CLINICAL PRACTICE

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Postmenopausal Osteoporosis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 69-year-old woman presents to review the results of her first dual-energy x-ray absorptiometry (DXA) scan. Her T scores are –2.6 at the lumbar spine and –2.3 at the total hip. She fell while walking 18 months ago and fractured her left humerus. Imaging of the spine, performed to investigate 5 cm (2 in.) of height loss and moderate thoracic kyphosis, reveals two vertebral fractures. How should this patient be evaluated and treated?

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THE CLINICAL PROBLEM

Postmenopausal osteoporosis is caused by estrogen deficiency, which leads to increased osteoclast differentiation and activation, accelerated bone resorption that outpaces formation, and rapid bone loss, particularly in the years immediately before and after menopause. This results in low bone mineral density, deteriorated bone microarchitecture, decreased bone strength, and increased risk of fragility fractures. Postmenopausal osteoporosis is diagnosed on the basis of the occurrence of a fragility fracture (with no associated trauma or with trauma equivalent to falling from a standing height or less) or bone mineral density at the spine, total hip, or femoral neck that is at least 2.5 standard deviations below the mean of that in a young adult reference population (T score of –2.5 or less), as measured with the use of DXA. In the United States, approximately 20% of women over 50 years of age and 30% of women 65 years of age or older meet DXA criteria for osteoporosis.[1,2] In the United States, osteoporosis is more common among White, Asian, and Hispanic women than among non-Hispanic Black women.[2] An additional 40% of postmenopausal women have low bone mass (osteopenia; defined as a T score between –1.0 and –2.49). Approximately 50% of postmenopausal women will have fragility fractures, which cause pain, disability, and decreased quality of life. After a hip fracture, many women never regain independence, 20% are institutionalized, and the risk of death within 1 year doubles.[3,4] Non-White women who have hip fractures are more likely to die within 6 months, are less likely to regain independence, and have less timely surgery and rehabilitation than White women who have hip fractures.[5] The annual health care cost associated with fractures related to postmenopausal osteoporosis in the United States, currently $57 billion, is projected to exceed $95 billion by 2040.[6]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Osteoporosis is asymptomatic until the first clinical fracture. Bone mineral density as measured with the use of DXA is the gold standard for identifying patients at risk. Each standard deviation reduction below a T score of 0 is associated with

KEY CLINICAL POINTS

POSTMENOPAUSAL OSTEOPOROSIS

- Fragility fractures are very common among postmenopausal women and are associated with increased morbidity, mortality, and health care expenditures.
- Dual-energy x-ray absorptiometry (DXA) is recommended in postmenopausal women 65 years of age or older and postmenopausal women younger than 65 years of age who have risk factors.
- Osteoporosis is diagnosed on the basis of a fragility fracture or a DXA T score of –2.5 or less.
- Treatment of postmenopausal osteoporosis is recommended for patients who have any of the following findings: a fragility fracture (or fractures), particularly of the hip or spine, regardless of the patient's bone mineral density; a T score of –2.5 or less at the lumbar spine, total hip, or femoral neck; or a high 10-year fracture risk (hip fracture risk of ≥3% or major osteoporotic fracture risk of ≥20%) according to the fracture risk assessment tool (FRAX).
- Evaluation should include risk stratification (based on the T score, presence of fractures, and FRAX score) to categorize candidates who meet treatment thresholds as "high risk" or "very high risk."
- The selection of therapy must include consideration of coexisting conditions and contraindications, but anabolic agents are the preferred first line of treatment in women at very high risk.

a doubling or tripling in the risk of fracture.[7] Most guidelines recommend DXA of the spine and hip for postmenopausal women 65 years of age or older and for postmenopausal women younger than 65 who have risk factors (Table 1).[8-11] Forearm bone mineral density predicts fracture and can be measured if recommended sites are not evaluable or if hyperparathyroidism is present. Fragility fractures of the spine, hip, forearm, humerus, and pelvis are diagnostic of osteoporosis, even with T scores higher than –2.5. The occurrence of a fragility fracture is associated with a marked increased in the imminent risk of additional fractures.[12]

Vertebral compression fractures, the most common osteoporotic fractures, are frequently painful and cause height loss but may be asymptomatic. Vertebral fractures are associated with increased mortality, and the presence of vertebral fractures influences diagnosis, risk stratification, and therapeutic decisions.[13] Vertebral fracture analysis, a low-radiation spine image obtained on a densitometer when bone mineral density is measured, has high sensitivity and specificity to detect moderate or severe (≥25%) vertebral compressions. Vertebral fracture analysis or spine radiography should be performed when suspicion is high (e.g., height loss of >1.5 inches [>3.8 cm]) or if the management strategy may be affected (Fig. 1). Fracture risk can be estimated with the use of the fracture risk assessment tool (FRAX) or other validated calculators. FRAX estimates the 10-year probability of major osteoporotic fracture and hip fracture on the basis of clinical risk factors (Table 1), with or without a measurement of bone mineral density. Many authorities recommend designating patients who have an elevated fracture risk but do not have T scores of –2.5 or less or a fragility fracture as having osteoporosis.[14]

Bone microarchitecture contributes to bone strength and can be assessed by means of several methods. The trabecular bone score — a Food and Drug Administration (FDA)–cleared, Medicare-covered, indirect measure of spine trabecular microarchitecture that is obtained from a DXA image with the use of additional commercially available software — predicts fracture risk independent of bone mineral density.[15] FRAX-estimated fracture risk or T scores can be adjusted with the use of the trabecular bone score to enhance risk stratification. The trabecular bone score is most useful when it influences treatment decisions (e.g., for osteopenia or when the level of fracture risk is close to an intervention threshold) but should not be used alone for diagnosis. FDA-approved, clinically available software now permits opportunistic screening of volumetric bone mineral density, bone strength, and prevalent vertebral fractures with the use of routine clinical computed tomography (CT) to identify persons at risk for future fractures. Evidence suggests that this technology performs at least as well as DXA. Measurement of bone microstructure and strength by means of high-resolution peripheral quantitative CT (HRpQCT) predicts fracture risk independent of bone mineral density but is not FDA-approved for diagnosis.[16]

OTHER EVALUATIONS

Medical history, medications, and risk factors should be assessed. Other metabolic bone diseases that are associated with low bone mineral density, such as osteomalacia, are important diagnostic considerations (Fig. 1). Conditions (e.g., celiac disease) and medications (e.g., glucocorticoids) that cause remediable bone loss should be addressed (Table 1). Because there is no consensus regarding the most cost-effective laboratory evaluation, testing depends on the clinical situation but must, at minimum, identify contraindications to specific therapeutics (Fig. 1 and Table 2).

Table 1. Risk Factors for Postmenopausal Osteoporosis and Fracture.

Older age
Low weight (<127 lb [<58 kg])
Previous fracture during adulthood (particularly hip, spine, or wrist); recent fracture indicates a higher risk than remote or unclear history
Parental history of hip fracture
Current or past glucocorticoid treatment (>5 mg prednisolone daily or equivalent for 3 mo or more)
Other medications that cause bone loss*
Current smoking
Excess alcohol intake
Causes of secondary osteoporosis†
Rheumatoid arthritis
Premature menopause (<40 yr of age) or hypogonadism
Frequent falls

* These medications include (but are not limited to) aromatase inhibitors, suppressive doses of thyroid hormone, chemotherapy, cyclosporine, unfractionated and low-molecular-weight heparins, antidepressants, thiazolidinediones, selected anticonvulsant drugs, and proton-pump inhibitors. Some drug categories have been associated with higher fractures in epidemiologic studies but have not been causally linked.

† Causes include (but are not limited to) organ transplantation, primary hyperparathyroidism, chronic kidney disease, type 1 and type 2 diabetes, anorexia nervosa, hypopituitarism, malabsorption, bariatric surgery, immobility, untreated hyperthyroidism, chronic pulmonary disease, human immunodeficiency virus infection, Cushing's disease, osteogenesis imperfecta, Gaucher's disease, and Marfan syndrome.

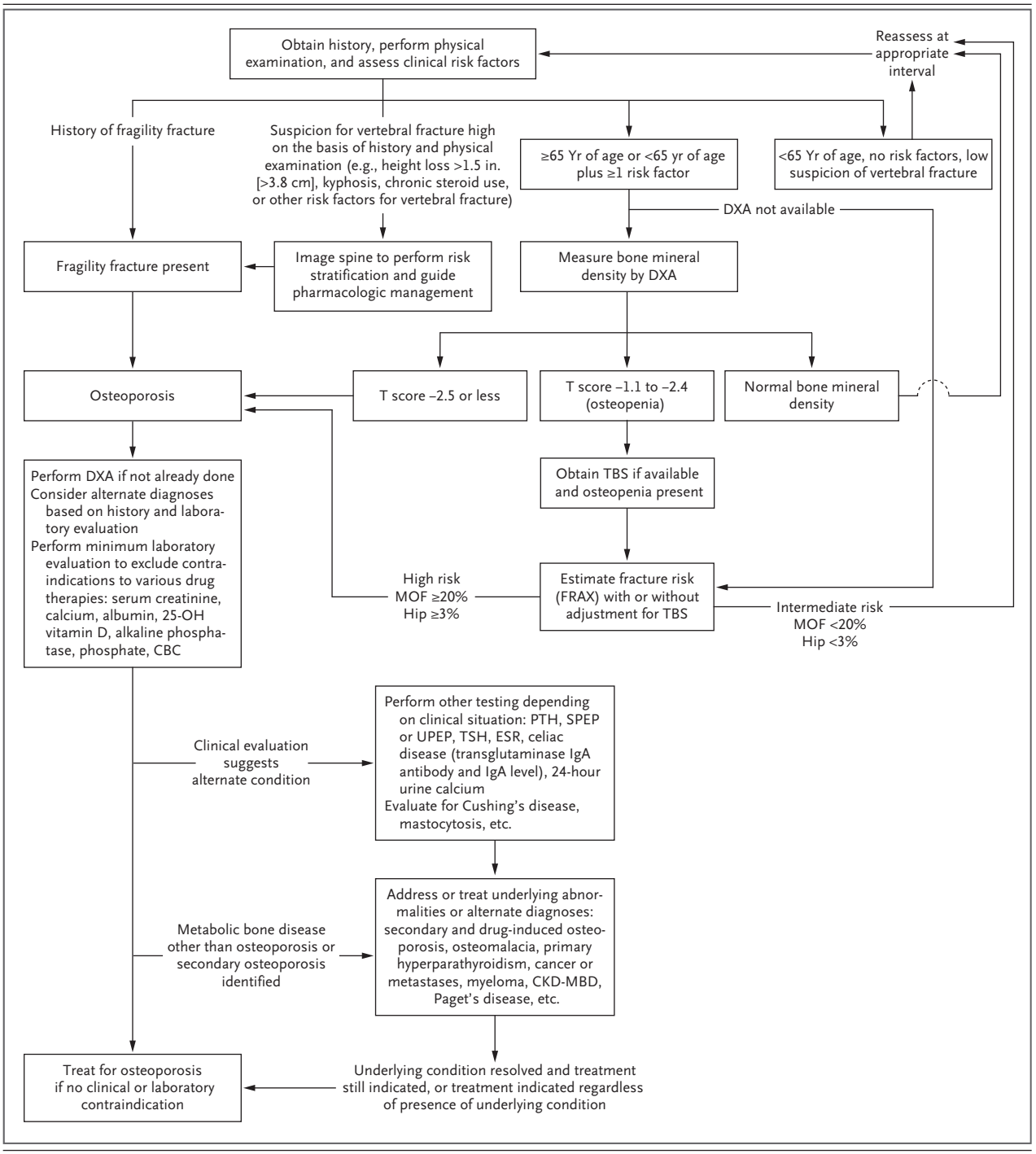
TREATMENT

The fundamental goal of treatment is to prevent fractures in women at high risk before their first fracture (primary prevention) or before a subsequent fracture (secondary prevention). Lifestyle modifications are applicable to all of these patients. Pharmacologic interventions (Table 2) are targeted to women at high risk for fracture. Intervention thresholds vary according to different guidelines (Table 3), but many guidelines recommend treating women who have fragility fractures of the hip or spine, regardless of bone mineral density; those with T scores of –2.5 or less at the lumbar spine, total hip, or femoral neck; and those with high 10-year fracture risk as assessed with the use of FRAX (hip fracture risk of ≥3% or major osteoporotic fracture risk of ≥20%).[8] Findings from randomized, controlled trials support the fracture-risk–reduction efficacy of FDA-approved treatments based on T scores or fracture criteria (or both). Evidence that supports treatment based on FRAX-estimated fracture risk is less robust.[8,25,26]

LIFESTYLE CHANGES

Patients should be encouraged to stop smoking, avoid excessive alcohol, increase weight-bearing exercise, and prevent falls.[27,28] Most guidelines recommend 1000 to 1200 mg of calcium daily in women with postmenopausal osteoporosis, preferably obtained from diet,[8,11] and 400 to 1000 IU of vitamin D daily.[8,11] Some experts and guidelines recommend adjusting vitamin D intake to achieve serum 25-hydroxyvitamin D levels higher than 20 to 30 ng per milliliter, but this approach is controversial and not supported by rigorous data.[8,24]

Whether calcium and vitamin D supplementation reduces fractures remains debated. Limited evidence suggests supplemental calcium combined with vitamin D significantly reduces hip fractures, but not nonvertebral or vertebral fractures, in patients with postmenopausal osteoporosis.[17] Because the efficacy of most osteoporosis medications has been studied in conjunction with calcium and vitamin D supplementation, and some osteoporosis medications can cause hypocalcemia, adequate calcium and vitamin D intake is prudent. Risks associated with calcium supplementation include nephrolithiasis and, according to some meta-analyses, increased incidence of cardiovascular events, although studies



included in the meta-analyses were not designed to assess cardiovascular outcomes.[29]

PHARMACOLOGIC APPROACHES

Therapies for postmenopausal osteoporosis act by reducing bone resorption (antiresorptive therapies), stimulating bone formation (anabolic therapies), or both. All pharmacologic approaches reduce vertebral fracture risk, and some reduce the risk of nonvertebral and hip fractures.[17] Table 2 summarizes available therapies and fracture risk reductions that have been assessed in randomized, controlled trials. Selection of a therapy must include the consideration of osteo-

Figure 1 (facing page). Diagnostic Algorithm for the Evaluation of Postmenopausal Osteoporosis.

The evaluation of skeletal health in postmenopausal women starts with a history focusing on previous fractures and clinical risk factors for osteoporosis and fractures. A physical examination should evaluate for significant kyphosis and height loss, which if present should prompt imaging of the spine. A fragility fracture (particularly of the spine, hip, wrist, humerus, or pelvis) is diagnostic of osteoporosis. Women 65 years of age or older, regardless of other risk factors, and women younger than 65 years of age who have risk factors for bone loss or fractures should undergo dual-energy x-ray absorptiometry (DXA) screening. The timing of spine imaging may occur before, coincident with, or after DXA. If software is available to assess a trabecular bone score (TBS), the score can be obtained with a measurement of bone mineral density for fracture risk stratification in women with low bone mass (osteopenia). A T score of –2.5 or less is consistent with osteoporosis. T scores of –1.0 to –2.49 are consistent with osteopenia or low bone mass. The fracture risk assessment tool (FRAX) can be used with or without DXA and TBS to estimate a 10-year probability of major osteoporotic fracture (MOF) and hip fracture. MOF risk of 20% or more or hip fracture risk of 3% or more is consistent with osteoporosis in the absence of a fragility fracture even if the T score is above –2.5. DXA can be obtained in women with a fragility fracture and used to monitor effectiveness of treatment but is not necessary for diagnosis. Laboratory evaluation should exclude contraindications to treatments. Additional laboratory evaluations and studies may be appropriate depending on the clinical situation; a complete blood count (CBC) should be performed to evaluate for myeloma, if results are not already available. Alternative diagnoses (e.g., drug-induced osteoporosis, osteomalacia, primary hyperparathyroidism, cancer, and chronic kidney disease–mineral and bone disorder [CKD-MBD]) should be considered and addressed on the basis of clinical and laboratory information. Treatment of postmenopausal osteoporosis should be initiated if there are no contraindications. 25 OH vitamin D denotes 25-hydroxyvitamin D, ESR erythrocyte sedimentation rate, PTH parathyroid hormone, SPEP serum protein electrophoresis, TSH thyrotropin, and UPEP urine protein electrophoresis.

porosis severity, fracture risk, coexisting conditions, and factors and preferences specific to the patient. "High risk" for fracture is typically defined as meeting the minimal intervention thresholds. "Very high risk" is typically defined as having a T score of less than –3.0, a fragility fracture and a T score of –2.5 or less, or multiple vertebral fractures. Most guidelines suggest initial treatment with anabolic agents in women at very high risk, unless contraindicated (Table 3).

Bisphosphonates

For women with postmenopausal osteoporosis who are at high risk for fracture, most guidelines recommend bisphosphonates as initial treatment, given their efficacy, safety, convenience, low cost, and enduring effects after discontinuation (Table 2). Four oral and intravenous bisphosphonates are FDA-approved for postmenopausal osteoporosis. All reduce the risk of vertebral fracture.[24] All but ibandronate reduce the risk of hip and nonvertebral fractures.[17,24] When administered within 90 days after hip fracture repair and annually for 3 years, zoledronate also reduced the risk of death, although the mechanism is unclear.

Oral bisphosphonates are poorly absorbed and may cause upper gastrointestinal mucosal irritation (Table 2). Intravenous zoledronate is preferred in patients who have this side effect and those with esophageal dysfunction. Acute-phase reactions may occur with zoledronate but can be mitigated with preinfusion and postinfusion oral hydration and acetaminophen. Long-term use of bisphosphonates has been associated with osteonecrosis of the jaw and atypical femur fractures. Osteonecrosis of the jaw is an area of exposed jaw bone that does not heal within 8 weeks after identification by a health care provider.[19] Atypical femur fractures are low-trauma subtrochanteric or femoral-shaft fractures with specific radiographic criteria.[22] In patients receiving bisphosphonates at doses used for postmenopausal osteoporosis, the estimated risks of osteonecrosis of the jaw and atypical femur fracture are very low.

Denosumab

In randomized, controlled trials conducted over a period of 3 years, denosumab lowered the risk of spine, hip, and nonvertebral fractures as compared with placebo.[17] In long-term, open-label extension studies, the lower risk of fractures was maintained.[30] Although gains in bone mineral density are greater with denosumab than with bisphosphonates, evidence for greater reduction of fracture risk is limited.[31] Denosumab is also rarely associated with osteonecrosis of the jaw and atypical femur fracture[30] and with hypocalcemia in patients with advanced chronic (stage 4 or 5) kidney disease or vitamin D deficiency (Table 2).

Table 2. Pharmacologic Therapies for Postmenopausal Osteoporosis.*

Drug Class and Medication	Mechanism of Action	Treatment Dose	Fracture Risk Reduction[17,18]†			Adverse Effects	Contraindications and Warnings
			Vertebral	Hip	Non-vertebral		
			percent				
Antiresorptives							
Bisphosphonates	Bind to bone hydroxyapatite, engulfed by osteoclasts, and inhibit bone resorption						
Alendronate‡		10 mg once daily or 70 mg once weekly orally	44	40	17	GI irritation, MSK pain; rarely ONJ, AFF[19]§	Esophageal varices or dysmotility, creatinine clearance <30–35 ml per min, hypocalcemia, bisphosphonate allergy
Risedronate‡		5 mg daily, 35 mg weekly, or 150 mg monthly orally	36	26	20	Same as for alendronate	Same as for alendronate
Ibandronate‡¶		2.5 mg daily or 150 mg monthly orally, or 3 mg every 3 mo IV	31	ND	ND	Same as for alendronate	Same as for alendronate
Zoledronic acid¶		5 mg per yr IV	56	42	18	Acute-phase reaction, renal impairment, hypocalcemia, atrial fibrillation, rarely ONJ and AFF[19]§	Creatinine clearance <35 ml per min, AKI, hypocalcemia, bisphosphonate allergy; important to ensure vitamin D sufficiency
RANK ligand inhibitor — denosumab	Human monoclonal antibody that binds RANKL; inhibits osteoclast formation, function, and survival	60 mg every 6 mo subcutaneously	68	40	20	MSK pain, skin infections, rashes, hypocalcemia, rarely ONJ and AFF[19]; rebound bone loss and fractures after stopping	Hypocalcemia, hypersensitivity; important to ensure vitamin D sufficiency
Estrogens — CEE‖	Decreases osteoclastic bone resorption	0.625 mg daily orally	34	29	21	CEE alone: stroke; CEE plus medroxyprogesterone: stroke, CHD, breast cancer, dementia, thromboembolic events	History of breast cancer, CHD, VTE, stroke, TIA; active liver disease; unexplained vaginal bleeding; increased risk of endometrial cancer

SERMs (e.g., raloxifene)**	Weak estrogen agonist activity in bone, decreases osteoclastic bone resorption	Raloxifene 60 mg daily orally	40	ND	ND	VTE, hot flashes, night sweats, peripheral edema, leg cramps, increased risk of death from stroke	History of VTE, PE, retinal vein thrombosis
Anabolic agents, PTH receptor agonists							
PTH analogue — teriparatide (PTH 1-34)	Increases bone formation	20 μg daily subcutaneously	74	ND	39	Hypercalcemia, muscle cramps, nausea, headache, dizziness, hypotension	Bone metastases, skeletal cancers, history of skeletal radiation, increased risk of osteosarcoma, Paget's disease, hypercalcemic disorders, unexplained elevated alkaline phosphatase, hypersensitivity
PTH-rP analogue — abaloparatide (PTHrP 1-34)	Increases bone formation	80 μg daily subcutaneously	87	ND	46	Same as for teriparatide (PTH 1-34)	Same as for teriparatide (PTH 1-34)
Anabolic–antiresorptive agent							
Sclerostin inhibitor — romosozumab	Human monoclonal antibody against sclerostin; increases bone formation, decreases bone resorption	210 mg per mo subcutaneously	73	38††	19††	Arthralgia, headache, MSK pain, hypocalcemia, CV events; rarely ONJ, AFF	Recent stroke or MI; other CV risks, hypocalcemia, or hypersensitivity; important to ensure vitamin D sufficiency

* AFF denotes atypical femoral fracture, AKI acute kidney injury, CEE conjugated equine estrogen, CHD coronary heart disease, CV cardiovascular, GI gastrointestinal, HRT hormone replacement therapy, IV intravenous, MI myocardial infarction, MSK musculoskeletal, ND not demonstrated, ONJ osteonecrosis of the jaw, PE pulmonary embolism, PTH parathyroid hormone, RANKL receptor activator of nuclear factor κB ligand, SERM selective estrogen-receptor modulator, TIA transient ischemic attack, and VTE venous thromboembolism.

† Reduction shown is as compared with placebo in randomized, controlled trials and meta-analyses and not in head-to-head comparisons.

‡ Patients should be instructed to take oral bisphosphonates with 6 to 8 oz of plain water at least 30 min before the first food, drink, or medication of the day and avoid lying down for at least 30 min after taking the bisphosphonate.

§ ONJ has been reported at a rate of 1 to 69 per 100,000 person-yr and 0 to 90 per 100,000 person-yr with oral and IV bisphosphonates, respectively. AFF has been reported at a rate of 1.78 per 100,000 person-yr with less than 2 yr of bisphosphonates, increasing to 113.1 per 100,000 person-yr after 8 to 10 yr.[19] The risk of AFF may be higher among Asian women than among White women.[20]

¶ Acute-phase reactions can be mitigated with preinfusion and postinfusion oral hydration and acetaminophen.

‖ Estrogen is approved for the prevention of postmenopausal osteoporosis.

** Bazedoxifene (20 mg) in combination with conjugated estrogen (0.45 mg), taken once daily, is approved for prevention of postmenopausal osteoporosis.

†† Vertebral and nonvertebral risk reductions are only as compared with alendronate in the ARCH trial[21] and not as compared with placebo in the FRAME trial.[18]

Table 3. Intervention and Treatment Guidelines.*

Guideline	Intervention Threshold	Initial Treatment		Duration
		High Risk of Fracture	Very High Risk of Fracture†	
AACE–ACE 2020[11]	T score of −2.5 or less at the spine, femoral neck, total hip, or 33% radius; osteopenia (T score, −1.00 to −2.49) and history of fragility fracture of the hip or spine; osteopenia and high probability of fracture as estimated with the use of FRAX	Alendronate, denosumab, risedronate, zoledronate‡; ibandronate or raloxifene are alternatives for spine-specific therapy only[22]	Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate‡; alternate therapy is alendronate and risedronate	Oral bisphosphonates[22] — treat for 5 yr, then consider holiday if fracture risk is no longer high; if fracture risk remains high, continue treatment for up to an additional 5 yr; in patients at very high risk, consider holiday after 6–10 yr of stable BMD; zoledronic acid[22] — consider holiday after 3 yr of high risk or until fracture risk is no longer high, continue for 6 years in patients at very high risk; holiday not recommended for non-bisphosphonate antiresorptive therapies; abaloparatide or teriparatide — treat for 2 yr, then follow with antiresorptives; romosozumab — treat for 1 yr, then follow with antiresorptives[22]
American College of Physicians 2023[10]	T score of −2.5 or less; individualize in those >65 yr of age with osteopenia	Bisphosphonates; denosumab if contraindications to or adverse effects from bisphosphonates	Teriparatide or romosozumab followed by antiresorptive§	Bisphosphonate use for >3–5 yr reduces vertebral fracture but not other fractures, with increased risk of long-term harms; consider stopping after 5 yr unless strong indication to continue
Bone Health and Osteoporosis Foundation[8]	T score of −2.5 or less at the femoral neck, total hip, lumbar spine, 33% radius¶; fracture of the hip or vertebra regardless of BMD by DXA; osteopenia at the femoral neck or total hip by DXA with 10-yr hip fracture risk ≥3% or MOF risk ≥20% by FRAX; osteopenia with fracture of proximal humerus, pelvis, or distal forearm; individualized approach for those with proximal humerus, pelvis, or distal forearm fractures without osteopenia	Generally follows Endocrine Society algorithm	Generally follows Endocrine Society algorithm	Oral and IV bisphosphonates — treat for 5 yr and 3 yr respectively; with modest risk of fracture (e.g., T score greater than −2.5 and no recent fracture), consider holiday; for patients who remain at high fracture risk (e.g., T score of −2.5 or less or recent fracture or both), consider alternative treatment or continued treatment with a bisphosphonate for ≤10 yr (oral) or ≤6 yr (annual IV zoledronic acid)[22]

Endocrine Society 2019–2020[23,24]	Postmenopausal women at high risk of fractures, especially those with a recent fracture	Bisphosphonates‖; alternative therapy is denosumab; SERMs, ET, and calcitonin recommended in specific groups only**	Teriparatide or abaloparatide; romosozumab if not at high CV risk	Bisphosphonates — reassess fracture risk in 3 yr (IV) or 5 yr (oral); if high risk, continue therapy or begin alternative therapy; if low to moderate risk, consider holiday up to 5 yr but reassess every 2–4 yr[22]††; denosumab — reassess fracture risk after 5–10 yr; women remaining at high risk should continue denosumab or be treated with other therapies; abaloparatide or teriparatide — treat for 2 yr, then follow with antiresorptives; romosozumab — treat for 1 yr, then follow with antiresorptives
ESCEO and IOF[9]	Women >65 yr of age with a previous fragility fracture and those without a previous fracture who have an age-specific probability of fragility fracture that is equal to that of women with a previous fragility fracture‡‡	Oral bisphosphonates; IV bisphosphonates or denosumab are the most appropriate alternatives with contraindications to or adverse effects from oral bisphosphonates; raloxifene and HRT are also options	Teriparatide is preferentially recommended	Bisphosphonate treatment should be reviewed after 3–5 yr; bisphosphonates should be used after discontinuation of denosumab; little evidence to guide decision making beyond 10 yr; treatment decisions should be individualized

* AACE denotes American Association of Clinical Endocrinology, ACE American College of Endocrinology, BMD bone mineral density, DXA dual-energy x-ray absorptiometry, ESCEO European Society for Clinical and Economic Aspects of Osteoporosis, ET estrogen therapy, FRAX fracture risk assessment tool, HRT hormone replacement therapy, IOF International Osteoporosis Foundation, MOF major osteoporotic fracture, and SERMs selective estrogen-receptor modulators.

† Very high risk is variably defined but is often used to describe patients with a T score of less than –3.0, spine or hip fracture and T score of –2.5 or less at the lumbar spine or hip, or multiple spine or fragility fractures. Some guidelines include in this category patients who have had a fracture within the previous 12 months, fracture occurring during therapy, fracture while receiving drugs causing bone loss (e.g., long-term glucocorticoid therapy), high risk of falling, and very high fracture probability according to FRAX scale (e.g., major osteoporosis fracture >30%, hip fracture >4.5%, or age).

‡ The AACE–ACE guidelines list the drugs in alphabetical order and not in sequence of the most appropriate therapy.

§ Abaloparatide and SERMs are not recommended by the American College of Physicians, which regards the evidence as inconclusive to recommend for or against use of these agents.

¶ On the basis of existing data, there is less certainty regarding the use of a T score of –2.5 or less at the 33% radius site as a threshold for treatment.

‖ Ibandronate is not recommended to reduce the risk of hip fracture.

** SERMs are recommended in patients at low risk of DVT when bisphosphonates or denosumab are not appropriate or if there is a high risk of breast cancer. HRT is recommended in women who are younger than 60 years of age or less than 10 years past menopause, who are at low risk of DVT, and in whom bisphosphonates and denosumab are not appropriate. Calcitonin is only recommended if adverse effects result with the use of SERMs, bisphosphonates, estrogen, denosumab, PTH analogues, and other therapies.

†† Consider reinitiating osteoporosis therapy earlier than the 5-year suggested maximum if there is a clinically significant decline in BMD, an incident fracture, or other factors that alter the clinical risk status.[22]

‡‡ Probability and intervention thresholds vary by country, health system, and willingness to pay.

Although denosumab is an alternative treatment option for women at high risk for fracture who have contraindications to bisphosphonates or cannot take them owing to unacceptable adverse effects, there is concern about accelerated bone resorption and rapid bone loss after discontinuation of denosumab therapy. Whether denosumab should be used as initial therapy in women who are at high risk — but not at very high risk — for fracture who have other treatment options is debated among some experts. In a post hoc analysis of a trial that compared denosumab with placebo, the incidence of vertebral fractures increased from 1.2 to 7.1 per 100 participant-years after treatment with denosumab was discontinued, a finding similar to that observed after discontinuation of placebo, but the incidence of multiple vertebral fractures was higher after discontinuing denosumab than after discontinuing placebo (3.4% vs. 2.2%).[32] Therefore, patients must continue denosumab therapy indefinitely or transition to treatment with bisphosphonates to maintain bone mineral density and prevent incident vertebral fractures.

Weekly administration of alendronate, initiated 6 months after receipt of the last dose of denosumab, may prevent bone loss.[33] The efficacy of zoledronate may depend on the timing and frequency of administration.[34] Some experts recommend administering zoledronate 6 to 7 months after the last dose of denosumab, with another dose 3 to 6 months later, depending on bone-turnover markers.[35] Administering denosumab on time every 6 months is also important. Retrospective data show that administering denosumab late (>16 weeks' delay) was associated with an incidence of vertebral fractures that was nearly four times as high as that seen among patients who received denosumab doses on time (≤4 weeks' delay).[36]

PTH Receptor Agonists

Parathyroid hormone (PTH) receptor agonists include teriparatide (PTH 1-34) and abaloparatide (PTHrP 1-34). As compared with placebo, treatment for 18 to 24 months with teriparatide or abaloparatide reduces vertebral and nonvertebral fracture risk.[17] Neither drug has been shown to reduce the incidence of hip fractures, but studies were underpowered for this outcome.[37] Both agonists require daily injections. Antiresorptive therapy is indicated after PTH receptor agonist therapy is complete and increases bone mineral density further; without it, bone mineral density decreases within a year.[38]

Most guidelines limit the use of PTH receptor agonists to patients at very high risk for fracture or to patients who have unacceptable side effects with or are unresponsive to other therapies (Table 3). Although both agents increase bone mineral density of the spine to a similar degree, an open-label comparison suggested greater increases in bone mineral density of the hip with abaloparatide.[39] Limited trial data indicate that teriparatide increases bone mineral density of the spine more than alendronate and decreases vertebral fractures more than risedronate, findings that support its use in patients at very high risk for fractures.[40,41]

Because studies in rodents showed that teriparatide increased the incidence of osteosarcoma, the original FDA package labeling included a black-box warning and limited treatment to 2 years. Recent data show that the incidence of osteosarcoma among patients who are treated with teriparatide is similar to the background incidence of the disease.[42] Although the FDA removed the time limitations for treatment with some PTH receptor agonists, limited safety and efficacy data exist for treatment of longer durations. These agents should be avoided in patients at increased risk for osteosarcoma (e.g., patients with Paget's disease or skeletal irradiation). Longer durations or repeated courses of treatment may be appropriate in patients whose risk of fracture remains at or returns to high or very high levels or who do not have a response to other therapies.

Romosozumab

Romosozumab, given monthly as subcutaneous injections, is the newest FDA-approved therapeutic for postmenopausal osteoporosis. In a phase 2 study, romosozumab increased bone mineral density more than teriparatide.[43] In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME), romosozumab reduced the risk of vertebral and clinical (composite symptomatic vertebral and nonvertebral) fractures at 12 months as compared with placebo.[18] The risk of vertebral fracture remained lower in the romosozumab group after 1 year of treatment with denosumab.

Similar to treatment with PTH receptor agonists, romosozumab therapy must be followed by treatment with bisphosphonates or denosumab.[18] In another trial that investigated treatment with romosozumab as compared with alendronate for 1 year, both followed by alendronate for 1 year,[21] romosozumab reduced vertebral, nonvertebral, and hip fractures more than alendronate. Although not observed in FRAME, a higher incidence of serious cardiovascular events with romosozumab (2.5% vs. 1.9%) led to a black-box warning against the use of romosozumab within 1 year after myocardial infarction or stroke. Many guidelines recommend romosozumab as initial therapy only for persons at very high risk for fracture, with use limited to 1 year (Table 3).

Other Antiresorptive Agents

Owing to adverse effects, estrogen therapy and selective estrogen-receptor modulators are recommended only in selected populations or circumstances (Table 3). Calcitonin, a weak antiresorptive agent, is rarely used for postmenopausal osteoporosis.

Combination Treatment

Concurrent treatment with teriparatide and bisphosphonates has no added benefit with respect to the bone mineral density of the spine and hip as compared with teriparatide alone.[41] The combination of denosumab and teriparatide increases bone mineral density of the hip and spine more than either alone, but is not endorsed by guidelines or routinely covered by insurance.[44]

MONITORING

Most guidelines suggest repeating DXA 1 to 2 years after initiating or changing therapy, but from there recommendations diverge.[8,11,24] Nonresponse, defined as a decrease in bone mineral density greater than the least amount of change that can be considered clinically significant, may occur in 10% or more of patients.[45] No treatment reduces fracture risk to zero. However, the presence of decreasing bone mineral density or the occurrence of multiple fractures should prompt evaluation and consideration of alternative therapy. Some clinicians measure bone-turnover markers 3 to 6 months after initiation of antiresorptive therapy to assess adherence and response. Although declines in bone-turnover markers are associated with a reduction in fracture risk in large trials, this approach is not routinely recommended.

AREAS OF UNCERTAINTY

The appropriate duration of bisphosphonate therapy is unclear. In extended trials of alendronate (10 years) and zoledronate (6 years),[46,47] participants who were assigned to discontinue therapy after 5 and 3 years, respectively, had lower bone mineral density at the study conclusion (although bone mineral density levels were higher than at pretreatment) and a higher incidence of vertebral (but not nonvertebral) fractures than participants who were assigned to continue treatment.[46,47] Concerns regarding long-term bisphosphonate therapy center on atypical femur fractures.[19] Among 196,129 women, the incidence of atypical femur fractures decreased from 4.50 per 10,000 person-years among current users of bisphosphonate to 1.81 per 10,000 person-years at 3 to 15 months after discontinuation and 0.5 per 10,000 person-years at more than 15 months after discontinuation.[20] Therefore, most guidelines recommend bisphosphonate "drug holidays" (temporary treatment breaks) to lower the risk of atypical femur fractures in women not at high risk for fracture after 5 years of treatment with oral bisphosphonate or 3 years of treatment with intravenous bisphosphonate.[22] Treatment up to 10 years (oral administration) or 6 years (intravenous administration) is suggested in women at high risk (Table 3), with periodic reevaluation of the risks and benefits of continued treatment.[22] Individualized decisions to resume bisphosphonates after a holiday should include the consideration of incident fractures, decreasing bone mineral density, increased bone-turnover markers to pretreatment values, and returns to intervention thresholds.[11] Likewise, the appropriate duration of denosumab is unclear. The Endocrine Society suggests reassessing fracture risk after 5 to 10 years of denosumab therapy and continuing or switching therapy in patients who remain at high risk. Because the risk of multiple vertebral fractures after discontinuation of therapy may rise as the duration of denosumab therapy increases, recommendations may evolve.[48]

Limited data are available to guide the use of sequential pharmacologic treatment. Although antiresorptives are considered to be first-line therapy (Table 3), they blunt or delay bone mineral density gains in response to anabolic agents.[49,50] In patients receiving treatment with bisphosphonates, switching to romosozumab led to greater increases in bone mineral density than teriparatide, although data regarding fractures are lacking.[43,51-53] In contrast, switching patients from denosumab to teriparatide should be avoided owing to bone loss.[51] Some experts recommend treat-to-target approaches, in which therapy is selected and modified according to the likelihood that it can decrease the patient's fracture risk to an acceptable level (e.g., T score greater than –2.0).[54] Appropriate thresholds are unclear and more data are needed to validate this approach.

GUIDELINES

Guidelines for diagnosis and management of postmenopausal osteoporosis vary with respect to the threshold for starting therapy and the choice and duration of treatment (Table 3). Our recommendations are generally consistent with the guidelines of the Endocrine Society and the Bone Health and Osteoporosis Foundation (Table 3).[8,23,24]

CONCLUSIONS AND RECOMMENDATIONS

The presentation of the patient described in the vignette is typical of postmenopausal osteoporosis in that the initial humerus fracture was not recognized as indicating osteoporosis, which was later diagnosed by the T score of –2.6 and prevalent vertebral fractures. History and laboratory testing should identify modifiable risk factors, medications, and underlying conditions affecting fracture risk and therapy decisions. The patient's multiple fragility fractures indicate a very high risk of additional fractures. Therefore, we favor therapy with anabolic agents first with either a PTH receptor agonist or romosozumab followed by treatment with a bisphosphonate or denosumab. If anabolic therapy was declined, we would favor denosumab over bisphosphonates, given her severe osteoporosis and the greater effects of denosumab on bone mineral density. Despite the debated utility of repeat DXA, we would reevaluate clinically and reassess bone mineral density with DXA 1 or 2 years after initiating therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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