CLINICAL PRACTICE

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 author's clinical recommendations.*

A 63-year-old woman presents with a history of acute low back pain. She had menopause at 44 years of age but never received postmenopausal hormone-replacement therapy. She reports a history of a Colles' fracture at the age of 60 years. Her mother sustained a hip fracture at 70 years of age. Lumbar-spine films reveal a new vertebral fracture. Dual-energy x-ray absorptiometry of the hip shows a bone mineral density T score of −1.3. How should her case be managed?

THE CLINICAL PROBLEM

Postmenopausal osteoporosis is a common disease with a spectrum ranging from asymptomatic bone loss to disabling hip fracture. The National Institutes of Health consensus conference defined osteoporosis as a disease of increased skeletal fragility accompanied by low bone mineral density (a T score for bone mineral density below −2.5) and microarchitectural deterioration.[1] In the United States, there are 1.5 million osteoporotic fractures per year, with an annual direct cost of nearly $18 billion.[2] It is predicted that the prevalence of fracture will increase by the year 2025, yet less than a quarter of all women who sustain an osteoporotic fracture currently receive appropriate treatment for osteoporosis.[3,4]

Fractures occur because of qualitative and quantitative deterioration in the trabecular and cortical skeleton. Bone quality cannot be measured clinically, but bone mineral density can be measured painlessly, quickly, safely, accurately, precisely, and relatively inexpensively; several methods are available, of which dual-energy x-ray absorptiometry is currently the most validated. Low bone mass at any skeletal site is associated with a substantially increased risk of fracture.[5,6] Other risk factors include advancing age, low body weight, maternal history of osteoporosis, the direction of a fall (a fall backward and to one side is most likely to result in a fracture), and most important, the presence of a previous fracture.[5-7] These and other risk factors for osteoporosis were reviewed in a recent Clinical Practice article in the *Journal.*[6]

STRATEGIES AND EVIDENCE

OVERVIEW

A comprehensive management plan for osteoporosis includes evaluation of those at highest risk, exclusion of secondary causes of low bone mineral density, and selection of the appropriate treatment. A history of fragility fractures (unrelated to substantial trauma) in a postmenopausal woman strongly supports a diagnosis of osteoporosis, regardless of bone mineral density. Secondary causes such as primary hyperparathyroid-

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ism, vitamin D deficiency due to low intake, lack of exposure to sunlight, or malabsorption, and multiple myeloma should be excluded, particularly if the z score (the number of standard deviations from the mean for an age- and sex-specific reference group) for bone mineral density is depressed (i.e., below −2.00). Biochemical markers of bone turnover such as N-telopeptide or osteocalcin rarely help in establishing a diagnosis or selecting treatment, although they may be useful in determining whether there is accelerated bone loss, particularly during the first few years of menopause.

Decision making should also take into account several caveats. Osteoporosis therapy can reduce the risk of fracture by as much as 50 percent, but some women have fractures despite treatment. Also, changes in lifestyle and the use of pharmacologic interventions are lifetime commitments, and therefore cost, compliance with a medication regimen, and safety must be considered in decisions on therapy.[8] Moreover, a substantial percentage of osteoporotic fractures occur in women who have T scores above −2.5. (A T score is the number of standard deviations the bone-mineral-density measurement is above or below the young-normal mean bone density.) In some cases, there is a substantial discrepancy between the spine and hip T scores. Thus, decisions with regard to treatment should not be based solely on bone mineral density.

PLANNING AN INTERVENTION STRATEGY

Therapy for postmenopausal osteoporosis is considered to be primary prevention when it is prescribed for those at risk without a T score below −2.5 or a history of fragility fracture and is considered to be treatment for those with established disease, including previous osteoporotic fracture, markedly reduced bone mineral density, or both.[9] The choice of an appropriate regimen will depend on whether the therapy is designed principally to prevent bone loss in patients with osteopenia (a T score between −1 and −2.5) or to reduce the likelihood of a first or subsequent fracture in patients with osteoporosis.

NONPHARMACOLOGIC OPTIONS

Calcium supplementation should be adjunctive treatment for all women with established osteoporosis and must be part of any preventive strategy to ameliorate bone loss. Increased calcium intake reduces the hyperparathyroidism associated with advancing age and can enhance mineralization of newly formed bone. A recent meta-analysis of 15 calcium intervention trials involving healthy women and postmenopausal women with osteoporosis demonstrated an increase of nearly 2 percent in spine bone mineral density after two years, although the risk of vertebral and nonvertebral fracture was not reduced to a statistically significant level.[10] A total calcium intake of 1200 to 1500 mg per day (through diet, supplements, or both) is recommended for all postmenopausal women.[9]

Vitamin D is essential for skeletal maintenance and enhancement of calcium absorption. Dietary insufficiency of this vitamin is a growing problem, with as many as two thirds of patients with hip fracture classified as having a deficiency of vitamin D (defined as a serum 25-hydroxyvitamin D [25(OH) vitamin D] level below 15 ng per milliliter [37.4 nmol per liter]).[11] Elderly persons with chronic conditions that require assisted-living situations are particularly vulnerable to vitamin D deficiency because of lack of adequate exposure to sunlight. One large trial showed a reduction of 33 percent in hip fracture among nursing home residents who were randomly assigned to receive calcium supplements and vitamin D, as compared with those given placebo.[12] In another trial, treatment with a single oral dose of 100,000 IU of vitamin D_3 every four months reduced nonvertebral fractures by nearly a third among elderly people who are able to walk.[13] Similarly, among older men and women in New England, calcium citrate (500 mg per day) and vitamin D_3 (700 IU per day) reduced the risk of nonvertebral fracture.[14] There is strong evidence that vitamin D supplementation enhances muscle strength and reduces the risk of falling.[15] Table 1 lists the various forms of calcium and vitamin D supplements.

Counseling with regard to avoidance of smoking and excessive alcohol intake is routinely warranted, particularly since smoking and alcohol intake have been linked in some studies to greater fracture risk.

Physical Activity

Bed rest or immobility due to other causes can result in rapid bone loss. Moreover, the number of falls and the percentage of falls that result in fracture increase with age.[16] A recent Cochrane meta-analysis found that muscle strengthening, balance training, assessment of the home for hazards, withdrawal of psychotropic medications, and the use of a multidisciplinary program to assess risk factors

Table 1. Calcium and Vitamin D Supplementation for Postmenopausal Women.*

Supplement	Preparation	Recommended Daily Total	Frequency of Doses	Comment
Calcium		1200–1500 mg	Two or three times daily	Side effects: nausea, constipation
Calcium carbonate		200–600 mg	Two or three times daily	Food enhances absorption
	Caltrate	600 mg	Twice daily	With or without vitamin D, at a dose of 200 IU; food enhances absorption†
	OsCal	250–600 mg	Two or four times daily	Fasting enhances absorption; with or without vitamin D
	Tums	200–500 mg	Two or three times daily	Available as chewable antacid tablets and pills
	Viactiv	500 mg	Twice daily	Available as flavored "chews"; with vitamin D†
Calcium lactate		42–84 mg	Five or six times daily	Requires taking many tablets very often
Calcium citrate				
	Citracal	200–500 mg	Two or four times daily	With or without vitamin D, at a dose of 200 IU; food enhances absorption†
Calcium phosphate	Posture	600 mg	Twice daily	Posture is the only calcium phosphate preparation available
Vitamin D	600–800 IU (15–20 μg) daily	Daily	Taken any time of the day	
	Multivitamin	400 IU per pill	Daily or twice daily	Good absorption; may contain vitamin D_2 or D_3
	Vitamin D	400 IU per pill	Daily or twice daily	Good absorption
	Calcium with vitamin D†	125–400 IU per pill	Daily or twice daily	The dose of vitamin D varies in different supplements
	Ergocalciferol (vitamin D_2)	50,000 IU per capsule	Once weekly	For vitamin D deficiency, vitamin D_3 is preferred
	Cholecalciferol (vitamin D_3)‡	50,000 IU per capsule	Once weekly	For vitamin D deficiency

* Adequate intake of vitamin D for older postmenopausal women, as established by the Institute of Medicine in 1997, is 600 IU daily; persons living in northern latitudes often have lower serum vitamin D levels and are thought to require 800 IU daily. The recommended daily totals are for elemental calcium and elemental vitamin D.

† Often calcium supplements contain vitamin D, but the dose and type of vitamin D vary (e.g., 125 IU to 400 IU per tablet). Similarly, vitamin D supplements often include calcium at various doses (e.g., 125 mg to 500 mg per tablet). Supplements need to be examined carefully by both the patient and the provider, so that proper doses are administered.

‡ Vitamin D_3 is preferred for replacement in persons with vitamin D deficiency, because it can be measured more accurately than D_2 and is absorbed better. However, high doses (e.g., 50,000 IU) can be difficult to obtain. Vitamin D_2 is derived from plant sources. It can be obtained from most formularies and pharmacies. Regardless of the type of vitamin D, treatment with high doses should not continue beyond three months and should be followed by a repeated measurement of the serum 25(OH)vitamin D level. If supplementation is successful in raising the serum level, a dose of 800 IU per day is used for maintenance. If supplementation is unsuccessful and the assay is valid, then consideration should be given to malabsorption, particularly gluten enteropathy.

all protect against falls.[17,18] Another approach is to pad the hip with a hip protector to reduce trauma during a fall; although patient compliance with this strategy is generally poor, when used properly, the strategy has been reported to reduce the risk of hip fracture.[19] Regular physical activity, including aerobic, weight-bearing, and resistance exercise, is effective in increasing bone mineral density of the spine and strengthening muscle mass in postmenopausal women, but there are no large trials establishing whether these interventions reduce the fracture risk.[20]

PHARMACOLOGIC OPTIONS

There is abundant evidence that an aggressive intervention program can reduce the risk of fracture and improve the quality of life among postmenopausal women with osteoporosis. Several pharmacologic options are available, and these can be classified according to their mechanism of action. The two main classes of drugs used to treat osteoporosis are antiresorptive agents (agents that block bone resorption by inhibiting the activity of osteoclasts) and anabolic agents (agents that stimulate bone formation by acting primarily on osteoblasts).

Table 2 is a review of agents for the treatment of osteoporosis that have been approved by the Food and Drug Administration.

Antiresorptive Agents

By suppressing osteoclast activity, antiresorptive agents slow the remodeling cycle, thereby enhancing mineralization of the bone matrix and potentially stabilizing the trabecular microarchitecture.[21] These agents increase bone mineral density in women with osteopenia or osteoporosis and reduce the risk of fracture in women with osteoporosis, although efficacy varies among the agents[22] (Table 2).

Postmenopausal Hormone-Replacement Therapy

Hormone-replacement therapy was once considered the primary therapy for postmenopausal women with osteoporosis. Estrogen slows bone resorption by blocking cytokine signaling to the osteoclast, increases bone mineral density, and reduces the incidence of new vertebral fractures by nearly 50 percent.[23] Treatment with low-dose conjugated estrogens (0.3 or 0.45 mg per day) or ultra-low-dose estradiol (0.014 mg per day) also increases bone mineral density, but the antifracture efficacy of these therapies has not been established.[24,25] Among women in the Women's Health Initiative trial, in

Table 2. Medications Approved by the Food and Drug Administration for the Treatment or Prevention of Postmenopausal Osteoporosis.*

Drug	Method of Administration and Dose	Reduction in Risk of Fracture	Side Effect	FDA Approval
Bisphosphonates	Oral		Esophagitis, myalgias	For treatment and prevention†
Alendronate	35–70 mg weekly, 5–10 mg daily	Vertebral, nonvertebral, and hip fracture		
Risedronate	30–35 mg weekly, 5 mg daily	Vertebral, nonvertebral, and hip fracture		
Ibandronate	150 mg monthly, 2.5 mg daily	Vertebral fracture	First dose‡	
SERM	Oral			For treatment and prevention
Raloxifene	60 mg daily	Vertebral fracture only	Hot flashes, nausea, DVT, leg cramps	
Anabolic agents	Subcutaneous, daily			
PTH (1–34) (teriparatide)	20 μg	Vertebral and nonvertebral fracture	Hypercalcemia, nausea, leg cramps	Approved for treatment only; generally used for severe osteoporosis
Calcitonin§	Subcutaneous or nasal, 100–200 IU	Vertebral fracture only	Nasal stuffiness, nausea	Approved for treatment only
Estrogens	Oral or transdermal		Risk of DVT, risk of cardiovascular disease, breast cancer	Approved for prevention only
Conjugated equine estrogens	Oral, 0.30–1.25 mg daily	Vertebral, nonvertebral, and hip fracture (at dose of 0.625 mg daily)		
17β-estradiol¶	Oral, 0.025–0.10 mg, or transdermal twice weekly	No data from randomized, controlled trials		For prevention only
	Ultra-low-dose (0.014 mg/day, given weekly)	No data available		

* All agents approved for treatment have demonstrated efficacy in reducing fractures, as determined in randomized, placebo-controlled trials with fracture as the primary end point. DVT denotes deep-vein thrombosis, SERM selective estrogen-receptor modulator, and PTH parathyroid hormone.
† There has been limited post-marketing experience with ibandronate for prevention.
‡ There may be a response to the first dose at 150 mg consisting of myalgias, joint aches, and low-grade fever, which is similar to a response to the first intravenous administration of bisphosphonates containing nitrogen.
§ The use of calcitonin is not generally recommended.
¶ A reduction in the risk of hip fracture has not been established for 17β-estradiol in a randomized, controlled trial.

those randomly assigned to receive conjugated estrogens, with or without a progestin, the reduction in hip fracture was 33 percent.[26] Discontinuation of estrogen results in measurable bone loss, although it is not certain whether discontinuation results in a greater fracture risk than continuation.[27] Recent concern about the nonskeletal risks associated with long-term use of estrogen (including the risk of breast cancer and the risk of cardiovascular disease), coupled with the availability of other drugs to treat osteoporosis has markedly lessened enthusiasm for hormone-replacement therapy in the treatment and prevention of osteoporosis.

Selective Estrogen-Receptor Modulators

A selective estrogen-receptor modulator such as raloxifene inhibits bone resorption through the same mechanism as do estrogens.[28] Raloxifene increases spine bone mineral density slightly and decreases the risk of vertebral fracture by 40 percent in women with osteoporosis, but it has no effect on the risk of nonvertebral fracture.[29] The risk of breast cancer is reduced with long-term use of raloxifene, although the drug is not approved for this indication.[30] New selective estrogen-receptor modulators are currently in phase 2 and 3 clinical trials.

Bisphosphonates

The bisphosphonates are the most widely prescribed antiresorptive agents and are often considered first-line therapy for the treatment of postmenopausal osteoporosis. These agents suppress resorption by inhibiting the attachment of osteoclasts to bone matrix and enhancing programmed cell death. First-generation bisphosphonates include etidronate and clodronate; neither drug is approved for the treatment of osteoporosis. Alendronate and risedronate, two second-generation nitrogen-containing bisphosphonates, have been shown in randomized trials to increase bone mineral density in postmenopausal women with osteopenia or osteoporosis; in women with osteoporosis, they have been shown to reduce the incidence of hip, vertebral, and nonvertebral fracture by nearly 50 percent, particularly during the first year of treatment.[22,31-34] As is the case with other antiresorptive drugs, increases in bone mineral density with alendronate or risedronate account for a small fraction of their antifracture efficacy.[8] Hence, follow-up measurements by dual-energy x-ray absorptiometry may substantially underestimate the reduction in fracture risk.

Recent data have shown that alendronate can be safely administered for at least seven years without adversely affecting bone strength.[35] Moreover, discontinuation of long-term (five years or more) alendronate therapy results in minimal bone loss over the ensuing three to five years.[27,35] Alendronate or risedronate once weekly has been shown to reduce the rate of drug-induced esophagitis, as compared with daily doses. In a recent one-year head-to-head study, alendronate increased spine and hip bone mineral density slightly more than risedronate, although the clinical significance of this finding is uncertain.[36]

Other bisphosphonates are available off-label or are being studied for the treatment of osteoporosis. Intravenous pamidronate has been used to treat women who cannot tolerate oral bisphosphonates; however, its efficacy in reducing fracture has not been established. Acute and delayed hypersensitivity reactions can occur with intravenous pamidronate, and its use is contraindicated in patients with vitamin D deficiency, since the drug can cause a precipitous drop in serum calcium levels.[37] In 2005, ibandronate, at a dose of 2.5 mg daily or 150 mg monthly, was approved by the Food and Drug Administration (FDA) for both the prevention and treatment of postmenopausal osteoporosis. Daily ibandronate has been shown to reduce significantly the incidence of vertebral fracture in women with osteoporosis and to reduce the incidence of nonvertebral fracture in women with severe osteoporosis (T score, below −3.0).[38] Intravenous zoledronate, which is approved for the treatment of malignant hypercalcemia, multiple myeloma, and skeletal metastases, can suppress bone resorption and increase bone mineral density in postmenopausal women for as long as one year after a single 4-mg dose.[39] Phase 3 trials are under way to evaluate the safety and efficacy of this drug in reducing osteoporotic fracture.

Calcitonin

Calcitonin is an endogenous peptide that partially inhibits osteoclast activity. Nasal calcitonin and subcutaneous calcitonin are approved for the treatment of postmenopausal osteoporosis. Although treatment of women with osteoporosis with nasal calcitonin at a dose of 200 IU per day has been shown to reduce the incidence of vertebral (but not nonvertebral) fracture in a single randomized trial, methodologic flaws in the study have limited enthusiasm for this agent.[40] In placebo-controlled studies, na-

sal calcitonin has reduced the pain associated with new spine fractures, although it is now considered preferable to treat osteoporosis with more potent agents and to manage pain separately.[41]

Strontium Ranelate

Strontium ranelate is orally administered and stimulates calcium uptake in bone while inhibiting bone resorption. In a randomized trial in postmenopausal women with osteoporosis, daily strontium ranelate reduced the risk of vertebral fracture by 40 percent.[42] However, a significant reduction in nonvertebral fracture was observed only in a post hoc analysis of a small subgroup of women.[42] This drug was recently approved by European regulatory agencies, but it is not currently approved by the FDA.

Anabolic Agents

The prototypical anabolic drug is sodium fluoride, which was widely used in the 1970s and 1980s because of its ability to stimulate the formation of new bone. However, a randomized trial in 1990 established that despite dramatic increases in bone mineral density, the risk of nonvertebral fracture actually increased with the use of fluoride.[43] In 2002, synthetic parathyroid hormone (1–34) (teriparatide) was the first anabolic agent approved by the FDA for the treatment of postmenopausal osteoporosis. Unlike antiresorptive agents, parathyroid hormone stimulates bone remodeling by increasing bone formation. In a large randomized trial involving postmenopausal women with severe osteoporosis, 20 µg of parathyroid hormone per day administered subcutaneously markedly increased bone mineral density and reduced vertebral and nonvertebral fractures by more than 50 percent.[44] However, the trial was stopped after 20 months because of concern about the development of osteosarcoma in rats treated with high doses of parathyroid hormone (1–34). As a result, a "black-box" warning was added to the teriparatide label. However, retrospective studies have found no association between osteosarcoma and primary or secondary hyperparathyroidism in humans, and no cases of osteosarcoma have been reported in the more than 200,000 patients treated with parathyroid hormone. The current recommendation is that parathyroid hormone therapy should be limited to persons with moderate-to-severe osteoporosis and that the duration of therapy should not exceed two years. Parathyroid hormone (1–34) is well tolerated, although mild but asymptomatic hypercalcemia (i.e., a serum calcium

level between 10.5 and 11.0 mg per deciliter [2.6 and 2.8 mmol per liter]) can occur rarely. Cost and the requirement of subcutaneous administration are major limiting factors.

Combination Therapy

Although studies have suggested that combining antiresorptive agents may slightly increase bone mineral density as compared with monotherapy, there are no data to indicate that combination therapies are superior for reducing the risk of fracture.[27,45] There is also no evidence that combining parathyroid hormone with an antiresorptive drug results in additive or synergistic effects,[46,47] but concurrent use of cyclic parathyroid hormone (i.e., daily parathyroid for 3 months followed by no treatment for 3 months for a period of 15 months) with alendronate may be just as effective as daily parathyroid hormone with alendronate.[48] Nevertheless, bone loss will occur after the discontinuation of parathyroid hormone, but it can be prevented if this therapy is followed by treatment with an antiresorptive drug such as alendronate.[49,50]

AREAS OF UNCERTAINTY

The optimal timing and type of preventive therapy are still not clearly defined. Many postmenopausal women have T scores between −1.0 and −2.5 but no other risk factors. Postmenopausal hormone-replacement therapy, once considered the best preventive approach for these women, is no longer recommended in light of the associated risks reported in the Women's Health Initiative trial.[26] Bisphosphonates prevent bone loss in women with osteopenia and can be used as prophylaxis, but cost-effectiveness and concerns about the effects on skeletal mineralization over decades may be limiting factors.[22] Studies such as the extension of the Fracture Intervention Trial (evaluating alendronate) have provided some reassurance with regard to long-term use.[35]

Also uncertain is the appropriate care for patients who continue to have fractures despite aggressive pharmacologic intervention. Whether new agents such as the synthetic antibody to the receptor activator of nuclear factor-κB ligand (AMG 162) or strontium ranelate will be effective in preventing new fractures in such patients needs to be tested.[42,51] Finally, controversy persists about the use of vertebroplasty or kyphoplasty, procedures that introduce material to expand compressed vertebrae

Table 3. Recommended Regimens for the Prevention and Treatment of Postmenopausal Osteoporosis.*			
Organization	Whom to Treat	Nonpharmacologic Intervention	Pharmacologic Intervention
National Osteoporosis Foundation	T score below –2.0 with no risk factors T score below –1.5 with one or more risk factors Any spine or hip fracture	1200 mg calcium daily 400–800 IU vitamin D daily Regular weight-bearing exercise	Antiresorptive agents or anabolic agents
American Association of Clinical Endocrinology	T score below –2.5 T score below –1.5 with fractures	1200 mg calcium daily 400–800 IU vitamin D daily Weight-bearing physical activity	Antiresorptive or anabolic agents
U.S. Surgeon General's Pyramid Approach†	No recommendations	1200 mg calcium daily 600–800 IU vitamin D daily Regular weight-bearing activity (30 minutes daily) Strength and balance training	Antiresorptive agents or anabolic agents

* Data in this table are from the National Osteoporosis Foundation (2003),[54] Hodgson et al. (2001),[55] and the Office of the Surgeon General (2004).[9] T scores are the number of standard deviations the bone-mineral-density measurement is above or below the young-normal mean bone mineral density.
† The pyramid approach consists, in ascending order, of lifestyle changes, the identification of a secondary cause of osteoporosis, and pharmacotherapy.

and reduce the pain associated with new fractures. Both the absence of randomized, placebo-controlled trials and concerns about the mechanical strength of adjacent vertebrae after these procedures preclude making recommendations for their use.[52,53]

GUIDELINES

Several professional societies and government agencies have provided guidelines for treatment options (Table 3).

SUMMARY AND RECOMMENDATIONS

A careful history taking and physical examination that address risk factors for or signs of osteoporosis (particularly previous fragility fractures, height loss, or both, as well as possible secondary causes of bone loss) combined with measurement of bone mineral density should guide therapeutic decisions.

Given the high prevalence of low levels of 25(OH) vitamin D in women with osteoporosis, measurement of a serum 25(OH) vitamin D level by a reliable laboratory is reasonable. Treatment plans for a patient such as the woman in the vignette should include calcium supplementation to a level of at least 1200 mg per day and 800 IU of vitamin D, as well as pharmacologic therapy. I would start with an oral bisphosphonate (alendronate or risedronate) once weekly or ibandronate once monthly, given the documented reductions in the incidence of hip and vertebral fracture with these agents. Alternatively, one could consider parathyroid hormone (1–34) for two years if a patient cannot tolerate a bisphosphonate or has had multiple fractures, although with this regimen, cost and compliance need to be taken into consideration. Irrespective of the choice of therapy, careful follow-up, with attention to pain, lifestyle, and risk factors for future fracture, is necessary.

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