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RELIAS MEDIA

Osteoporosis Review

Osteoporosis is a skeletal disorder in which bone density and quality are reduced. Patients experience loss of bone mass, deterioration of bone tissue, and a decline in bone quality, which leads to increased bone fragility and a higher risk of fractures.[1] Bones continuously remodel to maintain strength and to function as a reservoir of calcium and phosphorus.[2] The age at which peak bone density occurs is in the early 20s. Osteoporosis can develop as a result of suboptimal peak bone mass in young adulthood, excessive resorption of bone, or impaired bone formation during remodeling.[2]

An estimated 10.3% of the noninstitutionalized population older than 50 years of age have osteoporosis, and 43.9% have low bone mass at the femoral neck or lumbar spine. The prevalence of osteoporosis varies by age, sex, race, and ethnicity. The prevalence rises with increasing age, with the highest prevalence of osteoporosis being 16.4% in patients between 70 and 79 years of age and 26.2% in patients older than 80 years of age. Women are more prone than men (15.4% vs. 4.3%, respectively) to develop osteoporosis, with onset often at earlier age following menopause. Finally, Mexican-Americans have the highest prevalence (13.4%), followed by non-Hispanic whites (10.2%) and Asians (8.9%). Non-Hispanic blacks have the lowest prevalence (4.9%).[3]

Osteoporosis affects more than 54 million Americans older than 50 years of age and is expected to rise to 71.2 million Americans by 2030.[4] Falls and subsequent osteoporotic fractures lead to significant morbidity and to mortality that ranges between 21% and 30% within the first year of the fracture depending on the site.[3,4] Because of the increasing life expectancy of the U.S. population, the number of fractures per year is estimated to rise by 48% to more than 3 million fractures, and will be accompanied by an escalating cost of $25.3 billion by 2025.[5] Therefore, it is imperative that primary care providers address this challenge by implementing practices to screen patients for onset of osteoporosis to prevent and/or treat the disorder.

Pathophysiology

Bone architecture consists of a matrix formed by a protein collagen deposited with mineral crystal hydroxyapatite formed by calcium and phosphate. Thus, mineralization declines in the presence of lack of a matrix. Therefore, protein catabolic disorders are the major contributors to secondary osteoporosis. Alternatively, osteoporosis ensues because of an imbalance between bone resorption and bone formation. Osteoclasts promote bone resorption while osteoblasts facilitate bone formation. Increased bone resorption with a lack of compensation by formation is the most common denominator. Alternatively, decreased bone formation may overtake bone resorption in certain disorders. Moreover, decreased mineralization, rickets, and osteomalacia also affect architecture and bone strength leading to fractures.

Hormones play a major role in remodeling. Parathyroid hormone as a whole molecule (84 amino acids) promotes resorption, whereas its fraction (1-34 amino

EXECUTIVE SUMMARY

- An estimated 10.3% of the noninstitutionalized population older than 50 years of age have osteoporosis, and 43.9% have low bone mass at the femoral neck or lumbar spine.
- Osteoporosis affects more than 54 million Americans older than 50 years of age and is expected to rise to 71.2 million Americans by 2030. Falls and subsequent osteoporotic fractures lead to significant morbidity and to mortality that ranges between 21% and 30% within the first year of the fracture depending on the site.
- Because of the increasing life expectancy of the U.S. population, the number of fractures per year is estimated to rise by 48% to more than 3 million fractures, and will be accompanied by an escalating cost of $25.3 billion by 2025.
- Dual-energy X-ray absorptiometry is the gold standard for measuring bone mineral density (BMD) for the diagnosis of osteoporosis, predicting future fracture risk, and, more importantly, monitoring the effect of therapy.
- In addition to lifestyle measures, pharmacologic therapy is indicated in patients manifesting osteoporosis as well as in those at high risk for fracture.
- Improvements in BMD reach a plateau at three to four years, regardless of the drug used. A drug holiday is recommended by some, although it remains controversial.

acids), calcitonin, and RANK/RANKL (receptor activator of nuclear factor kappa-B ligand)/osteoprogerin system facilitate bone formation.[6-12] Finally, vitamin D, fibroblast growth factor (FGF) 23, and osteocalcin affect mineralization.[13-17] Hence, disorders involving these hormones and factors contribute to low bone mass and/or architecture, resulting in a predilection toward fractures. The enzyme bone-specific alkaline phosphatase also induces bone formation. Therefore, serum alkaline phosphatase concentration rises with growing bone during adolescence as well as with disorders inducing bone formation (e.g., osteoblastic metastasis, acromegaly, osteomalacia, Paget's disease). In contrast, congenital lack or total absence of this enzyme, known as hypophosphatasia, manifests as juvenile osteoporosis.

Risks Factors and Causes

Low bone mass and osteopenia or osteoporosis are used synonymously, although decreased mineralization also may be a contributing disorder. An increased risk of osteoporosis has been linked to multiple factors. (*See Table 1.*) Osteoporosis is a syndrome attributed to several causative disorders. Thus, it may be classified as primary or idiopathic if the cause is not recognized, but it is deemed to be secondary based on the cause of decreasing bone mass. Idiopathic or primary osteoporosis may be due to age-related loss of bone, although declining sex hormones apparently are contributors. Rarely, osteoporosis occurs in young patients without a known contributing disorder and also is labeled idiopathic or primary. Several conditions and diseases cause or contribute to osteoporosis and fractures, including endocrine, gastrointestinal, rheumatologic, and autoimmune diseases, as well as neurological and musculoskeletal disorders. Numerous lifestyle factors and medications also contribute to increased risks for both osteoporosis and fracture. (*See Table 1.*) Therefore, a thorough evaluation for the presence of pathophysiologic factors and pathogenic disorders that cause or contribute to decreased bone mass due to osteoporosis and/or demineralization play an integral part in making a definitive diagnosis prior to selecting an appropriate management strategy including pharmacotherapy.[1]

Manifestations

Osteoporosis or osteopenia is asymptomatic in many people and often is detected during screening because of the presence of well-established risk factors. (*See Table 1.*) Major manifestations include pain, fractures, and deformities as well as their consequences (e.g., cor pulmonale secondary to restrictive pulmonary disease caused by kyphoscoliosis resulting from thoracic vertebral fractures or pulmonary embolism due to immobilization caused by a hip fracture).

Screening

Osteoporosis is a preventable and a treatable disorder. Screening is an integral part of prevention and treatment. The screening process is essential in identifying patients with osteoporosis in the early phase of the disease when therapy is most effective.[1] The National Osteoporosis Foundation (NOF) and American Association of Clinical Endocrinologists/American College of Endocrinologists recommend that all postmenopausal women and men 50 years of age and older be assessed for osteoporosis risk factors to determine the need for bone mineral density (BMD) testing and/or vertebral imaging.[1,18] The U.S. Preventive Services Task Force advises all women older than 65 years of age and men older than 70 years of age to undergo BMD testing. It also recommends bone density assessment in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman and who have no additional risk factors.[3] BMD examination is not recommended in children, adolescents, and healthy young men or premenopausal women unless there is a history of fracture secondary to a trivial trauma or other risk factors for bone loss, including congenital disorders such as osteogenesis imperfecta or hypophosphatasia.[1]

When screening for osteoporosis, the physician should take a thorough history including recent loss of height or spinal deformity, perform a detailed physical examination including height measurement, and conduct a clinical fracture risk assessment with the Fracture Risk Assessment (FRAX) tool.[18] Assessment for the presence of secondary causes of osteoporosis also must be conducted to guide physicians in implementing the appropriate therapy if diagnosis of decreased bone density is documented. An individual fracture risk profile also should be used to determine the need for assessing bone density, primarily for future

Table 1. Factors That Cause or Contribute to Low Bone Density Including Osteoporosis

Lifestyle Factors	Alcohol abuse, smoking (active or passive), frequent falling, immobilization, inadequate physical activity, excess vitamin A, vitamin D insufficiency or deficiency, low calcium intake, excessive thinness, high salt intake
Endocrine Disorders	Central obesity, hyperparathyroidism, hyperthyroidism, Cushing's syndrome or disease, diabetes mellitus (types 1 and 2), hypogonadism, pheochromocytoma
Gastrointestinal Disorders	Celiac disease, inflammatory bowel disease, primary biliary cirrhosis, gastric bypass, malabsorption, gastrointestinal surgery, pancreatic disease
Rheumatologic and Autoimmune Diseases	Rheumatoid arthritis, ankylosing spondylitis, systemic lupus, other rheumatic and autoimmune diseases
Neurological and Musculoskeletal Risk Factors	Epilepsy, Parkinson's disease, multiple sclerosis, spinal cord injury, stroke, muscular dystrophy
Miscellaneous Conditions and Diseases	AIDS/HIV, amyloidosis, chronic obstructive lung disease, congestive heart failure, metabolic or renal tubular acidosis, depression, end-stage renal disease, hypercalciuria, idiopathic scoliosis, post-transplant bone disease, sarcoidosis, weight loss, eating disorders, mastocytosis, chronic liver disease, malnutrition, congenital disorders, osteogenesis imperfecta, hypophosphatasia
Medications	Aluminum (in antacids), anticoagulants (heparin), anticonvulsants, aromatase inhibitors, barbiturates, cancer chemotherapeutic drugs, depot medroxyprogesterone, glucocorticoids (> 5 mg/day prednisone or equivalent for > 3 months), gonadotropin-releasing hormone agonists, lithium, cyclosporine and tacrolimus, methotrexate, parenteral nutrition, proton pump inhibitors, selective serotonin reuptake inhibitors, tamoxifen, thiazolidinediones, SGLT2 Inhibitors, thyroid hormones (in excess)

comparisons to determine change following therapy. Bone density testing should not be conducted unless the result is likely to affect the patient's treatment decision. Finally, bone density examination rarely is conducted to establish diagnosis.

Screening for the onset of osteoporosis in appropriate populations is essential to identify at-risk patients who would benefit from BMD testing or vertebral imaging to start pharmacologic treatment to prevent fractures. The FRAX tool is the most widely used questionnaire used to screen patients for osteoporosis. The Garvan tool is another alternative.[19] In 2008, the World Health Organization (WHO) developed the FRAX tool to predict the 10-year probability of a hip, spine, wrist, or humeral fracture.[18] The FRAX tool incorporates various risk factors for osteoporosis and is intended for use in postmenopausal women and men 50 years of age and older. (*See Table 2.*) It may underestimate the risk of a future fracture in patients in the presence of an increased risk of falls, a recent fracture, and previous multiple fractures due to osteoporosis.

In a susceptible population with risk factors, the diagnosis of osteoporosis is confirmed in adults by BMD measurement or by the occurrence of a low-trauma hip or vertebral fracture. It is not caused by a major event such as a motor vehicle accident, a fall from the rooftop, or being thrown by a storm. Once the diagnosis is established, various appropriate laboratory tests must be performed to determine the presence of disorders known to cause osteoporosis.[1,18]

Dual-energy X-ray absorptiometry (DEXA) is the gold standard for measuring BMD for the diagnosis of osteoporosis, predicting future fracture risk, and, more importantly, monitoring the effect of therapy. BMD often is determined at multiple sites, including femoral neck, total hip, and/or spine, and occasionally forearm. Quantitative computed tomography (CT) scan is the other recommended technique. Quantitative CT scans provide three-dimensional volumetric measurements, while DEXA determines calcium content per area unit and thus is two-dimensional. However, DEXA has become the tool of choice because of convenience and the cost. Moreover, DEXA has been used in almost all clinical trials assessing the efficacy of most therapies. The BMD by DEXA is reported as calcium, g/m^2 bone surface area, as well as T-score and Z-score.[19] The T-score is the standard deviation of the patient's BMD from the mean value for healthy young white women 20 to 29 years of age, with no adjustments for postmenopausal women and men 50 years of age or younger, irrespective of race, nationality, or ethnicity. The Z-score indicates the patient's BMD in comparison to mean BMD for a healthy, age-matched reference population with the same sex and ethnicity.[1,18,19] The Z-score is reported mainly for children, men 50 years of age or younger, and premenopausal women, and if a secondary cause of osteoporosis is present.[20] In a postmenopausal woman with a very low T-score or Z-score, the physician should evaluate the patient further to determine if a secondary cause also is present.[18] The WHO T-score classification criteria provide the thresholds for classification of low bone mass into groups for determination of appropriate therapeutic approach. (*See Table 3.*) Finally, BMD is sensitive but not

Table 2. FRAX Tool Risk Factors

- Age
- Gender
- Prior fracture
- Femoral neck bone mineral density
- Low body mass index
- Parent history of hip fracture
- Rheumatoid arthritis
- Current smoker
- Current alcohol use of ≥ 3 drinks per day
- Secondary causes of osteoporosis
- Glucocorticoid use (≥ 5 mg prednisolone or equivalent for > 3 months)

specific for the diagnosis of osteopenia or osteoporosis. Low bone density indicates the presence of osteoporosis or osteopenia as well as osteomalacia and lyric disorders. Additional laboratory tests are essential to differentiate these disorders. Normal serum calcium, phosphorus, and alkaline phosphatase concentrations indicate the presence of osteopenia or osteoporosis, whereas subnormal calcium and/or phosphorus and/or vitamin D, as well as elevated alkaline phosphatase, clinch the diagnosis of osteomalacia. The other laboratory tests include serum markers of bone resorption or products of collagen breakdown (e.g., parathyroid hormone, telopeptides, and urinary hydroxyproline) and indicators of bone formation (e.g., bone-specific alkaline phosphatase, osteoprotegerin, phosphorus).[1,18] Finally, determination of serum concentrations of calcium, vitamin D and its metabolites, FGF 23, and osteocalcin provide the status of mineralization.[13-17]

Vertebral fractures often are asymptomatic and often remain undiagnosed for many years. Vertebral imaging with a lateral thoracic and lumbar spine X-ray confirms these fractures in at-risk patients. Another option is a vertebral fracture assessment (VFA), a test simultaneously conducted with the DEXA to detect abnormal compression of spinal vertebral bodies.[18] See Table 4 for a breakdown of which patients should receive vertebral imaging or VFA as well as BMD measurement.

Preventing Bone Loss and Fractures

A patient-centered approach is an integral part of osteoporosis management. Lifestyle modifications tailored to individual needs play a major role in prevention of bone loss and protection against future fractures. Lifestyle modifications to improve bone health include avoidance of caffeine, alcohol, and both active and passive exposure to tobacco smoke.[20-22] Caffeine consumption has been linked to decreased calcium absorption by the gut and thus an increased risk of bone loss and fractures.[1,18,19,21] Patients must be advised to discontinue or limit caffeine intake to fewer than two servings per day.[21] Alcohol consumption must be discouraged because it is associated with an increased risk of fracture attributed to multiple factors.[22]

Table 3. World Health Organization Criteria for Classification of Osteoporosis

Normal	T-score -1.0 or above
Low bone mass (osteopenia)	T-score between -1.0 and -2.5
Osteoporosis	T-score -2.5 or below
Severe or established osteoporosis	T-score -2.5 or below with ≥ 1 fracture

Table 4. Patients Who Should Receive Vertebral Imaging or Vertebral Fracture Assessment as Well as Bone Mineral Density Measurement

- Women ≥ 70 years of age and men ≥ 80 years of age with T-score ≤ -1.0;
- Women 65-69 years of age and men 70-79 years of age with T-score ≤ -1.5;
- Postmenopausal women and men ≥ 50 years of age with risk factors such as:
  - Low trauma fracture during adulthood (50 years of age and older)
  - Historical height loss of ≥ 4 cm (1.5 in)
  - Prospective height loss ≥ 2 cm (0.8 in)
  - Recent or ongoing long-term glucocorticoid treatment; ≥ 5 mg prednisone or equivalent per day for ≥ 3 months
  - Sexual hormone deprivation therapy; S/P breast or prostate cancer
  - S/P bariatric procedure
  - S/P organ transplantation
  - Thyroid hormone suppressive therapy, S/P thyroid cancer

S/P: status post

Alcohol intake is documented to decrease calcium intake and promote deleterious effects on bone formation.[22] Moreover, alcohol increases one's predisposition to falls that almost always are responsible for fractures.[22] Therefore, NOF recommends avoidance of excessive alcohol intake for patients who already manifest or pose a greater risk of osteoporosis. Likewise, NOF recommends total tobacco cessation, since either chewing or smoking one pack per day has been documented to induce a 5-10% reduction in BMD.[16,20]

Other forms of lifestyle changes involve resistance and weight-bearing exercises, which are well-established to increase BMD, improve balance, and reduce the risk of falls, thus resulting in prevention of fractures.[23,24] In prospective cohort studies, exercise was well-documented to reduce the overall risk of fracture in older adults.[23-26] The authors of another study demonstrated the most effective exercise for improving BMD of the femoral neck was non-weight-bearing, high-force exercise, such as resistance strength training, while a combined program of more than one exercise type was beneficial for lumbar spine BMD.[1,18,25,26]

Adequate vitamin D intake is crucial to maintaining bone health, as it is absolutely essential for bone mineralization. Vitamin D deficiency frequently is observed in patients with osteoporosis and leads to a further decline in BMD, predisposing to fractures, especially of the hips.[20] Vitamin D deficiency is deemed to occur because of a limited intake of food products with high vitamin D content, as well as a lack of direct exposure to ultraviolet rays in the sunlight due to an inadequate number of sunny days in certain geographic locations.[27-32] Alternatively, reduced absorption by the skin, perhaps because of use of sunscreens recommended for prevention of skin cancers in Caucasians and increased dermal pigment in populations with darker skin, also are implicated in induction of vitamin D deficiency. Daily therapeutic doses of vitamin D vary among individuals because of factors such as race, diet, medication interactions, and comorbid conditions.[27-30] Recent data suggest that the adequate daily dose of vitamin D3 cholecalciferol required to correct deficiency varies depending on the severity of deficiency and, thus, often is greater than 1,000 IU.[29,30] Alternatively, long-acting

vitamin D2 ergocalciferol may be administered once or twice weekly. Occasionally, physiologically active 1,25 hydroxyvitamin D3 may be required, especially in patients manifesting osteoporosis induced by steroids or chronic renal failure, as well as following organ transplantation.[33] Therefore, vitamin D supplementation often is recommended in patients with vitamin D insufficiency or deficiency.[1,27-33] It is important to note that vitamin D supplementation alone has not been shown to increase BMD or reduce the risk of fracture.[31,32]

Adequate calcium intake is another essential component in preserving bone mineralization and therefore plays a major role in prevention and/or treatment of osteoporosis. The recommended daily elemental calcium intake, derived from diet, supplements, or both, is 1,200 mg for women ≥ 50 years of age and men ≥ 70 years of age, and 1,000 mg for men 51-70 years of age.[29,30,32] Elemental calcium accounts for a certain fraction of the tablet containing calcium salt (e.g., calcium carbonate or lactate) and, therefore, is not the dose of the tablet. Appropriate calcium intake increases BMD and reduces fractures in conjunction with other therapeutic modalities.[1,18,32] Patients receiving adequate calcium amounts (1,000 mg to 1,200 mg) from diet do not require calcium supplements. However, those with inadequate intake should increase their daily intake of calcium-containing foods or take supplemental elemental calcium (generally 500 mg to 1,000 mg/day) in divided doses at mealtime.

The risks of excessive calcium intake are unclear. Intake of larger quantities is not more effective in improving BMD and actually may be detrimental because of promotion of renal calculi secondary to enhanced renal excretion, increased gastric acid secretion, and cardiovascular calcification.[30,31] Many calcium supplements are available. Calcium carbonate is an inexpensive option and contains a large amount of elemental calcium. It requires adequate gastric acid for absorption and is best taken with meals. In patients with higher gastric pH, such as the elderly or those on acid-suppressing therapy, calcium citrate may be a better option. However, it is more expensive and contains less elemental calcium. In addition to tablets, soft chew and gummy options recently have become available.[1,18,30]

Treatment

Osteoporosis treatment focuses on both nonpharmacologic and pharmacologic approaches. The goals of osteoporosis therapy include lowering osteoporosis-related morbidity and mortality by preventing fractures and deformities, as well as improving quality of life as a result of increasing bone mass or, at the least, reducing bone loss.

In addition to lifestyle measures detailed above, pharmacologic therapy is indicated in patients manifesting osteoporosis as well as those at high risk for fracture. According to the NOF, candidates for therapy include adults with a history of fragility fracture or those with established osteoporosis documented by BMD with a T-score ≤ 2.5. People at high risk for fracture are defined by BMD with a T-score between -1.0 and -2.5 combined with a 10-year probability of hip fracture at ≥ 3% or major osteoporotic fracture at ≥ 20% as determined by the FRAX tool.[1,18]

Pharmacologic agents for treating osteoporosis are classified as either antiresorptive (inhibiting osteoclast-mediated bone resorption) or anabolic (stimulating osteoblasts to enhance bone formation). Both groups of agents are documented to improve BMD and reduce fractures.[34] However, large comparative studies of safety and efficacy are lacking. Hence, selection of a therapeutic agent may be based on efficacy and safety. Cost, convenience, and other patient preferences, including compliance and adherence, often are more influential factors in a patient-centered approach.

Bisphosphonates

Evidence-based guidelines state that bisphosphonates should be considered as initial therapy because the main contributing pathophysiologic factor is the enhanced bone resorption in most patients manifesting osteoporosis.[1,18] These agents inhibit osteoclast activity and have been shown to improve BMD and reduce fractures.[34-38] Several bisphosphonates, including generic formulations, are available and are approved for both prevention and treatment. (*See Table 5.*) Oral formulations may appear as a convenient option, but bioavailability following oral administration is determined to be relatively poor when compared with intravenous (IV) preparations, which have almost 100% bioavailability. Moreover, oral bisphosphonates must be administered on an empty stomach for maximal absorption.[1,18,34,37] Therefore, patients should ingest oral bisphosphonates on an empty stomach, often in the morning on awakening with at least 8 ounces of water. Patients also must remain upright for 30 to 45 minutes to minimize the risk of esophagitis either due to reflux or the tablet remaining in and irritating the esophagus. Finally, patients should be reminded to wait at least 30 minutes before consuming food, drinks, or any other medications or supplements to enhance the drug's absorption. Because of these stringent requirements, compliance and adherence to oral bisphosphonates is relatively low. In contrast, compliance with IV bisphosphonates is impeccable because of administration in office or at an infusion center.

Oral bisphosphonates should be avoided in patients with active esophageal disorders, such as achalasia, stricture, varices, or dysmotility, as well as in those receiving agents for acid peptic diseases. Moreover, oral agents are contraindicated in patients with a history of potential gastrointestinal maldigestion or malabsorption and those who are unable to remain upright for 30-45 minutes. Therefore, these patients are suitable candidates for administration of IV formulations. Bisphosphonates must not be used in any patient with estimated glomerular filtration rate < 35 mL/min, as well as those with documented hypersensitivity. Correction of hypocalcemia and vitamin D deficiency is essential prior to oral or IV bisphosphonate administration to prevent onset of hypocalcemia. Many providers prefer IV formulations over oral administration because of better bioavailability, compliance, and convenience of yearly administration.

Side effects of bisphosphonate therapy include acute-phase reaction, a flu-like syndrome that can occur with both IV and high-dose oral administration.[34-38] The prevalence of the syndrome declines on repeated administration. Often, symptoms do not occur with prior exposure to any bisphosphonate. Hypocalcemia is rare and almost never ensues in the presence of normal vitamin D levels prior to administration of bisphosphonates. Gastrointestinal side effects, such as esophagitis, diarrhea, and heartburn, are common following administration of

Table 5. Pharmacologic Agents for the Treatment of Osteoporosis

Medication	Brand Name	FDA Indication	Dosing Regimen	Adverse Effects
Oral Bisphosphonates				
Alendronate	Fosamax	Prevention and treatment of hip, vertebral, and nonvertebral fractures	Prevention: 5 mg daily or 35 mg weekly Treatment: 10 mg daily or 70 mg weekly	Mild upper gastrointestinal events, esophageal ulcerations, perforations, bleeding events, muscular and joint pains Risk of atypical femur fractures, osteonecrosis of the jaw
	Fosamax Plus D	Treatment of hip, vertebral, and nonvertebral fractures	70 mg + 2,800/5,600 IU weekly	
Ibandronate	Boniva	Prevention and treatment of only vertebral fractures	150 mg monthly or 2.5 mg daily	
Risedronate	Actonel; Actonel with calcium	Prevention and treatment of hip, vertebral, and nonvertebral fractures	5 mg daily or 35 mg weekly or 75 mg x 2 days monthly or 150 mg monthly; 35 mg once weekly + 1,250 mg calcium x 6 days weekly	
Risedronate, delayed release	Atelvia	Treatment of hip, vertebral, and nonvertebral fractures	35 mg weekly	
IV Bisphosphonates				
Zoledronic acid	Reclast	Prevention and treatment of hip, vertebral, and nonvertebral fractures	Prevention: 5 mg every 2 years Treatment: 5 mg yearly	Risk of atypical femur fractures, osteonecrosis of the jaw Muscle and joint pain Acute renal failure Acute flu-like reaction
Ibandronate	Boniva	Treatment of only vertebral fractures	3 mg every 3 months	
Selective Estrogen-Receptor Modulator (SERM)				
Raloxifene	Evista	Prevention and treatment of only vertebral fractures	60 mg PO daily	Pulmonary embolism, thrombotic events, hot flashes
Conjugated Estrogen/SERM				
Conjugated estrogen/ bazedoxifene	Duavee	Prevention of only vertebral fractures	20/0.45 mg PO daily	Pulmonary embolism, thrombotic events
Calcitonin	Miacalcin	Treatment of only vertebral fractures	200 IU intranasal daily	Nasal congestion, nausea, flushing
Parathyroid Hormone				
Abaloparatide	Tymlos	Treatment of vertebral and nonvertebral fractures in high-risk patients	80 mcg SC daily	Arthralgia, pain, headache, nausea, orthostatic hypotension, hypercalcemia, hyperuricemia
Teriparatide	Forteo	Treatment of vertebral and nonvertebral fractures in high-risk patients	20 mcg SC daily	
RANKL Inhibitor				
Denosumab	Prolia	Treatment of hip, vertebral, and nonvertebral fractures	60 mg SC every 6 months	Muscle and joint pain, cellulitis, skin reactions Osteonecrosis of the jaw

PO: by mouth; SC: subcutaneously

oral forms. Postmarketing reports have documented the occurrence of bone, joint, and muscle pains, as well as atrial fibrillation.[34-36] Rarely, atypical femoral fractures have been reported.[39-41] However, pathophysiology of these fractures is poorly understood and is speculated to be secondary to concurrent presence of other bone disorders causing bone loss,

including osteomalacia, steroid therapy, and hyperparathyroidism.[39,41] Atypical fractures are reported to be less frequent in younger men compared to older women.[41] Moreover, the occurrence of these fractures appears to be drug dependent. The frequency of occurrence is reported most commonly with alendronate, followed by risedronate and zoledronic acid.[39] Osteonecrosis of the jaw is an even rarer reported side effect.[18,42-45] In most reports, osteonecrosis of the jaw is documented to occur with administering bisphosphonates to patients with malignancies or other cathectic disorders.[43,45] Therefore, the NOF and other organizations recommend performing dentoalveolar surgery if indicated only in patients who have used bisphosphonates for less than four years and have no other clinical risk factors promoting osteonecrosis.[42] In patients who have used bisphosphonates for more than four years, who have taken concomitant glucocorticoids, or who have a history of cancer, NOF guidelines recommend discontinuing bisphosphonates prior to dentoalveolar surgery to reduce the risk of osteonecrosis of the jaw.[42]

Denosumab

Denosumab is a human monoclonal antibody that targets RANKL, thereby preventing osteoclast formation.[10-12] Denosumab has been shown to improve BMD and reduce the incidence of new vertebral and nonvertebral fractures, including hip fractures in postmenopausal women.[1,18,46,47] It appears to be a reasonable alternative in patients in whom bisphosphonates may not be appropriate, such as those with reduced renal function or those who have contraindications to oral bisphosphonates. Denosumab 60 mg is administered subcutaneously in an office setting every six months. Calcium and vitamin D deficiencies must be corrected if documented prior to administration of denosumab. Atypical femur fracture and osteonecrosis of the jaw are reported occasionally, similar with bisphosphonates.[41-43,45] Few small studies have indicated an increased risk of infection (cellulitis, pancreatitis, endocarditis) with use of denosumab, although causality remains to be determined.[1,18,46-48] When treatment with denosumab is stopped after two years, BMD values return to baseline or above; therefore, a "drug holiday" is not recommended for denosumab.[48,49] Romosozumab, another antibody targeting RANKL, was FDA-approved recently for treatment of postmenopausal osteoporosis following a randomized clinical trial.[50,51]

Estrogen and Selective Estrogen-Receptor Modulator

Estrogen replacement therapy is established to prevent bone resorption and maintain bone structure. In the Women's Health Initiative (WHI) trial, estrogen therapy significantly reduced the incidence of vertebral and nonvertebral fractures, including hip fractures.[52,53] This finding is consistent with the data in several previous trials.[54] Thus, estrogen replacement therapy is well established to show a distinct benefit to bone structure and improve outcomes. However, long-term estrogen replacement therapy appears to increase the risk of breast cancer slightly, as documented in the WHI, although without raising mortality. Some experts believe that a lack of increased mortality may be due to increased surveillance and unmasking of cancer in the very early stage of the disorder. Furthermore, a slightly increased risk of breast cancer was neutralized by a decline in colorectal cancers of similar degree in the WHI.[52,53] Finally, an increase in cardiovascular outcomes noted in the initial WHI data was refuted by the same authors later because of the finding that initiation of hormone replacement therapy (HRT) in perimenopausal years actually reduced the cardiovascular events, including mortality, as documented in several previous observational studies.[54] Moreover, the maximum benefits regarding bone health are documented following initiation of HRT in women during the perimenopausal period.[52-54] Another established side effect is a significant rise in thromboembolic events, especially in the first two years following initiation of HRT.[55,56] However, these events can be avoided by simultaneous daily administration of aspirin 81 mg to 162 mg. Therefore, the FDA has approved HRT for prevention and treatment of osteoporosis beginning in the perimenopausal years. However, some experts still recommend that HRT should be reserved only for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.[53,54] This practice is being challenged by continued concerns about HRT-related adverse effects, such as breast cancer and cardiovascular, cerebrovascular, and thrombotic events, despite more recent data from the WHI trial.[52] In the same study (WHI), increased risk of breast cancer was almost totally neutralized by the same degree of decline in colorectal cancers.

Selective estrogen-receptor modulators (SERMs) activate distinctly selective tissue receptors for estrogen, which decrease bone resorption and increase bone density. Alternatively, they act as estrogen receptor blockers in other tissue.[57-62] Thus, they imitate estrogen effect in some tissues, specifically bone, endothelium, and coagulable function, and inhibit estrogen activity in other tissues (primarily breast but also in vasculature). Thus, many are effective in preventing or delaying recurrence of estrogen-responsive breast cancers and, therefore, are approved for this indication by regulatory agencies including FDA.[57-59] Finally, because of these dual opposing effects, side effects include thromboembolic disorders and possibly uterine cancer similar to unopposed estrogen receptor therapy, as well as hot flashes and night sweats due to estrogen receptor blockade.[60,61]

Raloxifene alone was FDA-approved for the prevention and treatment of osteoporosis because it demonstrated a reduced risk of spinal fractures in clinical trials, despite a lack of evidence in terms of benefit for nonvertebral sites including the hip.[18,57,58] Therefore, in women with a history of or susceptibility to breast cancer because of family history and low bone density, raloxifene may be a drug of choice to prevent the onset of both osteoporosis and breast cancer as well as recurrence of the latter since it demonstrated significant reduction in breast cancer in an osteoporosis trial.[57,58] When raloxifene therapy is discontinued, the BMD benefits are lost quickly during the next one to two years.[18]

The combination of the alternative SERM bazedoxifene with estrogen recently was approved for treating menopausal symptoms and preventing osteoporosis, but not for the treatment of osteoporosis.[62] Available data show this combination improves vertebral BMD; however, there are no data yet regarding fracture prevention, and long-term data are lacking.[60,62] It may become available in the future for treatment, as well as for

preventing estrogen withdrawal bleeding and breast tenderness in women with severe menopausal symptoms. The breast cancer risk for this combination is unknown, and common adverse effects consist of muscle cramps, nausea, abdominal pain, diarrhea, and oropharyngeal pain. Increased risks of stroke and venous thromboembolic disease also were evident.[60,61]

Calcitonin

Injectable and nasal formulations of recombinant salmon calcitonin are FDA-approved for treating postmenopausal osteoporosis. The daily nasal spray and subcutaneous injection inhibit osteoclastic bone resorption, although the efficacy of decreased fracture occurrence is evident only with new vertebral compression fractures as opposed to hip or other nonvertebral fractures.[63-67] Its effect on BMD is relatively modest compared to other agents, making it a suboptimal initial choice for treatment. Its adverse effect profile is acceptable, with nasal irritation and rhinitis with use of a nasal formulation. Subcutaneous administration may cause a transient local irritation and pain. A meta-analysis of nasal spray calcitonin showed a higher incidence of malignancy, although the FDA found no evidence of a causal relationship. When therapy with calcitonin is stopped, BMD benefits are lost within the first one to two years.[64,65] Because of reported analgesic effects,[63-67] calcitonin may be used for relief of pain caused by fractures, especially of vertebral compression variety. Calcitonin rarely is used except in the presence of contraindications (for example, estimated glomerular filtration rate < 35 or intolerance to newer agents).

Anabolic or Bone-Forming Drugs

Two parathyroid hormone simulating agents are approved for treatment of osteoporosis. Teriparatide, which has been available for several years, is a fractionated molecule of parathyroid hormone consisting of 1-34 amino acids. It is effective as an anabolic agent by stimulating osteoblast regeneration and function, in contrast to the whole parathyroid hormone molecule comprised of 84 amino acids known to promote bone resorption.[68-70] It also is likely to enhance mineralization via increasing circulating calcium by promoting gastrointestinal calcium absorption and facilitating renal tubular reabsorption of calcium. Alternatively, abaloparatide, which was approved recently, is a synthetic peptide of human parathyroid hormone-related protein.[71,72] Neither agent is a preferred initial option for osteoporosis unless antiresorptive agents (e.g., bisphosphonates or denosumab) are contraindicated or the disorder occurs mainly secondary to diminished bone formation (e.g., osteogenesis imperfecta).[68-72] Rather, they often are reserved for men or postmenopausal women with severe osteoporosis, a T-score of -3.5 or below in the absence of fracture, or a T-score of -2.5 or below plus an acute fragility fracture, since fracture healing is apparently facilitated by teriparatide in studies.[68-74]

Daily subcutaneous administration of these agents has demonstrated efficacy in reducing the risk of vertebral and other fractures, with the exception of hip fractures in postmenopausal women with osteoporosis.[18,68-72] Moreover, BMD often declines in bones in the forearms, making them susceptible to future fragility fractures. Short-term adverse effects are mild and transient and include nausea, orthostatic hypotension, and leg cramps. Hypercalcemia is reported rarely. Contraindications include hypercalcemia of any etiology as well as primary hyperparathyroidism and hyperparathyroidism secondary to chronic renal failure. These drugs may be used after resolution of the disorders causing hypercalcemia and secondary hyperparathyroidism (e.g., vitamin D deficiency). Therefore, extensive laboratory testing, including serum calcium, vitamin D, and parathyroid hormone levels, as well as markers of renal function, must be performed prior to making a decision on their administration.

Both agents have a boxed warning because of a documented occurrence of osteosarcoma in rats, and they are contraindicated in patients at increased risk of osteosarcoma (e.g., Paget's disease, open epiphyses, history of irradiation involving the skeleton, or unexplained elevation of alkaline phosphatase level). Currently, these agents are not indicated for treatment beyond two years because of the same concern.[68-72] After discontinuation of teriparatide or abaloparatide, BMD declines quickly, although fracture reduction may remain for one to two years.[73,74] Using alendronate or other bisphosphonates after cessation of parathyroid hormone-related agents can prevent this BMD loss and may be associated with further increases in BMD.[18,36,37,75-77] Therefore, therapy with antiresorptive agents (e.g., bisphosphonates) always is recommended for two years after treatment with teriparatide or abaloparatide.[18,68-74]

Other agents not FDA-approved but available as supplements in United States include strontium renelate and tibolone. After initial enthusiasm regarding efficacy of strontium renelate, especially in severe postmenopausal osteoporosis, the use declined because of serious adverse outcomes and alerts during surveillance for a few years. Alternatively, tibolone, a combination of progesterone and two weak synthetic estrogens initially tested for amelioration of menopausal symptoms, was noted to prevent onset of osteoporosis.[78-82] However, it is used rarely because of weak efficacy and availability of more effective agents for treatment of both menopausal symptoms and osteoporosis.[83,84]

Concomitant Use of Osteoporosis Therapy

A SERM and estrogen combination has been approved for osteoporosis prevention but not for treatment.[62] The combination of two antiresorptive agents, such as estrogen replacement therapy and bisphosphonates, has shown only modest improvement in BMD and bone turnover but without fracture reduction.[62,85] Similarly, adjunctive therapy, consisting of antiresorptive and anabolic agents, also has failed to add benefits. Moreover, potential remains for the deleterious additive risk of side effects.[86-91] Thus, no studies have demonstrated additional benefit of combination osteoporosis therapy on fracture reduction, the major outcome, compared to a single agent.[85-91] Finally, combination therapies are not likely to be cost effective. Therefore, combination therapy with any agents is not recommended for treatment of osteoporosis.[18]

Monitoring

Monitoring BMD during therapy is important to identify suboptimal response. However, no consensus

guidelines are available on the optimal approach. One approach is to repeat a DEXA measurement of the hip and/or spine after one to two years, and if BMD is stable or improved, continue with less frequent monitoring thereafter.[1,18] More frequent testing may be considered in patients with presumed rapid bone loss, such as chronic glucocorticoid users. If BMD is decreased or a fracture occurs while receiving therapy, other contributing factors should be reviewed. These include issues with medication efficacy, such as poor adherence, possible fear of side effects, inadequate gastrointestinal absorption, inadequate intake of calcium and vitamin D, or the development of a disease with adverse skeletal effects. If these concerns are eliminated, the next step in management includes initiating therapy with an alternative route of administration (e.g., oral bisphosphonates to IV bisphosphonates or intramuscular denosumab) or changing to drugs with different a mode of action (switching from an antiresorptive to an anabolic agent such as teriparatide especially at onset of fracture while being on previous therapy). Finally, measuring BMD a year later to ensure the initial result was accurate and taking action based on the result is recommended.[1,18] Routine monitoring of bone turnover markers with therapy is of unknown clinical utility and currently is not recommended, with the only exception being occurrence of fracture while receiving pharmacological therapy.[1,18] Routine monitoring of adherence and compliance, especially with oral drugs, is crucial since restrictions in terms of timing and modes of administration as well as potential adverse effects are recommended.

Duration of Therapy

With long-term use of osteoporosis treatment, the benefits of BMD improvement and fracture reduction must be weighed with potential adverse effects. Improvements in BMD reach a plateau at three to four years, regardless of the drug used.[1,18,34-36,46,50,52,54,60-62,68,71] Therefore, a drug holiday is recommended by some, although not by all, and remains controversial. Bisphosphonates are anticipated to accumulate in bones and may have persistent effects on bone after therapy cessation; "bisphosphonate holidays" may be considered. Patients who are low risk, have stable BMD, and have no previous vertebral fractures may consider stopping oral bisphosphonates after five years or IV zoledronic acid after three years. However, patients who are higher risk should receive a duration of 10 years of oral bisphosphonates or six years of IV zoledronic acid therapy. High-risk patients include those with a history of osteoporotic fracture before or during therapy, T-score below -3.5, increased fall risk, or frailty. The risk-benefit ratio of treatment beyond 10 years is unknown.[18]

During a "bisphosphonate holiday," no other treatment may be needed for low-risk patients (e.g., improvement in BMD or stable BMD without a fracture). Other agents, such as teriparatide or raloxifene, may be used for higher-risk patients. The optimal duration of a "bisphosphonate holiday" is unknown. It is theorized that due to binding affinity, it may be reasonable to continue a longer "holiday" with zoledronic acid, followed by alendronate, than perhaps the shortest "holiday" with risedronate.[40] It may be prudent to restart bisphosphonate therapy if a patient sustains a fracture or has significant and persistent bone loss of > 5% on at least two DEXA measurements. Alternatively, bisphosphonates may be restarted after a three- to five-year holiday in women who showed BMD improvement during the initial use of bisphosphonates. These recommendations regarding "bisphosphonate holidays" do not include ibandronate because cessation and resumption of use have not been evaluated fully. As stated earlier, other agents that result in a rapid decrease in BMD after therapy cessation, such as denosumab, calcitonin, and raloxifene, should not be stopped without a full evaluation of risks and benefits. Parathyroid hormone-related agents should not be used for more than two years because of the concern regarding the occurrence of osteogenic sarcoma.

As osteoporosis rates are set to continue rising, vigilance with screening and treating affected patients is paramount. Primary care providers should be able to identify patients at risk for osteoporosis and recommend appropriate prevention strategies. Timely screening should be performed, and based on results, an accurate diagnosis should be made. Primary care providers should be comfortable with varying osteoporosis treatment options and understand how and when to monitor and discontinue therapy.

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CME Questions

1. Which of the following factors increases the risk of osteoporosis?
   a. Hypothyroidism
   b. Celiac disease
   c. Hypertension
   d. Use of metformin
2. Which of the following has been proven to reduce fracture risk?
   a. Vitamin C supplementation
   b. Cardiovascular exercise
   c. Iron supplementation
   d. Alcohol cessation
3. Which of the following scenarios warrants osteoporosis treatment?
   a. History of fragility fracture
   b. T-score = +1.1
   c. Z-score = -0.9
   d. T-score = -1.5 with a FRAX 10-year probability of hip fracture of 2%
4. Which of the following medication regimens is considered an initial option to treat osteoporosis?
   a. Alendronate
   b. Bazedoxifene with estrogen
   c. Teriparatide
   d. Denosumab with ibandronate
5. Which of the following is a well-documented adverse effect associated with bisphosphonate use?
   a. Hypercalcemia
   b. Constipation
   c. Pulmonary embolism
   d. Esophageal perforation
6. Antiresorptive agents used in treatment of postmenopausal osteoporosis include which of the following?
   a. Recombinant parathyroid hormone
   b. Hormone replacement therapy
   c. Selective estrogen-receptor modulators
   d. Bisphosphonates
7. Which endocrine disorders can cause osteoporosis?
   a. Anorexia nervosa
   b. Sex hormone deprivation therapy
   c. Hypothyroidism
   d. Primary hyperparathyroidism

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