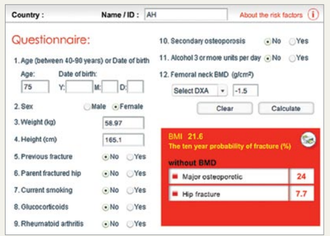
### Case 2

AH is a 75-year-old Caucasian woman who is 65 inches tall and weighs 130 lb. She does not have any risk factors for osteoporosis. A recent DXA demonstrated a hip T-score of –1.5; therefore, she does not meet the diagnostic criteria for osteoporosis. However, her 10-year risk of any osteoporotic fracture is 24% and her risk of a hip fracture is 7.7%.




### Discussion

AH meets the NOF criteria for pharmacologic treatment. This case illustrates the importance of age, rather than T-score alone, as a strong predictor of osteoporotic fracture risk. There are many pharmacologic treatment options for appropriate patients including bisphosphonates, estrogen, SERMs, PTH, and calcitonin. However, limited evidence is available to guide selection of a particular therapy and each patient should be evaluated individually.

**Ms Wysocki:** The emerging emphasis on adequate vitamin D, assuming we can assure that patients are vitamin D–replete, resolves many of the issues associated with using calcium supplementation correctly. Patients taking 1500 mg of supplemental calcium frequently have gastrointestinal (GI) complaints and must split the doses, making it difficult to achieve recommended intake levels.

**Dr Feldman:** Calcium bioavailability also must be considered. Many medications can interfere with calcium absorption (**TABLE**). Most commonly recommended supplements contain calcium carbonate; many women in their 70s are achlorhydric. Calcium citrate provides better bioavailability for these patients, as well as for individuals taking histamine-2 blockers or protein pump inhibitors.[37]

**Dr McClung:** However, when taken with a meal, both calcium salts are well absorbed and GI side effects are fewer.[37]

## Exercise, Fall Risk, and Skeletal Health

**Dr Kaunitz:** Does weight-bearing exercise improve skeletal health?

**Dr McClung:** The emphasis on weight-bearing for bone health came from old studies of patients put on bed rest that showed deteriorations in skeletal health when exercise was eliminated.[38,39] There is very little evidence that exercise significantly increases bone mass after childhood; however, physical activity in older adults is an important part of the strategy to retard bone loss.

**Dr Kaunitz:** Exercise does provide cardiovascular and metabolic benefits and helps prevent falls.[40]

**Dr Feldman:** To assess fall risk in the elderly, we assess patients' balance and muscle strength and also evaluate their history and patterns of falls, cognition, vision, and medical regimen. An assessment of the home environment is critical. Having physical therapists do this for high-risk patients is ideal, but we can use available assessment tools to obtain this information from family members.[41] The American Geriatrics Society website (www.americangeriatrics.org/education/falls.shtml) provides direction for clinicians.

**Ms Wysocki:** Vitamin D also seems to have an effect on balance and muscle mass,[42] which contribute to fracture protection.

## Conclusion

Multiple strategies can help clinicians improve osteoporosis management. Frequent discussion with patients is critical.[43] Clinicians should individualize patients' management plans, including nonpharmacologic therapy, such as supplementing vitamin D and calcium at effective levels, and working with patients on lifestyle modifications to reduce falls.[2] The evaluation of pharmacologic treatment options for appropriate patients should be considered, based on potential risk and benefits.

When initiating pharmacologic therapy, clinicians should set treatment goals and perform serial DXA 1 to 2 years after initiation of therapy.[44] These should be reviewed with patients, and the unique concerns and expectations of individual patients should be considered in any final therapeutic decision-making. It is important that physicians engage in frequent, ongoing dialogue with their patients. ■





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This manuscript and associated publication costs, including honoraria for the authors, were funded by Amgen. The supplement has been peer reviewed by OBG MANAGEMENT. The authors were responsible for the content and for providing final approval to publish. Please note: This is not an independent medical education program and not eligible for credit toward CME requirements.

SUPPLEMENT TO
OBG MANAGEMENT

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# Postmenopausal Osteoporosis: Fracture Risk and Prevention

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The editors thank **SARAH DOBBS-O'BRIEN** for medical writing support.

*Disclosures*

**DR FELDMAN** reports that he receives grant/research support from Amgen, Lilly, Eisai, and Wyeth. He is a consultant to Amgen and Lilly. He serves on the speakers bureaus of Novartis, Amgen, Lilly, Forest Pharmaceuticals, GSK, Roche, and Merck.

**DR KAUNITZ** receives funding (to University of Florida Research Foundation) from Bayer, Johnson & Johnson (Ortho), Medical Diagnostic Laboratories, Schering Plough (Organon), Procter & Gamble, and Teva (Barr). He is a speaker and/or consultant to Bayer, Johnson & Johnson (Ortho), Merck, Schering Plough (Organon), Procter & Gamble, and Teva (Barr). He is a stockholder in Becton Dickinson and sanofi-aventis.

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## Key Points

- In the estrogen-regulated RANK ligand (RANKL)/RANK/osteoprotegerin (OPG) pathway, estrogen deficiency favors osteoclast maturation, leading to increased bone resorption compared with bone formation.[1]
- Treatment of low bone mineral density (BMD) should be based on fracture risk, assessed using the WHO Fracture Risk Algorithm (FRAX®). Criteria for treatment are 10-year overall fracture risk ≥20% or 10-year hip fracture risk ≥3%.[2]
- Vitamin D supplementation at levels higher than those traditionally recommended may be appropriate for healthy menopausal women.[3]
- Multiple strategies are needed to effectively manage osteoporosis in postmenopausal women.

This monograph reviews advances in our understanding of the pathophysiology of postmenopausal osteoporosis and new recommendations for best practices in diagnosis and treatment. In Part 1, bone expert Michael R. McClung, MD, comments on new findings concerning bone metabolism. In Part 2, health care providers discuss how to identify and manage postmenopausal osteoporosis patients at risk for fracture.

## PART 1

## Rethinking the Pathophysiology of Postmenopausal Bone Loss and Patient Management

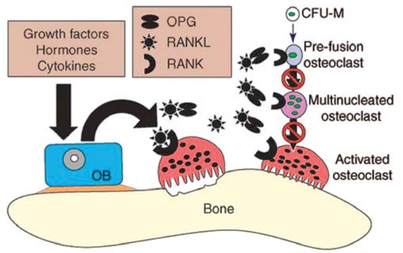
**Dr Kaunitz:** What have recent studies shown about the pathophysiology of osteoporosis?

**Dr McClung:** Prospective studies indicate that estrogen deficiency is the underlying cause of bone loss in early menopause. The result is a rapid and substantial—but finite—loss of BMD, with a duration of 5 to 6 years, during which time women lose an average of 2% to 3% of bone mass each year.[4] In the spine, this loss translates into a decrease in T-score of 1 to 1.5; in the hip, the loss in T-score is more modest. In healthy women, the rate of loss slows considerably after the late 50s.

Population studies show that a second interval of accelerated bone

Figure

**RANKL/RANK/OPG Pathway**




Current Opinion in Pharmacology

Pro-resorptive hormones, cytokines, and growth factors act via their cognate receptors on osteoblasts (OB) and other cells to induce the production of RANKL. Some of these factors also suppress osteoblast production of OPG, which further increases the RANKL:OPG ratio. When this ratio is high, free RANKL is able to activate RANK on osteoclast precursors (CFU-M, or colony forming unit-macrophage) and stimulate their fusion and differentiation into mature osteoclasts. Free RANKL also activates mature multinucleated osteoclasts to resorb bone and protects them from apoptosis. When RANKL is bound by OPG there is rapid cessation of osteoclast formation, activation, and survival.



loss occurs in elderly men and women,[5-7] more closely associated with vitamin D deficiency[8] and a decrease in physical activity and weight-bearing exercise.[9]

**Dr Kaunitz:** How does bone loss differ in women who use HT for treatment of vasomotor symptoms?

**Dr McClung:** Many studies have demonstrated that menopausal HT effectively prevents bone loss.[10-12] With discontinuation, a rapid bone loss occurs: Within 2 years of therapy cessation, a woman's bone density will be approximately what it would have been if she had not taken HT.[13-15] Therefore, although HT has positive effects on the skeleton for as long as it is taken, there are no long-term skeletal benefits after estrogen therapy is stopped.

### RANKL/RANK/OPG Pathway and Bone Metabolism

**Dr Feldman:** What do we know about the mechanisms that regulate bone loss at the molecular level?

**Dr McClung:** During menopause, a marked up-regulation of bone metabolism occurs. Bone resorption increases several fold, outstripping bone formation and leading to bone loss.[16] It recently has become clear that the process involves a final common pathway, the RANKL/RANK/OPG pathway **(FIGURE)**.[17,18] RANKL is a growth factor expressed on the surface of osteoblasts and bone lining cells. Binding of RANKL to its receptor RANK on pre-osteoclasts is required for the differentiation and proliferation of young osteoclasts into mature, active osteoclasts. With estrogen deficiency, an increased expression of RANKL occurs, accompanied by a down-regulation of its natural inhibitor, OPG. This tips the ratio of RANKL to OPG in favor of RANKL and thereby leads to the imbalance of bone resorption over bone formation that characterizes the early postmenopausal state. This results in bone loss and damage to skeletal structure that can result in osteoporosis.

**Ms Wysocki:** Do the currently available agents used to treat bone loss affect the RANKL/RANK/OPG pathway?

**Dr McClung:** Estrogen—and probably selective estrogen receptor modulators (SERMs), also known as estrogen agonists/antagonists, such as raloxifene—reduce RANKL production and increase the synthesis of OPG. This decreases osteoclast number and activity.[19] Bisphosphonates reduce bone turnover by interfering with the function of activated osteoclasts rather than by targeting the pathway that produces them. Treated patients have roughly the same number of osteoclasts as untreated patients; however, in the former, osteoclast function decreases and apoptosis increases.[20] Calcitonin also directly inhibits action of mature osteoclasts.[21] The effect of parathyroid hormone (PTH) on the RANKL-OPG system is complex. By increasing RANKL production, PTH increases bone resorption. Intermittent PTH treatment, however, increases bone formation by other mechanisms. The net result of intermittent PTH administration is increased bone formation.[22]

## Using FRAX® for Management Decisions

Based on a review of clinical and cost-effectiveness considerations, the NOF has updated clinical guidelines for the treatment of patients with osteoporosis. *The Clinician's Guide to Prevention and Treatment of Osteoporosis* incorporates FRAX®, calibrated to United States fracture and mortality rates.

Pharmacologic treatment is recommended for postmenopausal women who have a clinical diagnosis of osteoporosis—based on fractures of the hip or spine—or whose BMD values of the hip or spine are consistent with osteoporosis (T-score less than –2.5), regardless of risk factors.

Fracture risk, based on FRAX®, is used to determine which patients who have low BMD (not meeting criteria for osteoporosis) are appropriate candidates for treatment. According to the NOF guidelines, pharmacologic treatment for such women is recommended when the estimated overall fracture risk in 10 years is greater than or equal to 20% or the estimated hip fracture risk in 10 years is greater than or equal to 3%.

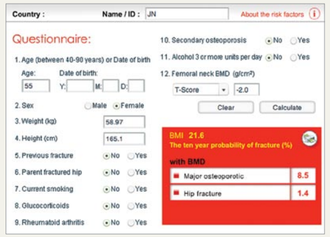
FRAX® data are useful for determining who to treat but are not useful for evaluating response to therapy.





**Case 1**

JN is a 55-year-old Caucasian woman, who is 65 inches tall and weighs 130 lb. She does not smoke, has not been on long-term corticosteroid therapy, and has no family history of fracture. Dual-energy x-ray absorptiometry (DXA) demonstrates a T-score of –2.0 at the hip. Based on FRAX®, her overall risk of fracture is 8.5% in 10 years and her risk of a hip fracture is 1.4%. Despite her low bone density, she is at low risk of an osteoporotic fracture.




**Discussion**

Per NOF guidelines, JN may not need pharmacologic therapy at this time. The effect of FRAX® is to shift the emphasis away from treating patients like JN and toward treating older patients who may not meet the criteria for osteoporosis.

If JN is within 2 to 3 years of menopause, it would be appropriate to reassess her fracture risk in 2 years. If JN is 5 to 6 years postmenopausal and otherwise healthy, considerable bone loss is unlikely to occur in 2 years. She can wait 3 to 5 years for her next DXA. If her T-score has decreased at that time, pharmacologic treatment may be necessary. The NOF guidelines are largely based on cost-effectiveness; it remains necessary to individualize treatment, given each patient's unique situation.

# PART 2

## Fracture Risk and Treatment Decisions

**Dr Kaunitz:** Our goal is to reduce the risk of fracture in our patients. Who should we screen for osteoporosis? How should we select appropriate patients for treatment?

**Dr McClung:** The 2008 National Osteoporosis Foundation (NOF) guidelines recommended BMD assessment for all women aged 65 and older, as well as postmenopausal women ages 50 to 64 when there is concern based on their risk profile. This group includes adults who have had a fracture after age 50, adults with a condition (eg, rheumatoid arthritis) or taking medications (eg, glucocorticoids) associated with bone loss, and anyone being considered for treatment or in treatment for osteoporosis.[2]

**Ms Wysocki:** Bisphosphonates are prescribed to many postmenopausal women with T-scores that do not meet criteria for osteoporosis. Is this appropriate?

**Dr McClung:** Early guidelines were based predominately on BMD values. Unfortunately, measurement of BMD is not a sensitive test for fracture risk.[2] Although patients with osteoporosis are at moderate or high risk of fracture, most fractures related to osteoporosis occur in women who do not have osteoporosis by BMD criteria.[23] This has led to the important clinical question of which patients to treat who do not have osteoporosis.[24] The decision to treat should most often be based on absolute fracture risk. Recently, the World Health Organization (WHO) developed a scientifically based algorithm, FRAX®, that combines BMD with other patient data to estimate probability of future fracture. It is available online at http://www.shef.ac.uk/FRAX. Based on a combination of clinical and cost-effectiveness considerations, the NOF has recommended that pharmacologic treatment be considered for postmenopausal women who have experienced fractures of the hip or spine, have BMD values consistent with osteoporosis, or who have low bone mass (T-scores between –1 and –2.5) with a 10-year risk for a major osteoporotic fracture (defined as a fracture of the spine, hip, wrist, or proximal humerus) of 20% or more or risk of hip fracture of at least 3%.[2] (See "Using FRAX® for Management Decisions," on page S2. Additionally, **Case 1** and **Case 2** illustrate how clinicians can use FRAX® to assess risk for individual patients.)

**Dr Feldman:** Is FRAX® a valid tool for a patient taking HT?

**Dr McClung:** Very few of the individuals in the cohorts that contributed data to FRAX® were taking estrogen,[25] so it may not be valid in this population. Furthermore, FRAX® is of value only in deciding whether a patient should be treated with an anti-fracture agent. Once HT is discontinued, FRAX® would provide a valid indicator of fracture risk.[26] As an aside, a patient who is already on estrogen rarely needs additional anti-fracture medication.

**Dr Feldman:** FRAX® should not be used in patients already on treatment because it is inaccurate.

### Supplementing With Vitamin D and Calcium

**Dr Kaunitz:** Many patients ask about the importance of nutrition for prevention of postmenopausal osteoporosis, specifically calcium and vitamin D. What does the current evidence suggest?

**Dr McClung:** Vitamin D deficiency is technically defined as a 25-hydroxyvitamin D value in the serum of less than 20 ng/mL.[27] However, it appears that values of at least 30 ng/mL are necessary for fracture risk reduction.[28,29] More than half of healthy adults have vitamin D levels lower than this level[30]; and insufficiency is even more prevalent in people who are obese,[31] have dark skin,[30] or are taking pharmaceutical agents that activate hepatic metabolism and clearance of vitamin D, such as antiseizure medications[30] and cimetidine.[32]

**Ms Wysocki:** People with minimal sun exposure also are at risk. Who should be screened for a deficiency?

**Dr McClung:** Patients who are hypocalcemic, those who have had bariatric or small bowel surgery, patients with celiac disease, and people taking antiseizure medications should be screened.[31] There are no recommendations regarding screening otherwise healthy adults, so clinicians have 2 choices: Either measure vitamin D in virtually everyone or treat everyone and monitor treatment.

**Dr Kaunitz:** How much supplemental vitamin D do patients need?

**Dr McClung:** The Institutes of Medicine recommend 400 to 600 IU/d, and the NOF recommends 800 to 1000 IU/d, but there is good evidence that these recommendations are inadequate.[27,29,33] Most younger individuals taking vitamin D3 need at least 1000 IU/d[31]; people older than 65 need at least 2000 IU/d.[3,34] Vitamin D2 is often given in a dose of 50,000 IU per week for 2 to 3 months to correct a deficiency and 50,000 IU every 1 to 2 weeks for maintenance.[31]

**Dr Feldman:** Correcting a deficiency differs from establishing a maintenance dose. Dosing must be individualized based on extent of deficiency, body composition, absorption, and other factors. After selecting an initial dose, it is important to measure levels and adjust the dosage accordingly.

Table

**Calcium: Drug and Nutrient Interactions**

| | |
|---|---|
| **Fiber** | Fiber may decrease absorption of calcium |
| **Iron, zinc, magnesium** | Calcium may cause decreased absorption of iron, zinc, and magnesium. |
| **Caffeine, sodium** | Caffeine and sodium increase urinary calcium excretion. |
| **Levothyroxine** | Calcium reduces levothyroxine absorption. |
| **H2 blockers and protein-pump inhibitors** | H2 blockers and protein-pump inhibitors decrease the absorption of calcium carbonate, which requires an acidic environment. |
| **Tetracyclines** | Calcium decreases the absorption of tetracycline. |
| **Bisphosphonates** | Bisphosphonates should be taken at least 30 min before calcium supplementation. |
| **Quinolone antibiotics** | Calcium decreases absorption of quinolone antibiotics. |
| **Digoxin** | Hypercalcemia increases the risk of fatal cardiac arrhythmias. |
| **Thiazide diuretics** | Thiazide diuretics decrease the excretion of calcium. |
| **Corticosteroids** | Corticosteroids (≥7.5 mg/d) decrease calcium absorption, increase calcium excretion, and inhibit bone formation. |
| **Anticonvulsants, phenytoin, fosphenytoin, carbamazepine, phenobarbital** | These anticonvulsants decrease calcium absorption by increasing the metabolism of vitamin D. |

Adapted from Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract. 2007;22:286-296.

For patients who have had a hip fracture, my goal is to increase their 25 OH vitamin D levels to 40 to 60 ng/mL. To accomplish this, I provide very high daily doses for 2 weeks, and then measure their 25 OH vitamin D levels. If the level is at goal, I place them on 1200 to 2000 IU/d for maintenance.

**Dr Kaunitz:** How do calcium requirements relate to vitamin D status?

**Dr McClung:** The recommendation to take 1200 to 1500 mg calcium per day came from studies of women who were vitamin D–deficient.[35] In newer studies of women who are vitamin D–replete, there seems to be no benefit of calcium intake greater than 800 mg/d.[36] A dairy-free diet has about 250 mg of calcium,[2] so people rarely require supplemental calcium >500 mg.