanical weight-bearing properties of the skeleton and confer a predisposition to fractures.

Even though bone loss occurs as a consequence of the decrease in estrogen levels during menopause, several other disorders can lead to accelerated bone loss regardless of age and estrogen status. These secondary causes of osteoporosis include hyperparathyroidism, vitamin D deficiency, hypercortisolism, hyperthyroidism, plasma cell dyscrasias (eg, multiple myeloma and monoclonal gammopathy of undetermined significance), inflammatory diseases (eg, rheumatoid arthritis), gastrointestinal disorders (eg, chronic liver disease, celiac disease, and inflammatory bowel disease), chronic renal disease, renal calcium losses, and drugs (eg, steroids, antiepileptics,

depot medroxyprogesterone acetate, anticoagulants, vitamin A, loop diuretics, and selective serotonin receptor uptake inhibitors).

DIAGNOSIS AND INITIAL EVALUATION

Measurement of Bone Mineral Density

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) measurement of the hip (femoral neck and total hip) and spine is the preferred method of diagnosing osteoporosis, predicting future fracture risk, and monitoring patients (**Fig. 1**). Bone mineral density (BMD) measured by DXA at the one-third radius site can be used for diagnosis when the hip and/or spine cannot be measured. DXA measures bone mineral content (BMC) grams in and bone area (BA) in square centimeters. The areal BMD in grams per square centimeter is calculated by dividing BMC by BA. The T-score, the value used for diagnosing osteoporosis, is calculated by subtracting the mean BMD of a young-adult reference population from the patient's BMD and dividing it by the standard deviation (SD) of the young-adult population. The Z-score, used to compare the patient's BMD with that of a population of peers, is calculated by subtracting the mean BMD of an age-matched, ethnicity-matched, and sex-matched reference population from the patient's BMD and dividing by the SD of the reference population.[3]

The BMD diagnosis of normal bone mass, osteopenia, and osteoporosis is based on the World Health Organization (WHO) diagnostic classification[4] (**Box 1**). This classification should be used for postmenopausal women. A diagnosis of osteoporosis can also be made on a previous fragility fracture, even if the BMD is in the normal range. A fragility fracture denotes a fracture in adult life occurring spontaneously, or a fracture arising from trauma that, in a healthy individual, would not have resulted in a fracture.

In premenopausal women the WHO BMD diagnostic classification should not be applied. In this group, the diagnosis of osteoporosis should not be made from

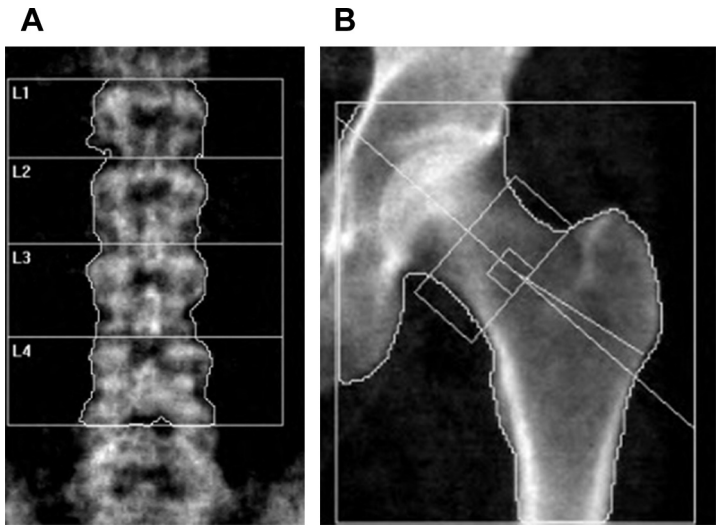

Fig. 1. Measurement of the bone density of the lumbar vertebrae and hip using DXA. (*A*) DXA of a normal lumbar spine L1 to L4. For clinical diagnosis of osteoporosis under almost all circumstances the bone density of all 4 vertebrae are used. (*B*) DXA of the left hip. For clinical diagnosis of osteoporosis, femoral neck and total hip are used.

Box 1
The WHO definitions based on BMD measurement at the spine, hip, or forearm by DXA devices

Normal:

BMD within 1 SD of a young normal adult (T-score equal to or greater than −1.0).

Low bone mass (osteopenia):

BMD between 1.0 and 2.5 SD less than that of a young normal adult (T-score between −1.0 and −2.5).

Osteoporosis:

BMD 2.5 SD or more less than that of a young normal adult (T-score at or less than −2.5). Patients in this group who have already experienced 1 or more fractures are deemed to have severe or established osteoporosis.

densitometric criteria alone. The International Society for Clinical Densitometry recommends that instead of T-scores ethnic or race-adjusted Z-scores should be used. Z-scores of −2.0 or lower are defined as either low BMD for chronologic age or less than the expected range for age, and those more than −2.0 as within the expected range for age.[3]

When using DXA to monitor change in BMD with time and therapy, the absolute BMD value (grams per square centimeter) should be used. Statistically significant change in BMD is calculated by 2.77 multiplied by precision at the site of measurement to provide least significant change. In an individual patient, an adequate interval of time (usually 18–24 months) is required between measurements to show significant change, unless larger changes in BMD are anticipated (eg, glucocorticoid treatment).[3] When using DXA to monitor change in BMD, it is important to use the same scanner and software because different manufacturers use different edge detection algorithms and different X-ray beam technologies.

Other technologies to measure bone mass

Other technologies, such as peripheral dual-energy X-ray absorptiometry, computed tomography–based absorptiometry, quantitative computed tomography (QCT), peripheral QCT, and quantitative ultrasonography densitometry, can be used to predict both site-specific and overall fracture risk. When performed according to accepted standards, these techniques are accurate and highly reproducible. However, T-scores from these technologies are not equivalent to T-scores derived from DXA and they cannot be used to diagnose osteoporosis based on the WHO classification.[3] Note that DXA is the only method that has been used in all osteoporosis treatment trials.

Assessment of Fracture Risk

All postmenopausal women should be evaluated clinically for osteoporosis risk in order to determine the need for BMD testing. Assessment of clinical risk factors that are independent of BMD is important for fracture prediction. Validated risk factors that are independent of BMD include advanced age, previous fracture, long-term glucocorticoid therapy, low body weight, family history of hip fracture, cigarette smoking, and excess alcohol intake.[5] In general, the more risk factors that are present, the greater the risk of fracture. Several of these risk factors have been included in the WHO 10-year fracture risk model (FRAX) available at http://www.sheffield.ac.uk/FRAX/. As validated by the WHO, these factors increase the risk for fractures independently of BMD, but can be combined with BMD measurements to assess an individual

patient's risk of fracture. FRAX is based on data collected from large prospective observational studies but it has never been used as an end point in treatment trials.

Who Should be Screened for Osteoporosis?

The decision to perform bone density assessment should be individualized based on the patient's fracture risk profile. Measuring bone density is not indicated unless the results will influence the patient's treatment decision.

Most expert groups recommend that all women 65 years of age and older be screened routinely for osteoporosis regardless of clinical risk factors. Consideration should be given to screening younger postmenopausal women who have had a fracture or who have one or more risk factors for osteoporosis. Also, anyone being considered for pharmacologic therapy for osteoporosis, anyone being treated for osteoporosis (to monitor treatment effect), anyone not receiving therapy and in whom evidence of bone loss would lead to treatment, and all postmenopausal women discontinuing estrogen should be considered for bone density testing.[3,6,7]

Initial Evaluation

Initial evaluation includes a detailed history to assess for clinical risk factors for fracture and secondary causes of bone loss, a thorough physical examination, and basic laboratory tests.

The history should be focused on fragility fractures, height loss, medications associated with bone loss, smoking, alcohol intake, kidney stones, falls, and family history of osteoporosis and/or hip fracture. Patients should be evaluated for coexisting medical conditions that may contribute to bone loss, such as rheumatoid arthritis, hyperthyroidism, Cushing syndrome, hyperparathyroidism, multiple myeloma, inflammatory bowel disease, and celiac disease. Initial laboratory evaluation includes serum creatinine, calcium, phosphorus, magnesium, 25-hydroxyvitamin D, and liver function tests. If clinically indicated, a complete blood count, PTH, thyroid-stimulating hormone, serum protein electrophoresis, and 24-hour urine calcium and free cortisol should be measured. If kyphosis is identified or 2.5 cm (1 inch) or more height loss can be documented, radiographs of the thoracolumbar spine should be obtained to exclude the presence of vertebral compression fractures.

Bone turnover markers are emerging as promising tools in the management of osteoporosis, because they provide dynamic information regarding skeletal status. Commercial bone turnover marker assays, such as serum C-telopeptide and urine N-telopeptide are available for assessment of bone resorption. Serum bone-specific alkaline phosphatase, serum osteocalcin, or serum procollagen type 1 N-terminal propeptide are available for assessment of bone formation. Most of these markers have a circadian rhythm, peaking in the early morning, with a trough in the afternoon and evening. Sampling the fasting serum, early in the morning or using the first or second voided urine, is suggested to minimize variability.

TREATMENT

Nutrition

Bone health depends on a combination of mechanical load and adequate intake of macronutrients and micronutrients. The most important nutrients are calcium, vitamin D, and proteins.

Calcium is important for the bone formation phase of bone remodeling. An inadequate calcium intake can result in decreased calcium absorption and secondary hyperparathyroidism, which can cause increased bone resorption. With aging, the

efficacy of intestinal calcium declines, thus adequate calcium intake is crucial in maintaining bone health. As noted earlier, vitamin D serves as the substrate for 1,25-dihydroxyvitamin D, which is a key regulator of intestinal calcium absorption. Recent meta-analyses of randomized controlled studies in postmenopausal women have shown that supplementation with calcium and vitamin D results in a reduced risk of fractures and a modest increase in BMD.[8]

The adequate intake of calcium and vitamin D, as well as the optimal levels of 25-dihydroxyvitamin D, have been controversial subjects for years. Recently the Institute of Medicine published recommendations regarding the dietary reference intakes on calcium and vitamin D. According to this report, the recommended calcium dietary allowance for women older than 50 years of age is 1200 mg per day. Although available data are inconclusive, some concerns remain about the safety of calcium supplements. Therefore, calcium supplements should be used only in patients who cannot achieve adequate dietary calcium intake. The recommended vitamin D dietary allowance is 600 IU per day for women age 50 to 70 years, and 800 IU per day for women older than 71 years of age. A serum 25-hydroxyvitamin D level of 20 ng/mL seems to be enough to protect most of the population from adverse skeletal outcomes such as fractures and falls.[8]

Data on the effect of protein intake on bone density are conflicting. Some studies suggest that higher protein intake may decrease the risk of hip fractures[9] and bone loss,[10] whereas others suggest that high protein intake may increase bone resorption and calcium excretion.[11] In general, available data suggest that an intake of 1.2 g/kg/day allows for normal calcium homeostasis.

Exercise

Physical activity has a modest antiresorptive effect but, in general, it has been associated with a decreased risk of hip fractures in older women[12] and decreased risk of falls by improving muscle strength, balance, mobility, and overall physical function. Women with osteoporosis (or seeking to prevent it) should exercise for at least 30 minutes 3 times per week. Any weight-bearing exercise regimen, including walking, jogging, tennis, and dancing, is acceptable. Non–weight-bearing exercises, such as swimming, can improve muscle strength, cardiovascular fitness, and coordination but they have less effect on BMD. A meta-analysis of 18 randomized trials on the exercise effect on BMD in postmenopausal women reports that aerobics, weight-bearing, and resistance exercises are effective of increasing BMD in the spine, whereas walking increases BMD at both spine and hip.[13]

Other Lifestyle Modifications

Smoking cessation should be stressed because smoking cigarettes is recognized as a risk factor for fractures and reduced BMD. Excess alcohol (3 or more drinks per day) is harmful to skeletal health and patients should be counseled on the importance of moderating alcohol intake.

Prevention of Falls

Most osteoporotic fractures occur as a result of a fall. Risk factors for falls include gait instability, visual impairment, weakness, cognitive impairment, vitamin D deficiency, home hazards, and treatment with medications such as benzodiazepines and other sedatives and antidepressants. Falls can be reduced by several interventions, such as initiation of an exercise regimen that improves gait, stability, and strength; avoidance of polypharmacy; vitamin D supplementation; vision assessment and correction; and the use of assistive devices. Hip protectors have not consistently been shown to decrease the risk of fractures.

Pharmacologic Treatment

Indication for treatment

The National Osteoporosis Foundation (NOF) has formulated treatment guidelines that have been widely promulgated in the United States. The NOF recommends treating postmenopausal women with a hip or vertebral (clinical or morphometric) fracture, postmenopausal women with osteoporosis at the femoral neck, total hip or spine (T-scores ≤ -2.5 by DXA) or with osteopenia at the femoral neck or spine (T-scores between -1.0 and -2.5), and a 10-year hip fracture probability greater than or equal to 3% or a 10-year major osteoporosis-related fracture probability greater than or equal to 20% based on the US-adapted WHO absolute fracture risk model (FRAX).[7] A suggested algorithm for diagnosis and management of postmenopausal osteoporosis is outlined in **Fig. 2**.

United States Food and Drug Administration–approved drugs for osteoporosis

Current US Food and Drug Administration (FDA)–approved drugs for the prevention and/or treatment of postmenopausal osteoporosis include bisphosphonates, estrogens, selective estrogen receptor modulators (SERMs), teriparatide, denosumab, and calcitonin (**Table 1**). All of these medications except teriparatide are classified as antiresorptive agents. As noted earlier, in estrogen-deficiency bone loss resorption outstrips formation, resulting in an increase in the numbers of excavated bone remodeling units that are not filled with new bone. Antiresorptive agents increase BMD in part by decreasing the rate of bone remodeling and allowing these open resorption pits to

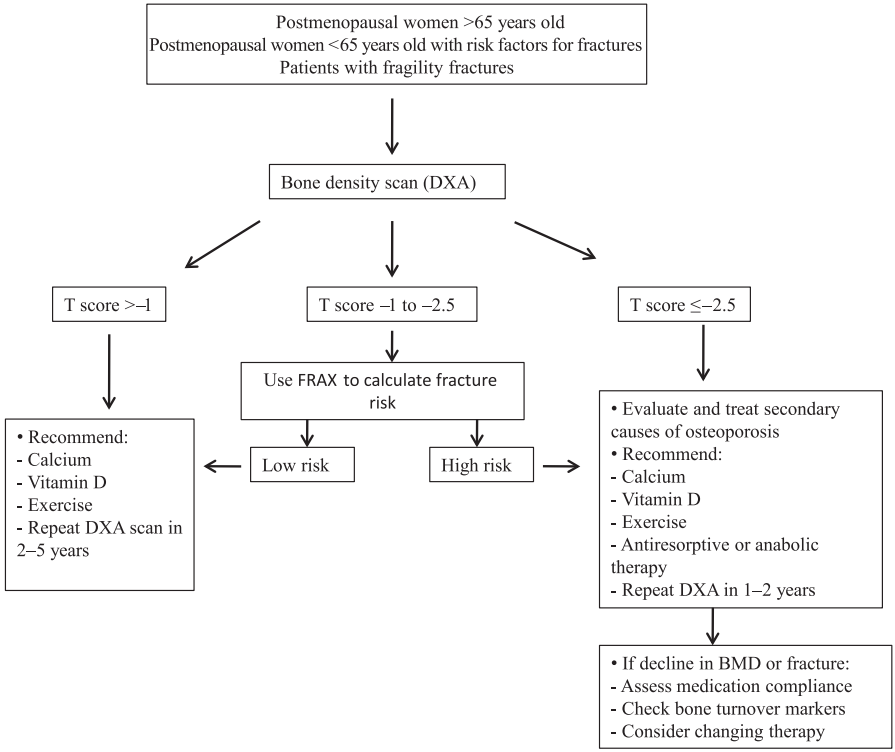

Fig. 2. Suggested algorithm for diagnosis and management of postmenopausal osteoporosis.

Table 1
Summary of fracture risk reduction of FDA-approved medications in postmenopausal osteoporosis

Drug	Vertebral Fracture	Hip Fracture	Nonvertebral Fracture
Alendronate	✓	✓	✓
Risedronate	✓	✓	✓
Ibandronate	✓	—	✓[a]
Zoledronic acid	✓	✓	✓
Estrogen	✓	✓	✓
Raloxifene	✓	—	—
Teriparatide	✓	—	✓
Denosumab	✓	✓	✓
Calcitonin	✓	—	—

[a] Effect shown in a post-hoc analysis.

be remodeled to a new bone. This so-called closure of the remodeling space explains most of the increase in BMD seen with these medications. There is additionally a change in extracellular matrix that occurs with antiresorptive therapy, which also contributes to their efficacy. Teriparatide is the only approved anabolic agent. It stimulates bone formation to a greater extent than bone resorption leading to increase in BMD. These medications have been shown to decrease fracture risk in patients who have had fragility fractures and/or osteoporosis by DXA. These drugs may also reduce fractures in patients with low bone mass (osteopenia) without fractures but the evidence is less strong.

Bisphosphonates Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate. They have high affinity for calcium crystals and concentrate selectively in the bone, decreasing bone resorption. Bisphosphonates are preferentially incorporated into sites of active bone remodeling, which commonly occurs in conditions characterized by accelerated skeletal turnover. Bisphosphonates inhibit bone resorption by rapidly inhibiting the activity of osteoclasts. This abrupt reduction in the bone resorption eventually results in concomitant slowing of bone formation. This new steady state is reached 3 to 6 months after the exposure to these medications. Besides decreasing bone turnover, bisphosphonates maintain or improve trabecular and cortical architecture, and increase bone mineralization and BMD.[14,15] Recent studies suggest that bisphosphonates also function to limit osteoblast and osteocyte apoptosis.[16] The net effect of these actions is the decrease of the risk of fractures.

A key feature governing the clinical pharmacology of bisphosphonates is their bioavailability. Their intestinal absorption is poor (1%–5%) and they are rapidly cleared from the circulation. About half of the dose concentrates in the bone, whereas the other half is excreted unmetabolized in the urine. Skeletal uptake primarily depends on renal function, bone turnover, binding site availability, and bisphosphonate affinity for bone matrix.

Early non–nitrogen-containing bisphosphonates (etidronate, clodronate, and tiludronate) are considered first-generation bisphosphonates. They are now rarely used because of low potency and an increased risk of osteomalacia. Second-generation and third-generation bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) have nitrogen-containing R2 side chains. The nitrogen-containing bisphosphonates act primarily by inhibiting the enzyme farnesyl

pyrophosphate (FPP) synthase in the mevalonate pathway (cholesterol biosynthetic pathway). Inhibition of FPP synthase disrupts protein prenylation, which creates cytoskeletal abnormalities in the osteoclast and promotes detachment of the osteoclast from the bone perimeter, ultimately leading to osteoclast apoptosis.[16,17]

Alendronate, risedronate, ibandronate, and zoledronic acid have been shown to improve BMD in postmenopausal women with underlying low bone density and to significantly decrease the risk of vertebral fractures. Alendronate, risedronate, and zoledronic acid have been proved to reduce the risk of hip and other nonvertebral fractures.[18–23]

Bisphosphonates are well tolerated when taken as prescribed. Side effects are few and rarely severe. The most common adverse effects include gastrointestinal problems such as esophagitis and esophageal ulcers with the oral preparations, and myalgia and arthralgia with both oral and intravenous (IV) bisphosphonates. Flu-like symptoms (arthralgia, myalgia, fever, headache) occur in about 30% of patients after the first dose of IV zoledronic acid. IV bisphosphonates have been associated with hypocalcemia. Serum calcium and 25-hydroxyvitamin D levels should be checked before initiating treatment. Adequate supplementation with calcium and vitamin D should be provided. Kidney function should be checked before initiating treatment and then periodically because bisphosphonates are generally not recommended for patients with creatinine clearance less than 30 to 35 mL/min. Other potential associations with bisphosphonate use include atrial fibrillation and esophageal cancer; however, a clear casual relationship has not been established.

Low-energy fractures of the femoral shaft (chalk stick fractures) have recently been observed in some patients on long-term bisphosphonate therapy, but the true prevalence is not known.[24] Atraumatic fractures can occur spontaneously in patients with osteoporosis, but there have been speculations that these atypical fractures are caused by skeletal fragility resulting from severely suppressed bone turnover. Patients on long-term alendronate (ie, >3 years) reporting femoral shaft or hip pain should undergo a bone scan or MRI to exclude the presence of an insufficiency fracture, which may be the harbinger for these atypical fractures.

Many articles have been published on the association of bisphosphonate therapy and the occurrence of osteonecrosis of the jaw (ONJ).[25] The incidence of ONJ is extremely low and it occurs primarily in patients with cancer treated with high-dose IV bisphosphonates.

There is currently no consensus on the length of bisphosphonate therapy. In the Fracture Intervention Trial Long-term Extension (FLEX), discontinuation of alendronate after 5 years of therapy resulted in a gradual decline in BMD and increase in biochemical markers of bone turnover, but no significant change in the risk of fracture (except for clinical vertebral fracture) compared with continuous therapy for 3 subsequent years.[26]

Based on data primarily from randomized controlled trials with oral bisphosphonates, Black and colleagues[27] suggested continuing the bisphosphonates beyond 3 to 5 years in patients who continue to have osteoporosis of the femoral neck (T-score ≤ -2.5) after 3 to 5 years of treatment and in patients with an existing vertebral fracture and a femoral neck T-score less than -2. These patients seem to be at the highest risk for vertebral fractures and therefore seem to benefit most from continuation of bisphosphonates. The evidence supporting the benefit of continuing treatment with zoledronic acid beyond 3 years is less conclusive.[28]

There are no data to support the appropriate length of drug holiday and it usually varies between 1 and 5 years. A decrease in BMD and/or increase in markers of bone turnover are indicators that can be used to evaluate the need for restarting treatment.

Estrogen therapy Estrogen therapy is approved by the FDA for the prevention of osteoporosis, and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. However, given potential risks (eg, myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombophlebitis) associated with hormonal therapy, especially when combined with a progestin, the FDA recommends that approved nonestrogen treatments should first be considered for treatment and prevention of osteoporosis. In the Women's Health Initiative, 5 years of combined estrogen and progestin therapy (Prempro) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23%.[29]

Selective estrogen receptor modulators: raloxifene (brand name Evista) SERMs bind with high affinity to the estrogen receptor and have estrogen agonist and antagonist properties depending on the target organ. The only SERM approved for prevention and treatment of postmenopausal osteoporosis is raloxifene 60 mg orally once daily. Raloxifene has estrogenic activity in bone, thus preventing bone loss, improving BMD, and reducing the risk of fracture. In a 3-year trial, raloxifene reduces the risk of vertebral fractures by about 30% in patients with a prior vertebral fracture and by about 55% in patients without a prior vertebral fracture. Raloxifene does not reduce the risk of nonvertebral fractures.[30] It seems to reduce the risk of estrogen receptor–positive breast cancer, does not stimulate endometrial hyperplasia or vaginal bleeding, but it does increase the risk of venous thromboembolism.

Teriparatide (brand name Forteo) Recombinant human parathyroid hormone (1-34) (teriparatide) is approved for the treatment of postmenopausal osteoporosis in women who are at high risk for fracture. It is an anabolic agent administered by a daily subcutaneous injection at a dose of 20 μg for up to 2 years. In patients with osteoporosis, teriparatide was shown to decrease the risk of vertebral fractures by 65% and nonvertebral fractures by 53% after an average of 18 months of therapy.[31] Myalgias and arthralgias can occur with teriparatide use. Although hypercalciuria is common, it is usually not of concern because of the short duration of use. An exception is patients with calcium oxalate nephrolithiasis, in whom teriparatide should be used cautiously. Increase in serum calcium can occur transiently after the teriparatide injections, but persistent hypercalcemia is uncommon. Occasional hypotension or tachycardia can occur with the first few doses; the drug is therefore administered at bedtime. Because teriparatide increases the incidence of osteosarcoma in rats, patients at risk for osteosarcoma (eg, patients with Paget disease of bone and who have had skeletal radiation exposure) should not receive teriparatide. Bony metastases or history of skeletal malignancy are also considered contraindications for its use. The safety and efficacy of teriparatide have not been shown beyond 2 years of treatment.

Denosumab (brand name Prolia) Denosumab is a fully human monoclonal antibody to the RANKL. It reduces osteoclastogenesis, induces osteoclast apoptosis, decreases bone resorption, increases BMD, and reduces fracture risk. Denosumab is approved by the FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture or of patients who have failed or are intolerant of other available therapies. It is administered by subcutaneous injection at a dose of 60 mg every 6 months.

In the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial, 7868 postmenopausal women with osteoporosis were randomly assigned to subcutaneous denosumab or placebo for 3 years. Denosumab increases lumbar spine BMD by 9.2% and the total hip BMD by 4.0%. Biochemical markers of bone turnover were significantly reduced in patients taking denosumab. In the same

trial, denosumab reduced the risk of vertebral fractures by 68%, the risk of hip fractures by 40%, and the risk of nonvertebral fractures by 20%.[32]

Available evidence suggests that denosumab is tolerated for up to 8 years.[33] Because denosumab is not cleared by the kidneys, it may offer a unique therapeutic option in patients with compromised renal function. Because of marked suppression of bone remodeling, concerns remain about increased risk of osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. The most common adverse effects include musculoskeletal pain and increased risk of infections such as cellulitis and cystitis.

Calcitonin (brand names Miacalcin or Fortical) Salmon calcitonin (intranasal or injectable) is FDA approved for the treatment of osteoporosis in women who are at least 5 years postmenopausal. The intranasal preparation at a dose of 200 IU daily is almost exclusively used in clinical practice. Studies show that calcitonin reduces the risk of vertebral but not nonvertebral fractures.[34–36] It may have an analgesic effect in patients who have acute painful vertebral fractures, thus it could be used in the short term for pain management. Recent concerns have been raised about a possible association between intranasal calcitonin for osteoporosis and an increased overall risk in cancer rates, which may limit its long-term use.

Choice of antiosteoporotic therapy Cost, safety profile, and efficacy should be factored into the therapeutic decision. In patients with osteoporosis of the hip, drugs proved to have effect at this site should be used. Thus ibandronate, raloxifene, and calcitonin should not be used in this circumstance. Also, teriparatide has not been shown to decrease the risk of hip fractures. For most postmenopausal women with osteoporosis, oral bisphosphonates are considered first-line treatment. Intravenous bisphosphonates are alternatives for patients who cannot tolerate oral bisphosphonates because of gastrointestinal side effects. Teriparatide and denosumab are reserved for patients with severe osteoporosis and are not considered first-line medications.

Combination therapy Combination therapy, usually a bisphosphonate with a nonbisphosphonate, is not recommended. It can provide additional small increases in BMD compared with monotherapy; however, the effect on fracture rates is unknown. The added cost and potential side effects, such as oversuppression of bone turnover, should be weighed against potential benefits.

Monitoring response to treatment Several studies have shown poor compliance with osteoporosis medications. One year after initiating treatment of osteoporosis, about 45% patients do not refill the prescriptions. Thus, it is important to ask patients whether they are taking their medications and to encourage compliance with therapy. Sharing the bone density results with patients modestly increases the adherence to therapy.

Central DXA measurement of the spine and hip is the preferred method for serial assessment of the BMD. There is no consensus on the optimal frequency of monitoring and the preferred site to monitor. The NOF recommends that BMD assessments should be repeated every 2 years, but recognizes that testing more frequently may be warranted in certain clinical situations.[7] The frequency of measurements is, in part, determined by the precision of the machine and the anticipated bone loss.

A stable or increasing BMD is an acceptable response to therapy. A decrease in BMD if there is ongoing antiosteoporotic therapy is a cause for concern and should prompt further studies to exclude the presence of factors such as poor compliance, malabsorption, inadequate calcium and vitamin D intake, or diseases that could negatively affect the skeleton.

Measurement of the bone turnover markers may also help in evaluating the efficacy of therapy. A significant decrease in bone turnover with antiresorptive therapy or an increase in bone turnover with anabolic therapy provides evidence of compliance and drug efficacy.

SUMMARY

Osteoporosis is a major public health concern that is underdiagnosed and undertreated. Fragility fractures of the spine and hip can result in chronic pain, depression, disability, and death. Central DXA measurements are the gold standard for assessment of the BMD. Bone loss is an inevitable consequence of the decrease in estrogen levels during menopause, but additional risk factors for bone loss should be identified and treated. Pharmacologic agents in conjunction with a well-balanced diet, exercise, and smoking cessation should be recommended in all patients at high risk of fracture. Close attention should be paid to fall prevention.

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