Review Article

Diagnosis and Treatment of Osteoporosis: What Orthopaedic Surgeons Need to Know

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Abstract

Osteoporosis, often called a silent disease, is a systemic condition of bone as a result of loss of bone mass and deterioration of its microarchitecture. The result is weakened bone, leading to an increased risk of fragility fractures. An estimated 9 million osteoporotic fractures occur every year worldwide. However, the true incidence of osteoporotic fractures is unknown because many are undetected. Astoundingly, this epidemic equates to an osteoporotic fracture every 3 seconds. Orthopaedic surgeons need to not only treat these fractures but also understand the underlying pathogenesis and risk factors to help prevent them. The management of osteoporosis is a critical part of musculoskeletal care. We must be familiar with the tools to assess osteoporosis and the treatments available, including risks and benefits. This review article is intended to deliver a review of the vast literature and provide the orthopaedic surgeon with the essential information necessary to manage the current osteoporosis epidemic.

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Osteoporosis has been defined by the National Osteoporosis Foundation (NOF) as a "bone disease that occurs when the body loses too much bone, makes too little bone, or both."[1] The World Health Organization operationally defines osteoporosis as a bone mineral density (BMD) measure by a dual-energy x-ray absorptiometry (DXA) that is "2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD).[2] As bone becomes less dense and weaker, there is an increased susceptibility to fracture. In both men and women, bone mass increases until approximately age 30 years after which it starts to decline. This decline is accelerated in women after menopause secondary to the decrease in estrogen levels resulting in an approximate 2% loss in BMD each year. Women usually have a lower BMD than men to begin with, and coupled with a more rapid loss in BMD, it results in the much higher rates of osteoporosis. According to the International Osteoporosis Foundation, one in three women and one in five men older than 50 years will experience an osteoporosis-related fracture.[3] Osteopenia is defined as a T score of less than -1.0 and is estimated to effect an even higher percentage of the population.

Pathogenesis

Bone is living tissue and therefore can remodel and respond to stress. This phenomenon is one of the main reasons why it is imperative that bone health is addressed throughout the lifespan as osteoporosis is a preventable disease. Bone is continuously being resorbed by osteoclasts

Table 1[5]

Factors and Their Effect on Bone Remodeling

Factor	Effect on Bone
Calcium (Ca)	90% of body calcium is stored in bones; a decrease in serum Ca will result in increase in bone resorption
Vitamin D	Helps increase Ca absorption
PTH	Stimulates the production of IL-6, which increases osteoclast formation and increases bone resorption; can also work to increase bone formation
1,25 dihydroxyvitamin D (calcitriol)	Stimulates the release of calcium in the blood
Calcitonin	Decreases bone resorption by inactivating osteoclasts
TSH	T3 and T4 stimulate osteoblasts
Estrogen	Regulates osteoclasts by inhibiting formation and increasing apoptosis (inhibits bone resorption)
Testosterone	Increases the proliferation and apoptosis of osteoblasts, converted to estrogen

PTH = parathyroid hormone, TSH = thyroid-stimulating hormone

and formed by osteoblasts. It is this homeostasis that maintains BMD.[4] Bone remodeling is dependent on many factors such as parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25-OH2D3), calcitonin, estrogen, and testosterone. These factors and the effect they have on bone remodeling are summarized in Table 1.[5] Menopause in women results in estrogen deficiency, which in turn results in increased bone resorption as osteoclasts live longer. Bone loss is accelerated in women because men do not experience a decrease in sex hormones resulting in an increase in bone remodeling. Men do experience reduced bone formation and thinning of trabeculae with aging, but at a decreased rate compared with women.[6]

Epidemiology

An estimated almost 9 million osteoporotic fractures occur annually worldwide. Of these, 51% occurred in Europe and the United States with hip, forearm, and vertebral fractures being the most common. As noted earlier, one in three women and one in five men older than 50 years are at risk of an osteoporotic fracture. Sixty-one percent of osteoporotic fractures occur in women, and it has been shown that women older than 45 years spend more days in the hospital secondary to osteoporosis compared with breast cancer, diabetes, or myocardial infarction. Many of these women are not identified as having osteoporosis and therefore are not treated, consequentially resulting in an 86% increased risk of sustaining a second osteoporotic fracture.[3] Although the fracture rates are higher for women, the mortality rates tend to be higher for men. Approximately 25% of osteoporotic hip fractures occur in men, and the 1-year mortality in men is 20% higher compared with women. Also, the lifetime risk for men to experience an osteoporotic fracture is 27%, more than twice the lifetime risk of prostate cancer (11.3%). Lastly, Gullberg et al projected that compared with rates of osteoporotic fracture in 1990, by 2050, the incidence of osteoporotic hip fractures will increase 240% in women and 310% in men.[3,7] Given these astounding statistics, it is imperative that orthopaedic surgeons can recognize, help manage, and prevent the growing osteoporosis epidemic.

Risk Factors

Multiple risk factors exist for osteoporosis and/or fractures as a result of low BMD. Nonmodifiable risk factors include female sex, white race, increasing age, and genetic/familial history. Modifiable factors include smoking (cigarettes), low body weight or body mass index, limited exercise, heavy alcohol intake, estrogen deficiency, and dietary factors such as low calcium and vitamin D intake.[8] Late menarche and early menopause have been associated with osteoporosis, as has hypogonadism in men.[9] Nutritional and hormonal compromise as a result of disordered eating or relative energy deficiency in sport can also lead to critical bone loss, including in adolescent patients.[9]

Secondary osteoporosis may be as a result of endocrine disorders such as hyperparathyroidism, hyperthyroidism, or diabetes or other diseases such as multiple myeloma, inflammatory bowel disease, inflammatory arthritis, or malabsorption.[10] Secondary localized osteoporosis may also be a result of regional radiation therapy. Medications such as glucocorticoids, anticonvulsants, aromatase inhibitors, androgen deprivation

Table 2

Risk Factors for Osteoporosis

Demographic	Female sex
	White race
	Increasing age
Dietary	Low calcium
	Low vitamin D
	Disordered eating/RED-S
Historical	Family history of osteoporosis or fracture
	Personal history of fracture
Hormonal	Low estrogen
	Late menarche
	Early menopause
	Hypogonadism in men
Medication	Glucocorticoids
	Thyroid medication
	Anticonvulsants
Lifestyle	Smoking
	Limited exercise
Secondary	Diabetes
	Hyperparathyroidism
	Hyperthyroidism
	Alcoholism
	Malabsorption
	Multiple myeloma
	Rheumatoid arthritis
	Inflammatory bowel disease

RED-S = relative energy deficiency in sport

therapy, proton pump inhibitors, and selective serotonin reuptake inhibitors are associated with osteoporosis[9] (Table 2).

Diagnosis

Because osteoporosis is unlikely to be symptomatic before the first fracture, accurate risk assessment is essential (Table 3).[11-13] As in most cases, the first step in diagnosis and assessment of osteoporosis is a detailed history and physical examination to elicit whether the patient has any relevant risk factors. Important points in the history include previous fractures, diseases associated with bone loss, chronic diseases, exercise, medications, alcohol and tobacco use, falls and fall risk, diet, and family history. For females, the number of pregnancies, lactation, menstrual history, and onset of menopause should be recorded. Menopause before age 40 years is considered early. Surgical history should include inquiring about oophorectomy or castration and parathyroid or adrenal procedures. Physical examination should include height and weight with assessment of loss of height. The spine should be inspected for kyphosis. The neurologic examination should include balance and mobility.[14] Sarcopenia and lower extremity muscle mass should be noted.[14] Signs of secondary osteoporosis should be noted, including hypogonadism, hyperthyroidism, diabetes mellitus, malnutrition, and liver disease.

With regard to laboratory testing, serum calcium and 25-hydroxyvitamin D may be checked. Other tests can help identify causes of secondary osteoporosis and include thyroid and parathyroid studies, complete blood count, urine calcium, protein electrophoresis, and testosterone (in men).[8,10]

The mainstay of testing for osteoporosis is DXA. DXA measures the areal BMD at the proximal femur and lumbar spine and compares it to the BMD of age-matched reference controls and of young adults. A typical DXA report includes the BMD of the intertrochanteric and trochanteric regions of the femur, the femoral neck, and lumbar vertebrae 1 to 4, as well as the T and Z scores for each region. The T score compares the patient's BMD to that of a young adult population (an average 30-year-old woman); the Z score compares the patient's BMD to an age, sex, and race or ethnicity-matched reference population. Both are reported as SDs from the mean BMD of the reference population. Indications for BMD testing are shown in Table 4.[12,13,15,16]

The World Health Organization defines osteoporosis as a T score below −2.5 in postmenopausal women and men older than 50 years. Osteopenia is defined as a T score between −1.0 and −2.5.[8,17] Osteoporosis can also be diagnosed on fracture criteria, that is a low trauma hip or spine fracture, regardless of BMD. In premenopausal women and men aged <50 years, osteoporosis cannot be diagnosed on densitometric criteria alone, and the Z score of −2.0 or lower is used to categorize these patients as having low bone density for chronologic age.[11]

High-resolution peripheral quantitative CT is an emerging technology

that is able to evaluate the microarchitecture of bone. High-resolution peripheral quantitative CT evaluates distal skeletal sites and is able to provide details such as volumetric BMD of both cortical and trabecular bone. Studies continue to determine its applicability to clinical practice.[18]

A BMD is recommended for all women aged 65 years and older and postmenopausal women younger than 65 years with increased risk determined by a formal clinical risk assessment. Data are not sufficient to recommend routine screening for men to prevent osteoporotic fractures.[12] Higher-risk men including those aged 70 years or older and those aged 50 to 69 years with associated risk factors (eg, low body weight, previous fracture, smoking) should be considered for BMD testing.[15] The prevalence of osteoporosis in US white men does not approach that of 65-year-old women until age 80 years.[19]

Table 3[11-13]

Evaluation of the Patient With Suspected Osteoporosis

Tools with scores associated with osteoporosis	Simple Calculated Osteoporosis Risk Estimation (SCORE, Merck): ≥6
	Osteoporosis Risk Assessment Instrument (ORAI): ≥9
	Osteoporosis Index of Risk (OSIRIS): <1
	Osteoporosis Self-Assessment Tool (OST): <2
	FRAX: computer algorithm
Screening tests	Bone mineral tests:
	Central DXA—measures the hip and lumbar spine
	Peripheral DXA—measures the forearm and calcaneus
	Bone biopsy
	Quantitative ultrasonography
Laboratory tests	Serum calcium, phosphate, creatinine with an estimated glomerular filtration rate, alkaline phosphatase, liver function, 25-hydroxyvitamin D, and glucose
	complete blood count
	24-hr urine calcium, creatinine, and sodium

DXA = dual-energy x-ray absorptiometry

Treatment

The orthopaedic surgeon may initiate general treatment strategies along with an evaluation and appropriate referral to osteoporosis consultants, as recommended by the American Orthopaedic Association Own the Bone Program (Figure 1). Many institutions have an osteoporosis multidisciplinary team, such as a fracture liaison service, for management and tracking, especially after hip and other major fractures. The treatment approach is best divided into prevention and treatment of low bone mass. Patients with low bone mass may be further classified using risk stratification predicting low-energy fracture and development of osteoporosis or using the presence of confirmed osteoporosis, as discussed later. Risk of future osteoporotic fracture is graded as low, moderate, or high. In general, patients with confirmed osteoporosis with moderate or high fractures meet indications for pharmacologic treatment as do those who present with an osteoporotic fracture.

Treatment should always include advice to maximize modifiable factors. These include increased activity (resistance and weight bearing exercise), adequate dietary calcium intake, ensuring vitamin D sufficiency, smoking cessation, and limiting alcohol. Pharmacologic treatments of osteoporosis include antiresorptive drugs and anabolic (bone strengthening) drugs, and those that do both. The specific prescription depends on the extent of low bone mass (osteopenia or osteoporosis), previous low-energy fracture, risk of osteoporotic fracture, and comorbidities.

Most patients will benefit from a discussion on diet, exercise, and other lifestyle issues to prevent osteoporosis and to augment pharmacologic treatment. The NOF performed a systematic review for recommendations on peak bone mass development and lifestyle factors.[20] This comprehensive position paper recommends physical activity, especially for growing bone, and calcium. The specific types of activity promoting bone formation (ie, frequency, intensity, and duration) are less clear for children and adults.[20] Weight-bearing activities (eg, walking, jogging, running, ballroom dance) and resistance training (eg, weight lifting, rubber bands) are recommended for adults. The Centers for Disease Control and Prevention reported that 120 to 300 minutes of moderate or higher intensity activity per week was associated with less hip fractures in older adults. Combining this with balance and muscle strengthening was associated with less falls.[21] Adequate dietary calcium and vitamin

Table 4[12,13,15,16]

Indications for BMD Testing	
Women	Women aged ≥65 yr
	Secondary osteoporosis
	Postmenopausal women with
	Low-energy fractures
	Incidental finding of radiographic fracture (spinal compression fx)
	Glucocorticoid treatment >3 mo
	Peri- or postmenopausal women
	Menopause before age 40 yr
	Family history of osteoporotic fractures
	Risk factors below
Men	Men aged ≥70 yr
	Men aged 50–69 yr with risk factors below
Women and Men	Low body weight
	Previous low-energy fracture
	Smoking
	Within at least 6 mo of initiation of glucocorticoid treatment (all adults aged ≥40 yr and adults aged <40 yr with high fracture risk)

BMD = bone mineral density

D are recommended for children and adults and preferred over supplements. The amounts depend on age and sex with increases during pregnancy and lactation. A maintenance dose follows treatment for insufficient or deficient vitamin D levels. Calcium and vitamin D supplementation in community and institutional dwelling middle-aged and older adults was associated with the decreased risk of hip fractures by 30% and all fractures by 15%.[22] There has been a question as to the effects of calcium on the cardiovascular system, but most evidence-based studies show no significant association between calcium dose and type with myocardial infarction or coronary artery calcification. Other modifiable factors promoting bone health are smoking cessation and moderation of alcohol intake. These strategies should be emphasized for prevention and for patients with low BMD. Indications for pharmacologic treatment beyond calcium and vitamin D depend on risk stratification for development of fracture, BMD, and history or presence of fragility fracture. The goals of therapy are to increase BMD, decrease resorption, and uncouple bone formation and resorption in favor of increasing bone density.

Determination of Risk Category

Both BMD and clinical risk factors for osteoporosis are considered to determine the likelihood that the patient will sustain an osteoporotic fracture. This likelihood is usually grouped by low, moderate, and severe. Several tools are widely available to determine future facture risk (Tables 3 and 7). Each has limitations. Lower-risk patients are generally not prescribed pharmacologic treatment beyond calcium and vitamin D. Higher-risk patients are considered for pharmacologic osteoporotic agents to improve bone mass and to prevent fractures. In general, the guidelines are different for men and women. For patients diagnosed with osteoporosis, treatment is most often based on the BMD, a fracture risk assessment such as the Fracture Risk Assessment Tool (FRAX), and the presence of fragility fracture. The World Health Organization developed the FRAX to help estimate fracture risk for individual patients and to guide treatment (www.shef.ac.uk/frax/). The FRAX uses studied clinical risk factors to predict a person's 10-year fracture risk (Figure 2). A FRAX 10-year probability score of >3% for hip or >20% for other major fracture with a BMD T score between −1 and −2.5 in postmenopausal American women aged 50 years or older is an indication for pharmacologic treatment. Many FDA-approved medications exist to reduce the incidence of osteoporotic fractures. There is at least moderate benefit in treating postmenopausal women aged 65 years and older and younger postmenopausal women with BMD consistent with osteoporosis. Repeat bone density testing is usually performed at 2-year intervals.

Patients with BMD-documented osteoporosis (with or without fracture) or those with a high risk of fracture usually have pharmacologic osteoporotic agents added to the treatment plan. The treatment chosen depends on the risk of fracture. In general, the treatment is not specific to the anatomic site of the fracture with one exception, spinal fractures. The American Academy of Orthopaedic Surgeons Clinical Practice Guidelines notes moderate evidence to support calcitonin for symptomatic osteoporotic spinal compression fractures. Moderate fracture risk patients often are considered for alendronate or risedronate, with alternatives including denosumab and zoledronic acid. High-risk patients are considered for denosumab, zoledronic acid, teriparatide, or abaloparatide.

Pharmacologic Treatments of Osteoporosis

Available treatments of osteoporosis fall into two broad classes: the antiresorptives and anabolic agents. Antiresorptive medications inhibit the formation and function of bone-resorbing osteoclasts, thus tipping the balance of bone remodeling toward bone formation. Anabolic agents target osteoblasts to promote bone formation. US guidelines for osteoporosis treatment have been published by the NOF, the American College of Endocrinology, the Endocrine Society, and the American College of Physicians and provide additional information.[11,13,15,23]

Because orthopaedic surgeons are frequently in the position of determining osteoporosis treatment in the immediate postfracture period, it is important to note that little data are available to guide the timing of treatment relative to an incident fracture. The limited data that exist address antiresorptive therapies only. In the HORIZON trial, administration of zoledronic acid early (ie, within 2 weeks of fracture) did not increase nonunion rates compared with later administration (ie, 2 to 12 weeks after fracture), and the incidence of delayed facture healing was similar between zoledronic acid–treated and placebo-treated patients (PMID 2115302, level II). Other studies have also failed to detect differences in time to fracture healing and other outcomes in early compared with late diphosphonate initiation in either surgically repaired hip fracture or distal radius fractures (PMID 22733953, level IV; 22992762, level IV). No formal recommendations exist regarding the timing of initiation of therapy in the setting of incident fracture.

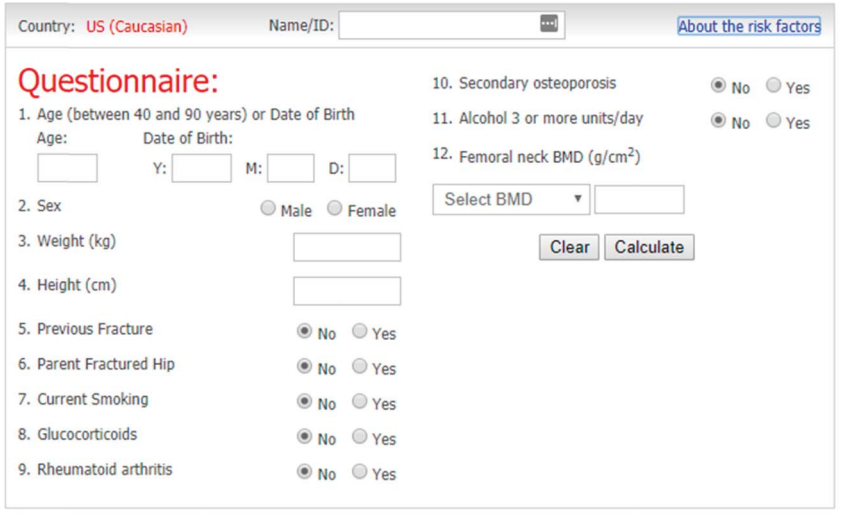
Because of the role of osteoclasts in callus remodeling, current antiresorptive could theoretically impair fracture healing. In the FREEDOM trial, denosumab did not increase delayed healing after nonvertebral fracture compared with placebo (PMID 23097066, level II). In patients already on diphosphonates, a clinically insignificant delay in healing of distal radius fractures was observed in one retrospective study (PMID 19345861, level IV). A case-control study of patients with humerus fractures found that current diphosphonate use increased the

Figure 1

Nutrition Counseling	1	Improving calcium intake
	2	Increasing vitamin D intake
Physical Activity Counseling	3	Weight-bearing and muscle strengthening exercise
	4	Fall prevention education
Lifestyle Counseling	5	Smoke cessation
	6	Limiting excessive alcohol intake
Pharmacotherapy	7	Pharmacotherapy
Testing	8	Testing bone mineral density: DXA (Dual Energy X-Ray Absorptiometry)
Communication	9	Physician referral letter to report the patient's fragility fracture, risk factors, and recommendations for treatment
	10	Patient education letter to explain bone health risk factors and recommendations for treatment

Table showing the AOA "Own the Bone" 10-point program to prevent additional osteoporosis fractures (after index osteoporotic fracture). https://www.ownthebone.org/OTB/About/What_Is_Own_the_Bone.aspx.

Figure 2



Screenshot showing the FRAX online assessment tool for osteoporosis.

Table 5

Antiresorptive Agents

Drug	Trade Name	Route	Typical Dosing Regimen	Sites With Demonstrated Fracture Risk Reduction	Estimated Cost, 1-mo Supply[a]	Contraindications
Diphosphonates						
Alendronate	Fosamax Binosto (effervescent tablet)	per os per os	70 mg weekly 70 mg weekly	Vertebral, nonvertebral, and hip	$1.16	CrCl < 35 mL/min Esophageal disorders including Barrett esophagus Roux-en-Y gastric bypass Vitamin D deficiency
Risedronate	Actonel	per os	35 mg weekly	Vertebral, nonvertebral, and hip	$108	CrCl < 30 mL/min Esophageal disorders including Barrett esophagus Roux-en-Y gastric bypass Vitamin D deficiency
Ibandronate	Boniva	per os	150 mg monthly,	Vertebral	$6.80	CrCl < 30 mL/min Esophageal disorders including Barrett esophagus Roux-en-Y gastric bypass Vitamin D deficiency
Ibandronate	Boniva	IV	3 mg every 3 mo	Vertebral	$57	CrCl < 30 mL/min Vitamin D deficiency
Zoledronic acid	Reclast	IV	5 mg yearly	Vertebral, nonvertebral, and hip	$87	CrCl < 35 mL/min Vitamin D deficiency
Other						
Denosumab	Prolia	subcutaneous	60 mg every 6 mo	Vertebral, nonvertebral, and hip	$196	Hypocalcemia Vitamin D deficiency Pregnancy
Raloxifene	Evista	per os	60 mg daily	Vertebral	$17	History of thromboembolism
Calcitonin	Miacalcin Fortical	Intranasal subcutaneous	200 IU daily 100 IU every other day	Vertebral	$258	Hypersensitivity to salmon products Hypocalcemia Vitamin D deficiency

[a] Based on the National Drug Acquisition Cost as of January 23, 2019, from https://data.medicaid.gov. Pricing provided is for generics, when available. Cost to consumer varies widely depending on prescription benefits and eligibility for manufacturer rebates, grants, and/or copay assistance.

risk of nonunion, although nonunion rates were overall very low (PMID 18843515, level IV). Given the risk of rebound vertebral fracture with denosumab discontinuation, existing guidelines recommend against discontinuation of denosumab without consideration of alternative therapy (PMID 28789921, level VII). However, no formal recommendations exist regarding continuation of osteoporosis therapy, specifically in the setting of incident fracture.

Antiresorptive Agents

The most widely used medications in this class are the diphosphonates. Diphosphonates, synthetic analogs of pyrophosphate that bind to hydroxyapatite in bone, are taken up by and inhibit osteoclasts as they resorb bone. Because of their incorporation into bone tissue, diphosphonates can be recycled onto the bone surface during bone remodeling, resulting in prolonged duration of

Table 6

Anabolic Agents

Drug	Trade Name	Route	Typical Dosing Regimen	Demonstrated Fracture Risk Reduction	Estimated Cost, 1-mo Supply[a]	Contraindications
Teriparatide	Forteo	SQ	Once daily for up to 24 mo	Vertebral and nonvertebral	$3,179	Hyperparathyroidism Hypercalcemia History of radiation therapy Paget disease of bone Unexplained elevated alkaline phosphatase History of skeletal metastases
Abaloparatide	Tymlos	SQ	Once daily for up to 24 mo	Vertebral, nonvertebral, and hip	$1,771	Hyperparathyroidism Hypercalcemia History of radiation therapy Paget disease of bone Unexplained elevated alkaline phosphatase History of skeletal metastases
Romosozumab (not yet FDA approved)	Evenity	SQ	Monthly for 12 mo	Vertebral, nonvertebral, and hip	Not yet available	

SQ = subcutaneous

[a] Based on the National Drug Acquisition Cost as of January 23, 2019, from https://data.medicaid.gov. Pricing provided is for generics, when available. Cost to consumer varies widely depending on prescription benefits and eligibility for manufacturer rebates, grants, and/or copay assistance.

action.[24] Diphosphonates are available in a wide variety of dosing regimens (Table 5). Orally available diphosphonates include alendronate, risedronate, and ibandronate and are typically dosed weekly or monthly. Alendronate and risedronate have demonstrated fracture reduction efficacy for vertebral, nonvertebral, and hip fractures, whereas trials for ibandronate showed statistically significant reduction for vertebral fractures only. Oral diphosphonates must be taken on an empty stomach with a minimum 30-minute wait before ingesting anything other than water. Oral diphosphonates are generally well tolerated, but can cause gastrointestinal upset and esophageal irritation, and are relatively contraindicated in patients with esophageal abnormalities. For patients unable to tolerate or adhere to oral formulations, zoledronic acid is a once-yearly intravenously administered diphosphonate with broad fracture reduction efficacy. The initial infusion of zoledronic acid is associated with a flu-like syndrome (eg, arthralgia, myalgia, headache, fever) in up to one third of patients[25]; premedication with acetaminophen may reduce this risk and treat symptoms. Diphosphonates should not be used in patients with reduced kidney function (GFR: Glomerular Filtration Rate <30 to 35 mL/min).[26]

Denosumab is a fully human monoclonal antibody that neutralizes receptor activator of NF-κB ligand, the key cytokine required for differentiation and survival of osteoclasts. Denosumab is a potent antiresorptive agent with a rapid onset and duration of action of approximately 6 months. It is administered subcutaneously by a healthcare professional. In contrast to diphosphonates, renal insufficiency is not a contraindication. Rebound fractures are a concern with denosumab, with numerous case reports of vertebral fractures occurring after discontinuation or delay in dosing.[27-29]

Potential adverse effects common to diphosphonates and denosumab are hypocalcemia and musculoskeletal complaints. Vitamin D and calcium should be normal before starting these agents. More serious potential adverse events are osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF). ONJ presents with exposed necrotic bone and jaw pain. It was initially seen in patients with cancer receiving high-dose antiresorptives, with subsequent case reports in patients with osteoporosis. The estimated incidence of ONJ in patients treated with diphosphonates or denosumab for osteoporosis is 1/10,000 to

Table 7

Resources for Osteoporosis Risk Assessment

Risk Assessment Tool	URL
FRAX	https://www.sheffield.ac.uk/FRAX/
FRAX desktop version	http://www.frax-tool.org
SCORE (Simple Calculate Osteoporosis Risk Estimation)	https://reference.medscape.com/calculator/osteoporosis-risk-score
IOF 1-minute risk test	https://www.iofbonehealth.org/iof-one-minute-osteoporosis-risk-test
Garvan Institute fracture risk calculator	https://www.garvan.org.au/promotions/bone-fracture-risk/calculator
FORE 10-yr fracture risk calculator	https://riskcalculator.fore.org
American bone health calculator	https://americanbonehealth.org/calculator/

1/100,000 patients per year, with common risk factors being invasive dental procedures and poor dental hygiene.[30] AFFs are subtrochanteric transverse fractures occurring with no or minimal trauma and typically originating in the lateral cortex. AFFs present with persistent thigh or groin pain. Although potent antiresorptives increase the risk of AFFs, these fractures also occur in patients not on treatment. The absolute risk of AFFs with diphosphonate treatment is low and estimated at between 3 and 50/100,000, although risk may increase with long-term use.[31,32] The risk of these rare adverse events must be balanced against the often substantial risk of fracture in the absence of treatment.

One hypothesis to explain the association of ONJ and AFF with potent antiresorptive therapies is the idea that long-term suppression of bone turnover leads to accumulation of bone microdamage. In addition, several trials have suggested that in low-risk patients a "diphosphonate holiday" may be considered after 5 years of oral diphosphonate or 3 years of IV zoledronic acid. Several guidelines support the use of diphosphonate holidays.[13,33] Whether treatment with alternative agents such as an anabolic or less potent antiresorptive during the holiday is beneficial is not clear, nor is the optimal duration for drug cessation.

Less potent antiresorptives that are approved to treat osteoporosis include the estrogen receptor agonist raloxifene and calcitonin. With fracture prevention efficacy at the spine only, raloxifene is typically reserved for younger patients with spine-predominant osteoporosis or for those for whom its additional benefit for breast cancer reduction is desirable. Raloxifene is associated with an increased risk of venous thromboembolism and menopausal symptoms. Calcitonin is rarely used to treat osteoporosis because fracture risk reduction is less robust than other agents and is limited to the spine. Short-term calcitonin has been suggested to be analgesic in the setting of acute painful vertebral fracture and is more commonly used in this situation.[13] Estrogens, although FDA approved for prevention of osteoporosis, are not approved for treatment. Available antiresorptives are summarized in Table 5.

Anabolic Agents

The two available anabolic agents, teriparatide and abaloparatide, are both peptide agonists of the PTH receptor and require daily self-injection for up to 24 months. Teriparatide is a recombinant peptide containing the first 34 amino acids of human PTH and was approved in 2002 for treatment of patients with osteoporosis at high risk of fracture or those who failed or were intolerant of other therapies. Abaloparatide, approved in 2017, is the newest osteoporosis therapy. Abaloparatide is a recombinant peptide containing the first 34 amino acids of human PTH-related peptide (PTHrP). Both drugs activate the PTH receptor to promote bone formation. Teriparatide reduces the risk of vertebral and nonvertebral fractures, without a detectable decrease in hip fractures in trials to date. A trial of abaloparatide in contrast showed fracture reduction at all sites.[34] When treatment is stopped, bone loss declines quickly, and PTH receptor agonist therapy is typically followed by treatment with antiresorptives. Both teriparatide and abaloparatide have a black box warning because of the occurrence of animal osteosarcoma in rodents treated with high doses for prolonged periods. In practice, the incidence of osteosarcoma is similar to the background incidence.[35] However, neither should be used in patients at an increased risk of osteosarcoma, including those with a history of skeletal radiation or Paget disease of bone. Hyperparathyroidism and hypercalcemia are additional contraindications. Potential adverse effects include nausea, orthostatic hypotension, and hypercalcemia that is usually mild and transient. A third anabolic agent, romosozumab, a human monoclonal antibody that blocks the action of sclerostin is under currently under review by the FDA. Romosozumab both promotes bone formation and has antiresorptive effects. A comparison of anabolic agents is provided in Table 6.

Although highly effective osteoporosis therapy is available, it is underused, including in those patients at high risk of future fracture, such as

those with hip fracture. A clear consensus exists that treatment of patients with hip fracture reduces the risk of recurrent fracture.[36] Despite this, a recent study found that in 2003, only 15% of patients with hip fracture were prescribed diphosphonates, and this number declined over the next decade to only 3%.[37] The current situation has been described as a "crisis" in osteoporosis treatment,[38] and the serious consequences of undertreatment are highlighted by the plateauing of age-adjusted hip fracture rates in the United States as of 2012, which had previously dropped steadily from the late 1990s.[39] Although patient perception of the risks of osteoporosis treatment and lack of public understanding of the morbidity associated with fragility fractures certainly contribute to lack of treatment, low DXA screening rates suggest that our identification of patients at risk is also lacking. Orthopaedic surgeons are well positioned to identify patients at high risk of osteoporosis by virtue of having sustained a fragility fracture and can play a critical role in improving care by referral of these patients for appropriate evaluation and treatment. Resources for identification of patients with osteoporosis that may be helpful for orthopaedic surgeons are included in Table 7.

Although osteoporosis is often managed by primary care physicians, organized programs designed to improve secondary prevention in patients with fragility fractures, or Fracture Liaison Services (FLS) have been developed by many hospital systems. FLS have demonstrated improvement in identifying patients at risk and preventing recurrent fractures. For example, the Health Service Trusts in Glasgow, Scotland, improved the rate of osteoporosis evaluation for fracture patients from less than 10% to close to 100%.[40] The Kaiser Permanente Southern California FLS program was started in 2002 and by 2006 resulted in a 37% reduction in hip fractures compared with expected, with considerable cost savings.[8] FLS models vary widely from centrally coordinated care to patient education only, with those models involving a coordinator resulting in improved rates for osteoporosis evaluation and treatment.[41]

Summary

In summary, orthopaedic surgeons are at the front line of recognizing patients with osteoporosis and those at high risk of osteoporotic fracture. Osteoporosis treatment provides clear and substantial fracture prevention benefit: treating 1,000 patients with a diphosphonate for 3 years has been calculated to prevent approximately 100 fractures.[38] The first step in getting patients into treatment is identification and referral of patients at risk. The orthopaedic surgeon can play an essential role in educating patients that they are at risk and that safe and effective therapies exist and referring them for appropriate assessment and management.

References

Levels of evidence are described in the table of contents. In this article, references 11-13, 15, 20-23, 26, 30, 34, and 36 are level I studies. Reference 32 is a level II study. References 6, 8, 10, 14, 19, 31, 37, 39, and 41 are level III studies. References 4, 7, 25, 27-29, and 40 are level IV studies. References 1-3, 9, 17, 24, 33, 35, and 38 are level V studies. Reference 18 is level VII study.

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