Osteoporosis

Screening, Prevention, and Management

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KEYWORDS

• Osteoporosis • Osteopenia • Fragility fractures • Prevention • Screening
• Management

KEY POINTS

- Osteoporosis is underdiagnosed and undertreated despite evidence-based recommendations for screening and the availability of efficacious treatments.
- Bone mineral density (BMD) testing should be offered to all women age 65 and older and many younger postmenopausal women with elevated risk.
- The BMD rescreening interval for healthy nonosteoporotic women should take into account the baseline T-score.
- Clinically silent vertebral fractures found incidentally on imaging should prompt evaluation and treatment of osteoporosis.
- Patients with established osteoporosis or a 10-year risk of any major fracture of 20% or hip fracture of 3% should be treated with an osteoporosis-specific medication, lifestyle measures, and adequate calcium and vitamin D intake.

INTRODUCTION

Osteoporosis, a skeletal disorder of low bone density and disrupted bone architecture leading to fractures, is a common and costly condition among postmenopausal women. Nearly one-half of Caucasian women aged 50 years and older will experience an osteoporosis-related fracture in their lifetime.[1] In 2011, there were approximately 2 million osteoporotic fractures affecting US adults.[2] Current estimates suggest that 9.9 million Americans are affected by osteoporosis, and the prevalence is expected to increase as the population ages.[3]

Largely a silent disease before fracture, osteoporosis often goes undetected until a sentinel fracture event. The most common fracture sites are vertebrae (spine),

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proximal femur (hip), and distal forearm (wrist). Osteoporotic fractures often cause pain, deformity, and decreased mobility and can have a significant impact on a patient's quality of life. These fractures frequently result in a short- or long-term need for a higher level of care. In fact, about 20% of patients who suffer hip fractures require a long-term skilled nursing facility stay, and 60% of patients never regain their prefracture level of functional independence.[1] Osteoporotic fractures are also associated with an increased risk of mortality. A 2009 systematic review found an 8% to 36% excess mortality in adults the first year after hip fracture as compared with similar adults who did not have hip fracture.[4]

The economic toll of osteoporotic fractures is significant. In 2005, it was estimated that direct care expenditures for these fractures, including medical office visits, hospital admissions, and nursing home admissions, was $19 billion annually.[5] Given the aging population, this cost has been projected to rise to $25.3 billion by 2025.[5]

Despite evidence-based guidelines for screening and the availability of effective treatment, osteoporosis remains underdiagnosed and undertreated, especially in nonwhite women.[6] Given the high prevalence, morbidity, and excess mortality of osteoporotic fractures, which primarily affect postmenopausal women, we advise clinicians to counsel all women on preventative measures, regularly assess female patients for excess risk, screen when appropriate, and treat osteoporosis when it is diagnosed.

DEFINITIONS

Table 1 provides a lexicon of common terminology used in discussing osteoporosis.

PATHOPHYSIOLOGY

Bone is a dynamic, constantly remodeling tissue composed of specialized bone cells (osteoblasts, osteoclasts, and osteocytes) and a mineralized collagen matrix. Osteoblasts build new bone by secreting collagen fibers upon which calcium and phosphate crystallize. Osteoclasts break down bone tissue by secreting acid and enzymes to resorb the mineralized collagen fibers. Osteocytes secrete growth factors that

Table 1
Definitions of common terms

Term	Definition
Fragility fracture	A fracture occurring in the absence of major trauma, such as a fall from standing height, coughing, or sneezing. Usually involves the spine, ribs, hip, pelvis, wrist, or humerus
T-score	The number of standard deviations a patient's BMD is above or below the mean BMD of a young adult reference population
Z-score	The number of standard deviations a patient's BMD is above or below the mean BMD of an age-matched adult reference population
Osteoporosis	Low bone mass, microarchitectural deterioration of bone tissue and decreased bone strength associated with increased fracture risk. Diagnosed as BMD T-score on DXA at the hip or lumbar spine that is less than or equal to −2.5 *or* the presence of a fragility fracture regardless of BMD.
Osteopenia	BMD T-score on DXA at the hip or lumbar spine that is between −1.0 and −2.5.

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry.

regulate osteoblast and osteoclast activity and hence bone formation. Multiple hormones, cytokines, growth factors, and other molecules act to influence the activity of osteoblasts and osteoclasts, including parathyroid hormone, calcitonin, calcitriol, human growth hormone, insulin-like growth factor I, glucocorticoids, thyroid hormones, and sex hormones.

Bone balance is determined by the relative activity of osteoblasts and osteoclasts. Most women achieve peak bone density by 18 to 25 years of age.[7] After peak bone density is achieved, bone continues to be remodeled throughout a person's lifetime to respond to new stresses and replace older, weakened bone. Age-related bone density loss begins shortly after peak bone density is attained owing to an imbalance of bone formation and bone resorption in the remodeling process. After menopause, the rate of bone remodeling increases, which accelerates bone loss owing to this inherent imbalance. Osteoporosis and other conditions of low bone density arise owing to an excess activity of osteoclasts that compounds age-related bone density loss (**Fig. 1**).

RISK FACTORS

Advancing age, female gender, and estrogen deficiency are widely recognized risk factors for osteoporosis; however, there are many other exposures that increase risk for bone density loss. These factors include behavioral factors, such as excess alcohol use, smoking, inadequate physical activity level, and inadequate calcium and vitamin D intake, as well as demographic factors such as white or Asian race, low body weight, and tall stature (**Table 2**). Several medical disorders can cause secondary osteoporosis, including hypogonadal conditions, rheumatoid arthritis, hyperparathyroidism, and many others (**Box 1**). Low bone density is also a recognized adverse effect of several classes of medications (**Box 2**). Glucocorticoids in particular are associated with a significant risk of bone loss and increased fracture risk. In fact, decreased bone density occurs with daily doses as low as 2.5 to 7.5 mg of prednisone or equivalent and is most rapid during the first few months of use.[8]

It is important to consider each woman's level of exposure to these risk factors when deciding when to initiate screening for osteoporosis (see section on screening).

In addition, because nearly all osteoporotic hip fractures and many vertebral compression fractures occur in the setting of falls, it is also important to consider a patient's risk factors for falls. These factors include environmental factors such as trip

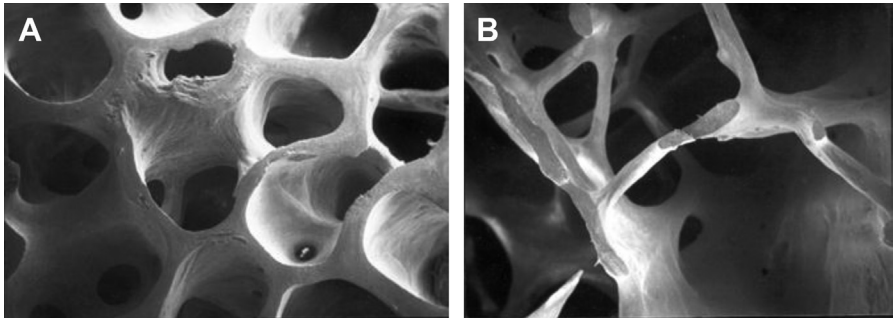

Fig. 1. Micrographs of normal and osteoporotic bone. (*A*) Normal bone. (*B*) Osteoporotic bone. (*From* Dempster DW, Shane E, Horbert W, et al. A simple method for correlative light and scanning electron microscopy of human iliac crest bone biopsies: qualitative observations in normal and osteoporotic subjects. J Bone Miner Res 1986;1(1):15–21; with permission.)

Table 2
Primary risk factors for osteoporosis

Demographic Factors	Behavioral Factors
Advancing age	Current smoking
Female gender	Excess alcohol use (>2 standard drinks per day)
White or Asian race	Inadequate weight bearing exercise
Low body weight (<127 lbs)	Inadequate calcium intake
Taller height	Inadequate vitamin D intake
Family history	

hazards in the home, patient neuromuscular factors such as impaired balance, reduced proprioception and deconditioning, and medical conditions such as orthostatic hypotension and vitamin D insufficiency (Table 3).

SCREENING

All women aged 65 and older should be screened for osteoporosis with bone mineral density (BMD) testing with dual-energy x-ray absorptiometry (DXA). This recommendation is universally endorsed by major society guidelines based on evidence of cost effectiveness in this age group (Table 4).[9,10]

Box 1
Secondary causes of osteoporosis

Hypogonadal conditions, including:

- Premature menopause
- Exercise oligomenorrhea
- Eating disorders

Hyperparathyroidism

Hyperthyroidism

Type 1 diabetes

Rheumatoid arthritis and other connective tissue diseases

Malabsorption syndromes, including:

- Celiac disease
- Bariatric surgery
- Pancreatic disorders

Chronic liver disease

Chronic kidney disease

Chronic obstructive pulmonary disease

Hematologic disorders, including:

- Multiple myeloma
- Hemoglobinopathies
- Hematologic malignancies

Box 2
Medications that cause or contribute to osteoporosis

Aluminum (in antacids)

Anticoagulants (heparin)

Anticonvulsants

Aromatase inhibitors

Barbiturates

Chemotherapy drugs

Cyclosporine

Depo-medroxyprogesterone

Glucocorticoids

Gonadotropin-releasing hormone agonists

Lithium

Methotrexate

Parenteral nutrition

Proton pump inhibitors

Selective serotonin reuptake inhibitors

Tacrolimus

Tamoxifen (premenopausal use)

Thiazolidinediones

Thyroid hormone (in excess)

Adapted from National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014. p. 12.

Table 3
Fall risk factors

Environmental Factors	Neuromuscular Factors	Medical Factors
Loose throw rugs	Poor balance/gait instability	Advanced age
Low level lighting	Low or impaired vision	Cardiovascular diseases including arrhythmia, congestive heart failure
Slippery surfaces	Reduced proprioception	Dehydration/orthostatic hypotension/vascular insufficiency
Obstacles on the floor	Impaired ability to transfer and mobilize	Vitamin D insufficiency (serum 25-OH-vitamin D <30 ng/mL)
Loose throw rugs	General deconditioning	Medications causing sedation
Lack of use of assistive devices	Neuromuscular, neurodegenerative, and joint diseases such as cerebrovascular accident, Parkinson's, arthritis	Dementia/cognitive impairment Urge urinary incontinence/ overactive bladder

Adapted from National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014. p. 12.

Table 4
Major guideline recommendations for osteoporosis screening

National Osteoporosis Foundation (NOF) 2014	United States Preventive Services Task Force (USPSTF) 2011
All women aged ≥65	All women aged ≥65 (Grade B)
Younger postmenopausal women with clinical risk factors for fracture	Women aged <65 y whose 10-y fracture risk is equal to or greater than that of a 65 y old white woman without additional risk factors[a] (Grade B)
Women who have a fracture after age 50	—
Women with conditions that can cause secondary osteoporosis	—

[a] Per the FRAX fracture risk assessment tool, the 10-year fracture risk in a 65-year-old white woman without additional risk factors is 9.3%.

For women aged 50 to 64, there is no universal consensus regarding when to begin BMD screening. The United States Preventative Services Task Force 2011 osteoporosis screening guideline recommends that clinicians utilize a "validated prediction tool" to identify higher risk asymptomatic younger women (aged 50–64).[11] Specifically, they advise screening younger women whose 10-year risk of any major osteoporotic fracture is equivalent to that of a 65-year-old white woman without additional risk factors, that is, 9.3% or higher.[11]

Several risk factor-based assessment tools have been validated to help identify asymptomatic younger women who are at greater risk to have osteoporosis and who would therefore benefit most from screening while avoiding unnecessary testing.[12] One frequently utilized risk assessment calculator is the web-based World Health Organization "Fracture Risk Assessment Tool" (FRAX). Originally developed as a treatment decision tool, the FRAX tool uses clinical risk factors with or without femoral neck BMD to estimate 10-year probability of hip and major osteoporotic fractures (hip, clinical vertebral, humerus, or wrist).

Clinicians may also use other validated risk assessment tools such as the Osteoporosis Self-assessment Tool.[13] The Osteoporosis Self-assessment Tool uses a mathematical formula, (weight in kg – age)/5, to generate a risk score: the lower the score, the higher the risk for osteoporosis. A score of less than 2 was 88% to 95% sensitive and 37% to 52% specific for identifying osteoporosis (T score ≤ -2.5) among postmenopausal women.[14] Some authors have found that older tools such as the Osteoporosis Self-assessment Tool are more sensitive than FRAX in identifying younger women with osteoporosis.[14] They suggest that clinicians consider using a lower cutoff point of 10-year major osteoporotic fracture risk greater than 4.1% to improve the sensitivity of the FRAX tool. Of note, none of these screening strategies for women less than 65 years of age have been prospectively evaluated for cost effectiveness.

Given that BMD decreases with advancing age among all women, it is advisable to consider rescreening women who did not meet criteria for osteoporosis on initial evaluation. There are no consensus guidelines regarding the most appropriate interval for rescreening. However, some experts advise rescreening individuals based on the severity of bone density loss on baseline DXA and demonstrated rates of bone density loss from large population-based observational studies.[15,16] **Table 5** provides suggested rescreening intervals using this approach. Clinicians may consider shortening the interval between screenings for woman with a low body mass index or who begin taking agents that increase resorption (eg, corticosteroids, aromatase inhibitors).

Table 5
Bone mineral density rescreening intervals in postmenopausal women

Category	T Score Range	Rescreening Interval (y)
Normal or mild osteopenia	>−1.5	7–15
Moderate osteopenia	−1.50 to −1.99	5
Advanced osteopenia	−2.00 to −2.49	1

CLINICAL SYNDROMES OF COMMON OSTEOPOROTIC FRACTURES

Hip Fractures

Osteoporotic hip fracture should be suspected in women aged older than 50 who present with new groin pain or pain with hip motion or weight-bearing after a fall from ground level height or greater.[2] In some cases, the affected leg may be shortened or rotated, depending on the fracture characteristics and degree of displacement. When hip fracture is considered, it is important to obtain plain radiographs of the affected hip including an anterioposterior image of the hip with maximal internal rotation, a lateral hip image, and an anterioposterior pelvis image to compare the unaffected side. Of note, hip fractures are radiographically occult in 3% to 6% of cases. Therefore, if the initial radiographs are normal but there is still a high clinical suspicion of fracture, further imaging such as a bone scan, CT, or MRI should be obtained.[17]

Initial care for a patient diagnosed with a hip fracture includes pain management and orthopedic surgery referral. Most hip fractures are treated surgically unless the patient is severely debilitated. Complications from hip fractures include pain, decreased mobility, leg length discrepancy, deep venous thrombosis, requirement for increased level of care, and increased risk of mortality (**Fig. 2**).

Vertebral Compression Fractures

Vertebral compression fractures are often asymptomatic and found incidentally on spine imaging obtained for other reasons.[18] These "morphometric" fractures are as important as symptomatic fractures in predicting future risk of fracture, found to be 19.3% in the first year after fracture.[19] When symptomatic, vertebral compression fractures usually present with acute onset back pain after a low mechanism insult, such as a ground level fall or lifting a heavy object, or, in the setting of severe osteoporosis, a very low mechanism insult such as sneezing, coughing, or even turning in

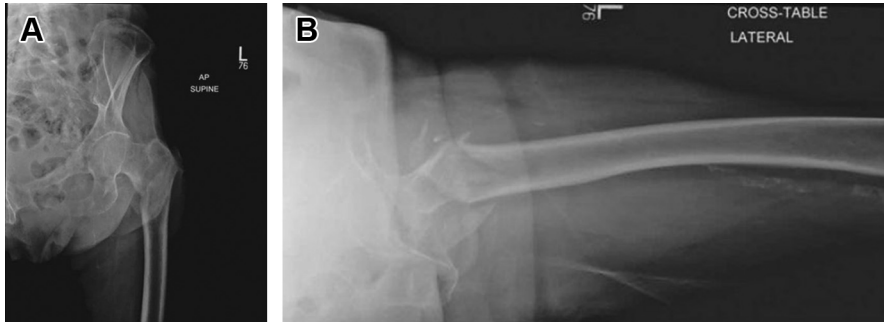

Fig. 2. Radiograph of hip fracture. Anteroposterior (*A*) and lateral (*B*) radiographs of the left hip, showing a hip fracture in a 94-year-old woman with a history of osteoporosis. (*From* Varacallo MA, Fox EJ. Osteoporosis and its complications. Med Clin North Am 2014;98(4):817–31; with permission.)

bed. The back pain typically increases with postural changes, may radiate around the truck as a "girdle of pain," and improves with lying flat on the back. There is often acute tenderness to palpation at the affected vertebrae.[20] Compression fractures usually do not cause neurologic deficits because they most often involve the anterior half of the vertebral body.[20] However, occasionally the fracture involves the entire vertebral body and may cause retropulsion of bone fragments into the vertebral canal, resulting in radicular pain and neurologic deficits.

Radiographs (and advanced imaging as needed) should always be obtained in patients older than age 50 with back pain after trauma, when accompanied by neurologic deficits, or when pain persists for longer than 4 to 6 weeks. Clinicians should also consider obtaining plain spine radiographs in all women older than 50 with new back pain even in the absence of trauma or neurologic symptoms to evaluate for compression fracture. In patients under the age of 50 who sustain a vertebral compression fracture in the absence of trauma, or in patients older than 50 with unusual fracture appearance or a history of malignancy, metastatic disease (pathologic compression fracture) should also be considered.

The treatment of vertebral compression fractures is usually nonsurgical, and includes pain management, external orthoses for stabilization, and physical therapy. Surgical management is indicated in patients with neurologic compromise, severe spine deformity, or intractable pain failing conservative therapy.[20] Complications of vertebral compression fractures include chronic back pain, spine deformity owing to progressive loss of vertebral body height leading to excessive thoracic kyphosis and lumbar lordosis, and respiratory compromise owing to alterations in thoracic cavity pressure (**Fig. 3**, **Table 6**).

DIAGNOSTIC EVALUATION

Osteoporosis is diagnosed in the presence of any of the following conditions provided other bone conditions that mimic osteoporosis (eg, osteomalacia) have been excluded:

- Screening DXA study T-score of −2.5 or less.
- Clinical fragility fracture regardless of bone density.
- Incidentally found (asymptomatic) vertebral compression fracture.

All patients should undergo a diagnostic workup to[21]:

- Evaluate the causes and contributory factors leading to low bone density;
- Exclude diseases that mimic osteoporosis;
- Assess the risk of subsequent fractures; and
- Select the most appropriate treatment.

This evaluation should include a focused history and physical examination, laboratory tests, and imaging.

History

A focused history should be obtained to determine possible exposures to the risk factors in **Boxes 1** and **2** and **Table 2**, and should include:

- Lifestyle factors such as dietary/supplemental calcium and vitamin D intake, smoking, alcohol use, activity level, fall history;
- Personal and family history of fractures;
- Comorbid medical conditions that cause secondary osteoporosis (from **Box 1**, eg, rheumatoid arthritis, hypogonadism from any cause, hyperthyroidism); and

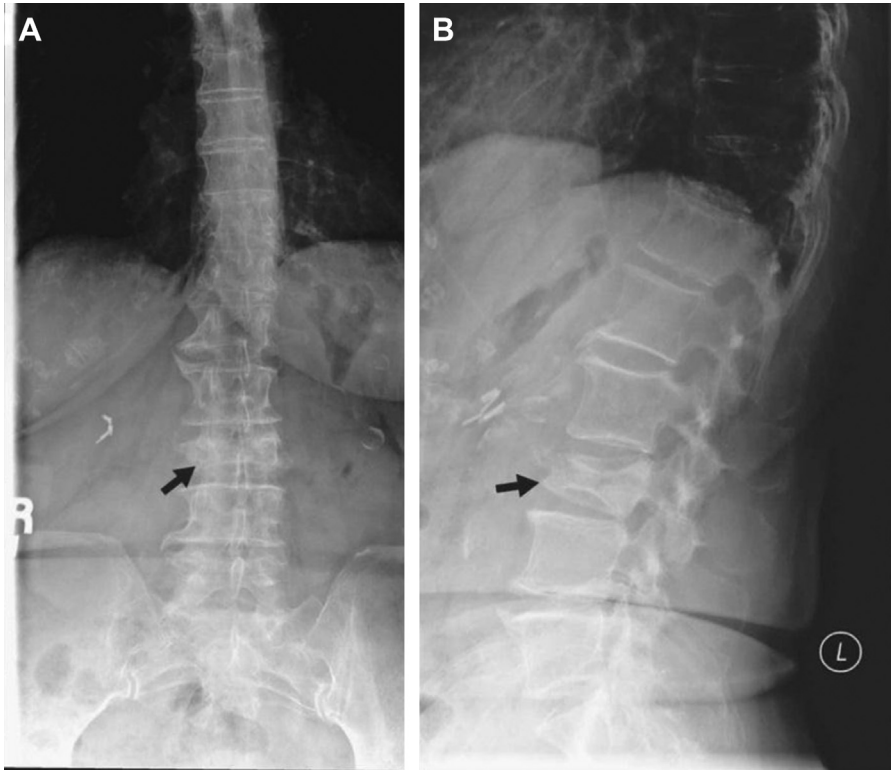

Fig. 3. Radiograph of vertebral compression fracture. Anteroposterior (*A*) and lateral (*B*) radiographs of the lumbar spine showing an L3 vertebral compression fracture in an 86-year-old woman with a history of osteoporosis. Arrows are pointing to the fractured L3 vertebral body. (*From* Varacallo MA, Fox EJ. Osteoporosis and its complications. Med Clin North Am 2014;98(4):817–31; with permission.)

Table 6
Common symptoms and complications of hip and vertebral compression fractures

	Symptoms	Complications
Hip fracture	Groin pain after fall Leg length discrepancy after fall Abnormal hip rotation after fall Inability to bear weight after fall	Chronic groin/hip pain Leg length discrepancy Decreased mobility Deep venous thrombosis Increased level of care requirement Increased risk of mortality
Vertebral compression fracture	None (often asymptomatic) Acute localized back pain after fall/lifting/forceful sneeze or cough (low mechanism insult) Tenderness to palpation of the affected level Decreased spinal mobility Acute back pain with radiculopathy after low mechanism insult (rare) Neurologic deficits such as numbness/weakness after low mechanism insult (rare)	Chronic back pain Spine deformity including thoracic kyphosis and lumbar lordosis Decreased respiratory capacity Deep venous thrombosis

- Medication use (past and present), particularly corticosteroids, antiepileptics, chemotherapy, and hormonal medications, as well as others listed in **Box 2**.

Physical Examination

The focused physical examination should evaluate for[22]:

- Physical manifestations of osteoporotic complications (eg, thoracic kyphosis, height loss);
- Signs of comorbid medical conditions that cause secondary osteoporosis; and
- Fall risk assessment (gait stability, muscle strength and balance).

Laboratory Testing

Certain tests should be obtained in all patients with osteoporosis to evaluate for common causes of secondary bone density loss. Others tests should be ordered only in select patients based on the clinical scenario (eg, patients whose BMD is more than 2 standard deviations below the age-matched mean or Z score <-2.0) and perceived likelihood of abnormal findings, for example, those in whom a specific secondary cause of osteoporosis is suspected. **Table 7** lists the advised tests.

Imaging

- BMD testing with DXA should be obtained in all patients at the time of diagnosis to determine severity of bone density loss and to establish a baseline for which to compare the effects of treatment.
- Consider radiographs (or advanced imaging such as CT bone scan, MRI, etc) if any concern for undiagnosed or subtle hip or vertebral compression fractures (eg, unexplained chronic back pain, height loss of >2 inches from maximum adult height, etc).

MANAGEMENT

Once the diagnosis of osteoporosis has been made and a workup for underlying causes initiated, we advise specific osteoporosis treatment with the goal to prevent future fractures. Unfortunately, studies indicate that many patients diagnosed with osteoporosis are undertreated despite the presence of a fragility fracture or abnormal DXA result.[23–25] Some barriers to initiating treatment include lack of knowledge and awareness by both patient and provider, perception by the provider (eg, orthopedic surgeon, primary care provider, emergency room provider) that osteoporosis diagnosis and treatment is not their responsibility, low rates of referral to osteoporosis clinics or specialists, costs of therapy, side effects of therapy, and multiple medical comorbidities.[23,24]

However, it is well-established that patients who suffer an osteoporotic fracture are at increased risk (between 2- and 5-fold depending, on the site of initial fracture) to suffer subsequent fractures.[20,26] At the same time, effective treatments as outlined herein are available to decrease this risk.[23] Thus, prompt evaluation and treatment of osteoporosis is indicated to prevent further fracture-related morbidity and mortality. **Box 3** provides indications for prescribing osteoporotic-specific medications. Treatment for osteoporosis includes both pharmacologic agents (**Table 8**) and nonpharmacologic therapies including behavioral modifications as outlined.

Table 7
Laboratory evaluation for diagnostic workup of osteoporosis in women

	Test Name	Evaluates for
Essential tests	Complete blood count	Hematologic cancer, anemia
	Serum calcium	Hyperparathyroidism or other disorder of calcium homeostasis
	Serum phosphate	Osteomalacia or other disorder of phosphate homeostasis
	Serum creatinine	Kidney disease (may cause secondary hyperparathyroidism)
	Serum thyroid stimulating hormone	Thyroid disorders
	Serum liver transaminases	Chronic liver disease
	Serum alkaline phosphatase	If high: chronic liver disease or Paget's disease of bone If low: hypophosphatemia
	Serum 25-OH vitamin D	Vitamin D insufficiency
Optional tests according to clinical scenario	Serum parathyroid hormone (in patients with elevated serum calcium)	Hyperparathyroidism
	24-h urinary calcium	If low (<50–100 mg/24 h): calcium malabsorption If high (>250 mg/24 h in women): excessive calcium absorption or renal calcium leak
	Serum and urine protein electrophoresis, kappa and lambda light chains	Multiple myeloma
	Serum celiac antibodies when malabsorption is suspected	Celiac disease (small bowel biopsy required to confirm diagnosis)
	24-h urinary free cortisol or dexamethasone suppression test when hypercortisolism is suspected	Cushing syndrome
	Serum tryptase	Systemic mastocytosis
	Serum rheumatoid factor and anti-citrullinated peptide antibodies	Rheumatoid arthritis

Adapted from Lewiecki EM. In the clinic: osteoporosis. Ann Intern Med 2011;155(1):ITC1-1–15.

Box 3
Indications to prescribe osteoporotic specific medications

Osteoporotic fracture of the vertebra (symptomatic or asymptomatic) or hip

T score of ≤ -2.5 at the femoral neck, total hip, or lumbar spine on DXA

T score between -1.0 and -2.5 and United States adapted WHO (FRAX) 10-year hip fracture risk $\geq 3\%$ or 10-year major osteoporotic fracture risk $\geq 20\%$ (primary prevention)

Abbreviations: DXA, dual energy x-ray absorptiometry; FRAX, Fracture Risk Assessment Tool; WHO, World Health Organization.

Adapted from National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014; and Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis: executive summary of recommendations. Endocr Pract 2010;16:1016–19.

Table 8
Pharmacologic treatments for osteoporosis

Drug Category	Drug Names/Dose	Mechanism of Action	Benefits	Side Effects	Notes
Bisphosphonates	Alendronate 10 mg PO daily or 70 mg PO weekly Ibandronate 150 mg PO monthly or 3 mg IV every 3 mo Risedronate 5 mg PO daily, 35 mg PO weekly, 150 mg PO monthly Zoledronic acid 5 mg IV yearly	Decrease bone resorption by attenuating osteoclast activity	All bisphosphonates have been shown to increase bone density and decrease both vertebral and nonvertebral fractures by 25%–70% except for ibandronate, which only has evidence for vertebral fracture risk reduction[27–29]	Esophageal irritation Osteonecrosis of the jaw (very rare when used for long-term osteoporosis treatment[30] Low trauma atypical femur fractures (very rare, associated with long term use >5 y[31])	Oral bisphosphonates should be taken on an empty stomach with lots of water Patients should remain upright for 30–60 min after ingestion; Do not use if creatinine clearance is $\leq$35 mL/min
Parathyroid hormone antagonist	Calcitonin 200 U (1 spray) intranasal daily	Decrease bone resorption by attenuating osteoclast activity	Slight increase in bone density Decrease risk of vertebral fractures only (30% risk reduction)[32]	Rhinitis, irritation of nasal mucosa Possible increased risk of malignancies[33]	Not considered a first-line agent for fracture risk reduction May help to decrease pain in acute or subacute vertebral compression fracture
Estrogen	Conjugated estrogens (+progesterone if intact uterus); dosing varies	Suppressive effects on osteoclasts; decreases bone resorption	Increase bone mass Decrease risk of vertebral and nonvertebral osteoporotic fractures by 23%–34%[34]	Deep venous thrombosis and pulmonary embolism Cardiovascular disease (in women >10 y postmenopause) Stroke Invasive breast cancer (only seen in combined estrogen/progesterone group)	Not first line for treatment of osteoporosis owing to risks

Estrogen agonist/ antagonists (formerly called "SERMs")	Raloxifene 60 mg PO daily	Acts as estrogen agonist on bone tissue thus suppressive effects on osteoclasts Acts as estrogen antagonist in uterine and breast tissue	Increases bone mass Decreases vertebral compression fractures by 30%–55%[35] Reduces risk for invasive breast cancer	Deep venous thrombosis and pulmonary embolism Hot flashes Leg cramps	Consider in women with a history of breast cancer who have osteoporosis Does not reduce risk for nonvertebral fractures
Parathyroid hormone (1–34)	Teriparatide 20 μg daily SQ injection	Stimulates bone formation	Increases bone mass Decreases vertebral (65%) and nonvertebral fracture risk (53%)[36]	Leg cramps Nausea Dizziness Possible increased risk of osteosarcoma	Avoid in patients with an increased risk of osteosarcoma (history of Paget's disease; bony radiation; skeletal metastases, etc) Lifetime duration of use should not exceed 18–24 mo When stopped, should be replaced by other antiresorptive osteoporosis treatment, such as bisphosphonate
RANK ligand inhibitor	Denosumab 60 mg SQ every 6 mo (administered by health care professional)	Decreases bone resorption by attenuating osteoclast formation, activity, and survival	Increases bone mass Decreases risk of vertebral fractures by 68%, hip fractures by 40% and other nonvertebral fractures by 20%[37]	Hypocalcemia Increased risk of cellulitis Osteonecrosis of the jaw (very rare) Atypical femur fractures (very rare)	No restrictions in dosing according to renal function

Abbreviations: PO, per os; SQ, subcutaneously.

Pharmacologic Treatment

Osteoporotic-specific medications

When choosing which osteoporosis medication to utilize, it is important to consider:

- Demonstrated benefit (eg, does the medication reduce all fracture types or only vertebral fractures)
- Ease of administration
- Side effect profile
- Cost
- Patient-specific indications
  - Personal or family history of breast cancer may make raloxifene a more favorable agent
- Contraindications
  - Advanced chronic kidney disease precludes bisphosphonates
  - History of bone cancer or bone radiation precludes teriperatide

We advise clinicians to involve patients actively and use a shared decision making approach to help guide medication choice. Regarding duration of treatment, in general osteoporosis-specific medications seem to have decreased efficacy and increased concern for adverse effects (eg, insufficiency fractures with long-term use of bisphosphonates) when used longer than 5 years. Therefore, the recommended approach is that these medications should be used for an initial treatment period of 5 years (except teriparatide, which should be used for 2 years or less), at which time the patient should be reevaluated with history, physical examination, and repeat BMD testing.

If the patient seems to be at relatively low risk for recurrent fractures (stable or improved bone density, no interval fractures, no new high-risk exposures such as glucocorticoids), then it is reasonable to stop therapy and monitor closely. Of note, the reduction in fracture risk associated with bisphosphonate use does extend for several years after therapy is stopped; this is not the case for all other osteoporosis medications, whose benefits end when therapy is stopped. If instead the patient seems to be at high risk for recurrent fractures (history of fractures while on therapy, decreased interval bone density, new high-risk exposure), then it is advisable to consider extending the duration of bisphosphonate use or switch to another agent.[38] Primary care clinicians may also consider consultation with an osteoporosis treatment expert regarding treatment duration.

Calcium and vitamin D

In addition to disease-specific medications, clinical guidelines recommend that patients with osteoporosis receive adequate calcium and vitamin D.[22,39–41] There has been some recent debate in the medical literature about possible adverse effects of supplemental calcium, including kidney stones and cardiovascular disease.[42,43] However, current consensus is that, for patients with established osteoporosis who are at the highest risk for future fracture events, the benefits of adequate calcium intake outweigh the possible risks. Current clinical guidelines from the National Osteoporosis Foundation and Institute of Medicine recommend that women age 51 and older, especially those with osteoporosis, take in 1200 mg of calcium each day.[39,41] Ideally, this should be achieved through diet, which seems to carry less risk of cardiovascular events,[43,44] but supplements should be used if dietary intake is inadequate.

For vitamin D intake, the Institute of Medicine recommends that women aged 70 years and younger take in 600 IU daily and those 71 and older take in 800 IU daily.[41] The National Osteoporosis Foundation recommends a higher dose, 800 to 1000 IU of

vitamin D daily for all adults aged 50 and older.[39] They also advise checking a serum 25-OH vitamin D level in women at risk for deficiency, such as those with malabsorption, chronic renal insufficiency, other chronic illnesses, taking antiepileptics, housebound, institutionalized, limited sun exposure, or very dark skin. For these patients, the National Osteoporosis Foundation advises a target serum 25-OH vitamin D level of 30 ng/mL or greater whereas the Institute of Medicine recommends a target of greater than 20 ng/mL. Patients with a serum 25-OH Vitamin D level of 20 ng/mL or less will likely require an initial bolus regimen of ergocalciferol (vitamin D_2) 50,000 IU by mouth weekly for 8 to 12 weeks to achieve goal vitamin D level, followed by maintenance dosing of cholecalciferol (vitamin D_3) 800 to 2000 IU daily.[39] Per the Institute of Medicine, the safe upper limit of daily vitamin D intake is 4000 IU. We advise against exceeding serum 25-OH vitamin D concentrations of 50 ng/mL owing to concern for hypercalcemia and other adverse effects.

Nonpharmacologic Treatments

It is important to counsel patients diagnosed with osteoporosis regarding specific lifestyle and behavioral recommendations to decrease their risk of future fractures, including:

- Participation in regular weight-bearing and muscle strengthening exercise, targeting 30 minutes on most days of the week.
- Cessation of tobacco use.
- Decrease alcohol intake if excessive (limit one drink daily for women).
- Fall risk reduction[45,46]:
  - Physical therapy for balance/gait training/strength training;
  - Appropriate use of assistive mobility devices such as canes or walkers;
  - Home and environmental modifications, such as removal of rugs and cords, and improved lighting, use of glasses, and proper footwear.
  - Consider physical therapy and occupational therapy consultations for home safety evaluation.

MONITORING

Patients undergoing treatment for osteoporosis should be evaluated regularly to ensure appropriate calcium and vitamin D intake, adherence to lifestyle modifications, medication adherence and tolerance, and fracture occurrence or new exposures that increase risk for fractures. There is no universal consensus regarding the appropriate frequency to repeat DXA tests. The National Osteoporosis Foundation practice guidelines advise obtaining surveillance bone density tests approximately every 2 years or when the outcome will affect management, including after 3 to 5 years of medication use to guide further medication management decisions.[39] Clinicians may consider other monitoring tools, such as biochemical markers of bone turnover and sequential vertebral imaging, in select patients based on risk profile and consultant recommendations.

PREVENTION

Patients who do not meet diagnostic criteria for osteoporosis, that is, a T-score greater than −2.5, but who are at high risk—for example, presence of osteopenia, chronic use of glucocorticoids, or family history of osteoporosis—should be advised regarding strategies to reduce their risk.

Table 9
Institute of Medicine recommended daily allowance for calcium intake

Population Group	Recommended Daily Allowance (mg)
Children 1–3 y	700
Children 4–8 y	1000
Preteens and teens 9–18 y	1300
Adults 19–50 y	1000
Adults ≥51	1200

Nonpharmacologic Interventions to Prevent Osteoporosis or Osteoporotic Fractures

These interventions parallel the lifestyle and behavioral recommendations advised for patients diagnosed with osteoporosis; please see "Nonpharmacologic treatments" in the Management section.

Calcium and Vitamin D

Most organizations, including the Institute of Medicine, American Association of Clinical Endocrinologists, and the National Osteoporosis Foundation, advise adequate calcium intake across the life spectrum (**Tables 9** and **10**). However, the US Preventative Services Task Force concluded in 2013 that there was insufficient evidence to assess the benefits and harms of calcium and vitamin D supplementation for the primary prevention of fracture in community-dwelling postmenopausal women.[47] This is because the medical literature shows some discrepancy in the effectiveness of calcium and vitamin D supplementation in reducing fracture risk among community-dwelling versus institutionalized individuals for primary prevention.[42,48] Current literature supports the conclusion that the patients who most benefit from higher calcium and vitamin D supplementation for primary prevention are those at highest risk to be deficient, particularly institutionalized adults or others with poor food access or malabsorption.

Another recent area of debate in the medical literature is a possible adverse cardiovascular risk associated with calcium supplementation (not dietary calcium). Thus far, this risk has been demonstrated primarily through secondary analyses of previous trials that did not have cardiovascular disease as a prespecified endpoint.[43] Of note, a large, retrospective analysis of the Nurse's Health Cohort did not show an adverse cardiovascular risk effect with calcium supplement use.[44] Further randomized studies with cardiovascular disease as a pre-specified outcome are needed to evaluate this risk further.

Overall, for primary prevention, we advise that clinicians counsel patients on the importance of adequate calcium and vitamin D for general bone health, emphasizing that calcium intake is safest if achieved through diet, and consider supplementation

Table 10
Institute of Medicine recommended daily allowance for vitamin D intake

Population Group	Daily (IU)
Birth to 11 mo	400
Age 1 to 70	600
Age 70 and over	800
Homebound/institutionalized elderly	800

Box 4
Indications to consider osteoporosis medications for the prevention of osteoporotic fractures

T score between −1.0 and −2.5 and U.S. adapted WHO 10-year hip fracture risk ≥3% or 10-year risk for any major osteoporotic fracture ≥20%

High risk premenopausal and postmenopausal women who are receiving chronic glucocorticoids >5–7.5 mg/d prednisone or equivalent for anticipated duration ≥3 months[a]

Abbreviation: WHO, World Health Organization.
[a] See the 2010 American College of Rheumatology guidelines for a detailed recommendation.[49]

primarily in women who clearly have inadequate dietary intake, malabsorption, or in those who are institutionalized.

Pharmacologic Interventions to Prevent Osteoporosis

The use of osteoporosis-specific medications is recommended to reduce the risk of developing osteoporosis (see **Box 3**) in some high risk women, including those with a 10-year risk of hip fracture of greater than 3% or any major osteoporotic fracture of greater than 20%, or who use glucocorticoids chronically (**Box 4**).[39,49] Bisphosphonates and raloxifene are the most commonly utilized medications for prevention of osteoporosis in high-risk postmenopausal women.

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