NEW OSTEOPOROTIC/VERTEBRAL COMPRESSION FRACTURES

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CLINICAL RECOGNITION

Osteoporosis is a prevalent disease characterized by reduced bone mass and architectural deterioration, which leads to structurally weakened bone and an increased risk of fragility fractures. A fragility fracture is defined as a fracture occurring with minimal trauma, such as falling from standing height. These fractures rise exponentially with age and most commonly involve the spine, hip, humerus, and wrist. Vertebral compression fractures are the most common osteoporotic fractures with an estimated 700,000 per year in the United States (1). However, most patients with vertebral fractures are unaware that they have fractured as only ~1/3rd are clinically diagnosed. While there are effective treatments to reduce the risk of fractures, only 23% of patients with fragility fractures receive osteoporosis evaluation and treatment.

PATHOPHYSIOLOGY

Bone is a dynamic organ with continuous remodeling to maintain a healthy skeleton—osteoclasts resorb bone and osteoblasts form new bone (2). Osteoporosis results from a net increase in bone resorption relative to bone formation. The receptor activator of nuclear factor-kappa β (RANK), RANK ligand (RANKL), and osteoprotegerin (OPG) are key regulators of bone resorption. Interaction between RANKL and RANK stimulates osteoclastic differentiation, while OPG, made by osteoblasts, binds with RANKL and inhibits bone resorption. In addition, the Wnt signaling pathway is a network of proteins that is involved in activating the transcription of genes that direct the differentiation and proliferation of osteoblasts. Sclerostin, produced by the osteocytes embedded in bone, is the product of the SOST gene. Sclerostin reduces the Wnt signaling pathway, thereby, suppressing bone formation by osteoblasts. Some of the key factors that are mechanistically involved in bone turnover are therapeutic targets for osteoporosis treatment. See Table 4 for summary of treatments.

Fragility Fractures

Vertebral compression fractures are associated with substantial morbidity including: acute and chronic back pain, height loss, kyphosis, restrictive lung disease, early satiety, reduced quality of life, and increased mortality (1). A spine fracture is associated with a 5-fold risk of a subsequent spine fracture and a 2-fold risk of hip and other fractures. Hip fractures are serious fractures that can lead to pain, disability, loss of independence, and high mortality. A Danish registry study published in 2018 found that one-year excess mortality was 20-25% after femur or pelvic, 10% following vertebral, and 5-10% following humerus fractures.

There is a high prevalence of low vitamin D levels among hip fracture patients. Since there is a large care gap for patients with fragility fractures, there are critical ongoing efforts to try to implement inter-disciplinary, hospital-based approaches to advance fracture care. It is imperative to ensure timely outpatient follow-up to correct the vitamin D deficiency, evaluate patients for other secondary causes of osteoporosis, and institute osteoporosis treatment. See Treatment section for further description of management of these fractures.

DIAGNOSIS and DIFFERENTIAL

Assessment of osteoporosis risk factors and measurement of bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) are important to determine which individuals are at increased risk of fractures. Low bone mass (osteopenia) is present when the BMD is between 1.0 and 2.5 SDs below peak bone density of young, healthy individuals. More than 50% of fragility fractures occur in these patients. Osteoporosis, according to the World Health Organization, is defined as a BMD ≤-2.5 SDs of young normal. BMD testing is typically measured at the proximal femur and lumbar spine, though the 1/3 radius should be measured in patients with hyperparathyroidism (https://www.iscd.org/official-positions/). The Bone Health & Osteoporosis Foundation (BHOF; formerly the National Osteoporosis Foundation) currently recommends that women ≥65 years, men ≥70 years, and postmenopausal women and men ≥50 years with risk factors or fracture after age 50 receive screening DXA scans (3). The BHOF recommends monitoring osteoporosis by an annual measurement of a patient's height, preferably with a mounted stadiometer, and BMD testing 1-2 years after initiating therapy and every 2 years thereafter. Because spine fractures are often not clinically evident, imaging for spine fractures (vertebral fracture assessment by DXA or X-ray) is recommended, particularly in older adults with osteopenia and after adult-age fracture (>50 years of age), glucocorticoid use, or diagnosis of hyperparathyroidism (See Table 1) (3, 4).

The FRAX® calculator was designed to quantify an individual's absolute fracture risk (http://www.shef.ac.uk/FRAX). In addition to BMD, the following risk factors are included—ethnicity, age, body mass index, prior fracture history, glucocorticoid use, alcohol use, smoking, rheumatoid arthritis, and other secondary causes of osteoporosis. If the 10-year absolute fracture risk is ≥3% for hip fractures or ≥20% for other major osteoporotic fractures, pharmacologic therapy should be considered. Note that the FRAX calculator is not designed for those with osteoporosis on BMD testing but mainly for those with low bone mass.

Using a specialized software (incorporated in DXA machines), Trabecular Bone Score (TBS) can be generated from lumbar spine DXA images and is a measure that reflects bone microarchitecture and predicts fracture risk independent of bone density. TBS can now also be incorporated in the FRAX score.

Table 1. Imaging Assessment Recommendations
DXA Tests: Women aged ≥65 and older men aged ≥70 Younger postmenopausal women and men aged 50-69 with risk factors for bone loss or fractures Adults who have a fracture at age ≥50 Adults with a medical condition or taking a medication associated with bone loss and/or fractures
Vertebral Imaging Tests: Women aged ≥65 if T-score is ≤ -1.0 at the femoral neck Women aged ≥70 and men aged ≥80 if T-score is ≤ -1.0 at the lumbar spine, total hip, or femoral neck Men aged 70-79 if T-score is ≤ -1.5 at the lumbar spine, total hip, or femoral neck Postmenopausal women and men aged ≥50 with specific risk factors: Fracture(s) during adulthood (age ≥50) from any cause Historical height loss of ≥1.5 inches (4 cm) Prospective/interval height loss of ≥0.8 inches (2 cm) Glucocorticoid therapy Hyperparathyroidism

When the diagnosis of a low bone density is made, a work-up to look for secondary causes of osteoporosis should be considered. See Table 2.

Table 2. Secondary Causes of Osteoporosis	
Endocrinological Abnormalities	Glucocorticoid excess, hyperthyroidism, hypogonadism, anorexia, prolactinoma, hyperparathyroidism
Hematologic Disorders	Multiple myeloma, mastocytosis, leukemia
Renal Disease	Metabolic bone disease, nephrolithiasis
Connective Tissue Disorders	Osteogenesis Imperfecta, Ehlers-Danlos syndrome
Gastrointestinal Diseases	Celiac disease, inflammatory bowel disease, post-gastrectomy, bariatric surgery
Rheumatological Disorders	Ankylosing spondylitis, rheumatoid arthritis
Medications	Glucocorticoids, cyclophosphamide, aromatase inhibitors, heparin, methotrexate, androgen deprivation therapy, gonadotropin releasing hormone agonists, proton-pump inhibitors, selective serotonin reuptake inhibitors

Laboratory evaluation may include the following: calcium, phosphorus, liver tests (including alkaline phosphatase), CBC, 25-hydroxyvitamin D, 24-hour urine calcium, +/- parathyroid hormone, and thyroid stimulating hormone (if clinical evidence of hyperthyroidism or those already on thyroid hormone replacement), and serum testosterone level in men. For select cases one may consider obtaining specialized tests for gastrointestinal disorders (tissue transglutaminase for celiac disease with an IgA level), infiltrative diseases (serum tryptase for mastocytosis), neoplastic (serum and urine protein electrophoresis), or excess glucocorticoid (24-hour urine cortisol, dexamethasone suppression test).

TREATMENT

Fractures

The management of a vertebral compression fracture involves both pharmacologic and non-pharmacologic approaches. The acute pain typically subsides over several weeks, but pain management with non-steroidal anti-inflammatory drugs, neuropathic pain agents, or narcotics may be needed. A 2-4 week course of calcitonin, administered as one spray (200 IU) per day intranasally, may help patients who need additional acute pain management. Spinal bracing may help with pain by limiting movement of bone fragments against one another, and physical therapy may improve mobility and reduce fear of falling. Vertebral fractures are common in older adults and secondary fracture prevention is important. After a vertebral fracture, patients should immediately start osteoporosis treatment to prevent subsequent vertebral fractures, particularly teriparatide, abaloparatide, zoledronic acid, denosumab, or romosozumab, which have been shown to reduce vertebral fracture risk within the first year of treatment.

Procedures such as vertebroplasty or kyphoplasty have been thought to be effective for acute fracture pain; however, this finding has not been replicated across studies, especially in those controlled by sham operations. This lack of a clear benefit is also offset by the small but serious risks of these procedures, which include epidural cement leak leading to possible nerve root compression, osteomyelitis, cement pulmonary embolism, and the possibility of subsequent vertebral fractures in adjacent vertebrae. A Cochrane review published in 2018 found no demonstrable clinically important benefits for vertebroplasty compared with placebo (sham procedure), and the results did not differ according to duration of pain (≤6 weeks vs. >6 weeks) (5). A 2019 American Society for Bone and Mineral Research (ASBMR) task force concluded that, for patients with painful vertebral fractures, there was no significant benefit for vertebroplasty compared to placebo or sham procedures and recommended against the use of balloon kyphoplasty (6). If vertebral augmentation is considered in select patients with disabling spine fractures, osteoporosis treatment should be initiated concurrently.

Glucocorticoid-induced osteoporosis affects the spine greater than other sites. Glucocorticoids have a major effect on reducing bone formation and also increase bone resorption. Thus, there are two sites for targeted intervention—anabolic and anti-resorptive treatments, respectively. The American College of Rheumatology has recommended starting bone protection therapy for adults ≥40 years taking prednisone at a dose of ≥2.5 mg/day for ≥3 months if at moderate to high risk for fracture (i.e., FRAX 10-year risk of major osteoporotic fracture >10%, FRAX 10-year risk of hip fracture >1%, osteoporosis by bone density criteria, or prior osteoporotic fracture) (7). The Food Drug Administration (FDA) has approved the following anti-resorptive agents — risedronate, alendronate, zoledronic acid, and denosumab — and the anabolic agent teriparatide for glucocorticoid-induced osteoporosis. In a randomized trial, teriparatide was superior to alendronate in preventing BMD declines at the spine and hip.

With regards to hip fractures and the use of zoledronic acid once yearly, the timing of this FDA-approved treatment for secondary fracture prevention is important. There is a significant reduction in vertebral and non-vertebral fractures and mortality as well as an increase in hip BMD in those who receive zoledronic acid and supplemental vitamin D between two weeks and 90 days following a hip fracture.

Osteoporosis

Adequate calcium and vitamin D intake are essential. In 2010, the Institute of Medicine (IOM) set recommendations for daily calcium and vitamin D requirements (8). See Table 3.

Table 3. Recommended Daily Intakes of Elemental Calcium (adapted from 2010 IOM report)	
Calcium Intake	
Women 19 to 50 years / Men 19 to 70 years Women ≥51 years / Men ≥71 years	1000 mg 1200 mg
Vitamin D Intake	
Women and Men < 70 years Women and Men > 70 years	600U 800U

Obtaining calcium through the diet is preferred. However, if taking calcium supplements, for those on proton pump inhibitors, calcium citrate (e.g., Citracal®) is preferred given better absorption over calcium carbonate and can be taken on an empty stomach. Preparations of Citracal® include Maximum Plus (315 mg of calcium per tablet) and Petite (200 mg of calcium per tablet). Calcium carbonate (e.g., Oscal®, Caltrate®), ranging from 500 to 600 mg per tablet, should be taken with food to allow optimal absorption.

Vitamin D deficiency is a prevalent problem. The IOM guidelines recommend a daily dose of vitamin D_3 of 600 IU for individuals ≤70 years of age and 800 IU daily for those ≥71. Other societies recommend 800-1000 IU of vitamin D for high-risk adults with osteoporosis. Patients with vitamin D deficiency need much higher doses. Although there is debate, the BHOF and other organizations currently recommend a 25-hydroxyvitamin D level ≥30 ng/mL. There are ongoing, population-based studies that are evaluating the effects of supplemental vitamin D on fractures and bone health measures.

Recommendations for lifestyle and dietary modification include weight-bearing exercises, balance training, muscle-strengthening, fall prevention interventions, smoking cessation, and moderate alcohol consumption.

PHARMACOLOGIC THERAPIES

Table 4 lists the currently available osteoporosis drugs approved by the FDA, their dosage, indication, and general efficacy to reduce fractures.

Table 4. FDA-approved Treatments for Osteoporosis: Dose, Fracture Indication, Efficacy and Side Effects			
Drug	**Dose & Administration**	**Fracture Reduction ***	**Side Effects**
Bisphosphonates			
Alendronate	70 mg PO once weekly	V, N, H	Upper GI symptoms, rare bone pain, osteonecrosis of the jaw (rare), atypical femur fracture (rare).
Ibandronate	150 mg PO monthly; 3 mg IV every 3 months	V	
Risedronate	35 mg PO once weekly; 150 mg PO once monthly	V, N, H	
Zoledronic Acid (ZA)	5 mg IV once yearly	V, N, H	Mild flu like syndrome during and after ZA infusion (pre-treat with acetaminophen); ZA should not be given if severe renal impairment (GFR <35

			mL/min). After a hip fracture, vitamin D and ZA should be initiated 2 weeks to 90 days after the fracture.
SERMs (Selective Estrogen Receptor Modulators)			
Raloxifene	60 mg PO daily	V	Hot flashes, deep vein thrombosis (rare)
Parathyroid Hormone			
PTH Teriparatide (PTH 1-34)	20 mcg SC daily	V, N	Nausea, hypercalcemia, hypercalciuria, hypotension (rare)
PTHrP Abaloparatide (PTHrP 1-34)	80 mcg SC daily (for maximum of 2 years)	V, N	Nausea, hypercalcemia, hypercalciuria, dizziness, osteosarcoma (in rodents)
RANKL inhibitor			
Denosumab	60 mg SC every 6 months	V, N, H	Skin infections, other uncommon infections, osteonecrosis of the jaw (rare), atypical femur fractures (rare), bone loss/vertebral fractures upon discontinuation
Sclerostin inhibitor			
Romosozumab	210 mg SC every month for 12 months	V, N, H	Injection site reaction, major adverse cardiac events, osteonecrosis of the jaw (rare), atypical femur fracture (rare)
Other			
Calcitonin	200 IU nasally or 100 IU subcutaneously every other day	V	Nasal congestion, malignancy

V: vertebral, N: non-vertebral, H: hip

CURRENT THERAPEUTIC APPROACH

Pharmacologic treatment is indicated for those with osteoporosis by BMD criteria; fragility vertebral or hip fracture regardless of BMD; fragility fracture of the pelvis, proximal humerus, or wrist with osteopenic range BMD; and elevated FRAX scores.

The most commonly used therapy is a bisphosphonate, which has long skeletal retention, decreases bone turnover, and reduces the risk of fractures (see Table 4). Alendronate, risedronate, and zoledronic acid decrease vertebral, non-vertebral, and hip fractures, whereas ibandronate decreases vertebral but *not* hip or non-vertebral fractures. There is concern about the association of its long-term use and risk of atypical femur fractures. These fractures (1) can occur along the subtrochanteric femur, (2) are associated with minimal or no trauma, (3) are in transverse or short oblique configuration, and (4) usually are complete fractures through both cortices. Some patients have prodromal symptoms of thigh or groin pain in the affected leg; bilateral atypical femur fractures may also be present. The incidence of these types of fractures is very low, and the consensus has been that the number of fractures prevented far exceeds the number of these fractures occurring as a result of bisphosphonates. According to the available limited, post-hoc data analyses, continuation of therapy after 3 years for zoledronic acid and 5 years for oral bisphosphonates may be considered in those with hip, spine, or multiple other osteoporotic fractures

before or during therapy, osteoporosis at the hip after treatment, or high fracture risk. According to the 2011 FDA review, more data are needed concerning long-term bisphosphonate use. Until these data are available, annual evaluation and follow-up should involve decisions as to whether a 1-2 year or greater bisphosphonate holiday is needed, according to each individual's risk, or to consider the use of alternative treatments as needed. It is important, however, to follow patients with a history of low bone mass or osteoporosis who are on a bisphosphonate holiday. Another rare complication is osteonecrosis of the jaw, which usually occurs in the setting of an invasive dental procedure. This complication is primarily seen in cancer patients who are receiving zoledronic acid on a monthly basis to prevent cancer-related fractures.

Denosumab, FDA approved in June 2010, is a monoclonal antibody that reduces RANKL, inhibiting the cellular mechanisms underlying bone resorption. It decreases the risk of vertebral, non-vertebral, and hip fractures and can be judiciously used in those with renal dysfunction. Denosumab has also been associated with rare cases of atypical femur fractures and osteonecrosis of the jaw. Of note, a drug holiday from denosumab is *not* recommended due to rebound bone loss and risk of multiple vertebral fractures with discontinuation. If denosumab is to be discontinued, it should be followed by bisphosphonate treatment.

Anabolic agents teriparatide (1-34 recombinant PTH) and abaloparatide (1-34 recombinant PTHrP) stimulate overall bone formation, improve bone structure, increase BMD particularly at the spine, and reduce risk of vertebral and non-vertebral fractures. In postmenopausal women with history of vertebral fracture, teriparatide has been shown to reduce incident vertebral and clinical fractures more than risedronate. Abaloparatide appears to be more effective at increasing bone density at the total hip compared to teriparatide and is less likely to cause hypercalcemia. They are administered as daily subcutaneous injections. Due to increased risk of osteosarcoma in rodents, these agents were limited to 2 years in a lifetime. However, due to twenty years of post-surveillance data showing no increased risk of osteosarcoma in humans, use of teriparatide is no longer restricted to 2 years. Use of abaloparatide, which was FDA approved in 2017, continues to be restricted to 2 years. These treatments should not be used in patients with active malignancy, history of radiation therapy, elevated alkaline phosphatase, or Paget's disease. Anabolic agents should be followed by anti-resorptive therapy to consolidate gains in BMD.

Romosozumab, FDA approved in April 2019, is fully human monoclonal antibody that inhibits sclerostin and simultaneously reduces bone resorption and stimulates bone formation. Clinical studies of romosozumab have shown reduced risk of vertebral and nonvertebral, and hip fractures compared to placebo as well as alendronate. However, there were more adjudicated serious cardiovascular events in the romosozumab treatment arm compared to the alendronate arm. Thus, according to the FDA, romosozumab should not be used in patients who have had a myocardial infarction or stroke within the preceding year. A course of romosozumab is 12-months long, as the anabolic effects of romosozumab wane before then. There is no limit of courses. Similar to the parathyroid hormone analogues, romosozumab should also be followed by anti-resorptive therapy.

FOLLOW-UP

Once an initial bone density is measured, a follow-up BMD should be done 1-2 years after the initial screening and depending on whether pharmacologic therapy was initiated. Biochemical bone turnover markers and collagen breakdown products (e.g., N-telopeptide, C-telopeptide, collected in the morning) at baseline and after 3 months of treatment may be helpful in select patients to determine patient response to a therapeutic intervention. Clinical musculoskeletal evaluation and annual height measurements are important in the identification of spine fractures. Fragility fractures increase exponentially with

advancing age, and evaluation and treatment of new fractures are critical for secondary prevention of fractures and healthy aging.

GUIDELINES

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