Highlights from the 2010 Santa Fe Bone Symposium

Learning Objectives

This activity is designed for physicians who treat postmenopausal women or other patients at risk for osteoporosis. There are no prerequisites for this activity. At the conclusion of this activity, participants should be able to:

- Employ consistently the current guidelines for osteoporosis screening and assessment.
- Make appropriate use of the FRAX tool to define fracture risk.
- Describe age- and sex-related changes in bone microarchitecture and macroarchitecture, the pathogenesis of skeletal fragility, and the implications these have on clinical care.
- Employ bone turnover markers to assess response to treatment and monitor patient compliance.
- Discuss emerging data on the use of parathyroid hormone levels in combination with other agents and in diverse settings.
- Discuss with patients the benefits and risks of long-term bisphosphonate therapy.
- Discuss current expert recommendations for drug holidays for patients taking long-term bisphosphonates.
- Compare current and emerging therapies, including their mechanisms of action, efficacy, safety, and administration for patients with osteoporosis.
- Consider options for timing and sequencing treatment using antiresorptive and anabolic agents to maximize their unique benefits, particularly in patients at highest fracture risk.
- Apply current insights in treatment to optimize bone health in complex cases.

CME Information

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Length of time to complete the activity: 3 hours.

Disclosure Information

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E. Michael Lewiecki, MD, Executive Editor

The diagnosis of osteoporosis and related bone disorders presents a number of clinical challenges, as does treatment and monitoring. As our knowledge of bone biology has advanced, diagnostic modalities have improved, diversified, and become more complex. As some controversies related to treatment have resolved, others have emerged to take their places. During the 2010 Santa Fe Bone Symposium, a distinguished panel of experts addressed the current state of many of these advances, complexities, and controversies. Their insights offer both practical advice for today's clinical practitioners and previews of tomorrow's clinical conundrums.

Assessing Bone Structure: Can We Do Better than DXA?

Sundeep Khosla, MD

Dual energy x-ray absorptiometry (DXA) is the clinical standard for bone densitometry. However, DXA measurements are confounded by bone size and cannot differentiate cortical bone from trabecular bone. Peripheral quantitative computed tomography (pQCT) is often used as an alternative to DXA for bone assessment. Standard pQCT, however, has a resolution of approximately 400 μm, and, therefore, cannot be used to assess bone microarchitecture or to evaluate bone strength. We and other researchers are assessing newer approaches to measuring bone structure to determine if any are better than DXA for predicting risk of fracture in adolescent and elderly individuals.

During adolescence the distal forearm is the most common site of fracture, and the incidence of such fractures peaks near the time of the pubertal growth spurt in both boys and girls.[1] We conducted a study using high-resolution pQCT (HRpQCT) to quantify changes in bone microarchitecture and strength at the distal radius in girls and boys during puberty. Because HRpQCT has a voxel size of 82 μm, it can be used to define trabecular and cortical microstructure. HRpQCT also strongly correlates with *ex vivo* micro-CT,[2,3] and it can be used to construct microfinite element (μFE) models of bone strength.[4] Therefore, we used HRpQCT and μFE modeling to quantify changes in bone microarchitecture and

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strength at the distal radius during puberty and to test whether changes in bone microarchitecture during puberty explain the peak in forearm fractures during this period of growth.[5]

Healthy girls and boys (N = 127) between the ages of 6 years and 21 years who had no history of fracture were classified into 5 groups according to bone age: prepuberty, early puberty, midpuberty, late puberty, and postpuberty. Trabecular parameters, such as bone volume fraction, trabecular number, and trabecular thickness, increased in boys during late puberty, but did not change significantly in girls during those years. In contrast, the cortical parameters of thickness and density declined to minimum values at midpuberty in both sexes, though the decline was more pronounced in girls. During mid-to-late puberty, however, cortical thickness and density increased in both sexes, which we believe corresponds with the onset of sex steroid action. At this site, at least, the cortical thickness in boys and girls was similar after puberty.

When we looked at the correspondence between bone strength and the incidence of fractures in patients of the same age range, there was no clear explanation for the increases in fracture rates during early puberty in girls and late puberty in boys. Bone strength increased monotonically in both sexes. Likewise, there was no relationship between fall force or the factor of risk (known as Φ; essentially, the load:strength ratio) and the rate of fractures at different ages. However, using finite element models to estimate the percent of load carried by cortical bone, we found that this parameter declines to its minimum at the same time the incidence of fractures peaks in both sexes. Likewise, the cortical bone to trabecular bone ratio also reached a minimum at the same time.

These results support a similar phenomenon proposed by Mike Parfitt in 1994,[6] which was that during the adolescent growth spurt there is such a strong demand for calcium that it leads to some degree of secondary hyperparathyroidism and cortical thinning. To investigate this idea further, we asked Ralph Muller to estimate the cortical porosity index using an electronic method for detecting pores in cortical bone. As predicted by Parfitt, we found a peak in cortical porosity that corresponded in time to the peak of distal radial fractures. As expected, cortical porosity was also related to parathyroid hormone (PTH) levels, consistent with the idea that some degree of secondary hyperparathyroidism is driving changes in cortical structure during the adolescent growth spurt and contributing to the increase in risk of fracture. Similar results were published recently by Seeman's group in Australia.[7] Our results are also consistent with those from studies using cadavers, which have demonstrated the importance of cortical bone as a determinant of failure load at the distal radius.[8]

In another study, we used 3-dimensional pQCT to define effects of sex and age on bone microstructure at the wrist.[9] This cross-sectional study included 602 participants between the ages of 21 years and 97 years. In young adulthood, men exhibited properties of trabecular structure that predict stronger bones and a greater resistance to fracture, notably higher trabecular bone volume:tissue volume (BV/TV) ratio, and higher trabecular thickness. Both sexes exhibited similar gradual declines in BV/TV throughout life. However, there were marked differences in trabecular structure with aging. In women between the ages of 20 years and 90 years, trabecular number declined by 13% and trabecular spacing increased by 24%; these parameters, however, did not change appreciably in men. Rather, men exhibited a greater decline in trabecular thickness compared with women (24% vs 18%). These results suggest that aging is associated with trabecular loss in women and trabecular thinning in men. This difference is expected to have important implications for age-related changes in bone strength. For example, on the basis of finite element modeling, reductions in trabecular number are expected to have a 2-fold to 5-fold greater effect on bone strength as compared with reductions in trabecular thickness that result in the same decrease in bone volume.[10] This study also demonstrated that 3-dimensional pQCT yielded valuable information about bone structure that would not be available from DXA, which would have shown similar declines in bone density in men and women.

This last conclusion raises the question of whether HRpQCT, with or without subsequent μFE modeling, can predict the risk of fracture better than DXA. We have examined this in several ways, but I will focus on 2 specific studies. The first study was a case-control study in which 100 women with distal forearm fractures were compared with age-matched control patients.[11] DXA revealed that the women with fractures had 8% and 6% lower areal bone mineral density (BMD) than the control women at the femoral neck and radius, respectively. HRpQCT also revealed several significant differences, including a 17% lower trabecular volumetric BMD, a 12% lower trabecular number, and a 15% increase in trabecular spacing in the fracture group versus the control group. μFE modeling predicted that the women with fractures had a 12% lower failure load and 15% higher fall load:failure load ratio than the control women.

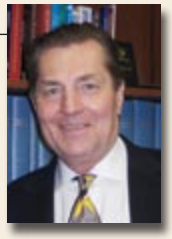
To compare predictive abilities of DXA with those of HRpQCT and μFE modeling, we calculated the odds ratio for a distal forearm fracture associated with a standard deviation change in each of the various bone parameters. For example, using DXA, the odds ratio for a distal forearm fracture was 2.0 (95% CI, 1.4-2.8) for each standard deviation decline in areal BMD at the femoral neck. To assess the sensitivity and specificity of each parameter, we calculated the area under the curve of the receiver-operator characteristic curve (AUC ROC) for that parameter. The AUC ROC for areal BMD of the femoral neck was 0.66. Overall, the AUC ROC values for areal BMD of the radius, for 6 parameters measured by HRpQCT (trabecular volumetric BMD, trabecular number, trabecular thickness, trabecular spacing, cortical thickness, and structure model index), and for 2 parameters obtained by μFE modeling all ranged from 0.60 to 0.68. Thus, no parameter stood out as stronger than the others with regard to its ability to predict distal forearm fracture. However, a multivariable model found that incorporation of the structure model index marginally improved the predictive ability of areal BMD of the femoral neck. We performed a similar study looking at predictive ability of these techniques for vertebral fractures and deformities, and obtained very similar results, except that μFE modeling was a stronger predictor of severe (grade 2–3) vertebral deformity.[12]

Together, results of these studies indicate that HRpQCT and μFE modeling provide important information about changes in bone structure during aging and about the structural basis of bone fractures. At this time, however, these techniques provide only modest improvements over DXA in our ability to predict fracture. With the help of statisticians, we have begun to examine combinations of parameters in an effort to identify the most accurate way to predict distal forearm fracture using data from HRpQCT and μFE modeling. We are also looking toward improvements in imaging resolution, image analysis algorithms, and the fidelity of μFE models as ways to improve the predictive abilities of HRpQCT and μFE modeling.

Put It Into Practice

- Be aware of the potential for cortical thinning and secondary hyperparathyroidism associated with increased risk of distal forearm fractures in adolescents.
- Low BMD accounts for only part of the explanation for increased fracture rates in elderly women. Changes in bone microstructure, which cannot be detected by DXA, are likely to play an important role.

Challenges in Laboratory Testing for the Management of Osteoporosis



Paul D. Miller, MD

When presented with a postmenopausal woman who has osteoporosis, a clinician must assess risk factors for fractures, as well as secondary causes of the osteoporosis. Assuming that other primary causes, such as glucocorticoid use, have been ruled out, what are the potential causes of osteoporosis in such a patient, and what laboratory tests should be performed?

Basic Laboratory Testing

Besides the most common causes of osteoporosis—age and postmenopausal status—there are also a number of secondary causes that can be detected by basic laboratory tests (Table 1) that should be performed after taking a careful history and performing a complete physical examination.[13-15] Common disorders detectable by such tests—including vitamin D deficiency, hypercalciuria, gastrointestinal malabsorption, and hyperparathyroidism—account for a significant percentage of cases of osteoporosis in asymptomatic postmenopausal women.[15,16] As I will discuss in more detail below, additional targeted laboratory testing should be done on individual patients.

As a nephrologist, I have some specific thoughts and advice regarding 24-hour urine testing. In general, the results of 24-hour urine collections are superior to ratios of calcium to creatinine clearance performed at a single time point. Furthermore, it is important to be thorough and perform calcium and creatinine measurements for the entire 1440 minutes (24 hours), to make sure the patient is well hydrated and to ensure that serum creatinine and serum calcium measurements are also obtained. It can be challenging to determine which patients with urinary calcium levels above the reference range (> 4.0 mg/kg/day for women; > 4.5 mg/kg/day for men) should be investigated further. In brief, further workup is warranted for patients with hypercalcemia or a history of renal stones, as well as for patients with nephrocalcinosis, renal tubular acidosis, unexplained elevated bone alkaline phosphatase, unexplained fractures, or loss of BMD. In patients with renal stones and hypercalciuria, for example, there is evidence that such patients are at higher risk of fracture than hypercalciuric patients without renal stones.[17,18] Furthermore, other urinary metabolites may be involved in stone formation. As a general principle, it is important to treat the patient as a whole, not simply as a number indicating hypercalciuria.

More Complex Laboratory Testing of Postmenopausal Patients with Osteoporosis

When a more complex laboratory workup is warranted to uncover causes of postmenopausal osteoporosis, a number of tests can be considered on the basis of individual patient factors (Table 2).

Secondary Hyperparathyroidism

Secondary hyperparathyroidism can have a number of underlying causes, including low 25-(OH)-vitamin D levels, hypercalciuria, calcium malabsorption or low calcium intake, in addition to chronic kidney disease (CKD). Thus, it is important not to automatically ascribe secondary hyperparathyroidism to CKD. Nevertheless, it is established that glomerular filtration rate (GFR) decreases during aging,[19] and this decline is accompanied by an increase in intact PTH levels.[20] At this time, the preferred method of screening for CKD is estimated GFR (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation because it adjusts for body surface area. However, be reminded that the reporting of MDRD eGFR on commercial laboratory printouts is not intended for management decisions, but is intended as a population screening tool for the early detection of CKD.

- **Clinical chemistry**
  - Calcium, phosphorus alkaline phosphatase, liver function, creatinine, total protein
- **Complete blood count**
  - Anemia may indicate other problems, such as myeloma
- **25-OH-vitamin D**
- **24-hour urine calcium**
  - (See text for details)
- **Thyroid-stimulating hormone**
  - For patients taking thyroxine or with hyperthyroid abnormalities

25-OH denotes 25-dihydroxycholecalciferol.

Table 1. **Basic laboratory testing for the evaluation of secondary causes of osteoporosis.**

Monoclonal Gammopathy of Undetermined Significance (MGUS)

MGUS is a premalignant proliferative disorder of plasma cells (monoclonal gammopathy) with a prevalence of approximately 3% in persons older than 50 years that increases with age.[21] MGUS is distinguished from other monoclonal gammopathies by: serum monoclonal antibodies equal to or greater than 3 g/dL; the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the proliferation of monoclonal plasma cells; and a proportion of plasma cells in the bone marrow of 10% or less.[22] Although MGUS is known to be a precursor of multiple myeloma and other serious diseases, most cases of MGUS do not develop into overt

myeloma. However, the risk of osteoporotic fractures is increased in patients with MGUS even in the absence of progression to myeloma. Evidence suggests that MGUS is associated with increased levels of receptor activator of nuclear factor kappa beta ligand (RANKL).[23] The differential diagnosis between MGUS and multiple myeloma can be challenging. If the diagnosis is in doubt or if teriparatide therapy is being considered, a bone marrow biopsy is warranted.

Intact PTH
Serum electrophoresis
Celiac testing
Bone-specific alkaline phosphatase
Biochemical markers of bone resorption (NTX, CTX)
Free T4 and plasma cortisol
1,25-$(OH)_2$-vitamin D
24-hour urine collection for protein, phosphorus, and cortisol
FGF-23
Prolactin
IGF-1
Bone biopsy

PTH denotes parathyroid hormone; NTX, N-telopeptides of type 1 collagen; CTX, C-telopeptides of type 1 collagen; 1,25-$(OH)_2$, 1,25-dihydroxycholecalciferol; FGF-23, fibroblast growth factor 23; IGF-1, insulin-like growth factor 1.

Table 2. **More complex laboratory workup for postmenopausal osteoporosis.**

Celiac Disease

Celiac disease is an autoimmune disorder caused by a permanent sensitivity to gluten in genetically susceptible individuals. The prevalence of celiac disease is probably higher than once thought, approaching 1% of the population, and is even higher among persons with other autoimmune conditions.[24] Celiac disease is associated with selective malabsorption of calcium (and sometimes iron). In patients without gastrointestinal symptoms, celiac disease should be suspected if the patient has: 24-hour urine calcium less than 50 mg per day despite having normal calcium intake and GFR; fractures, loss of BMD, or sustained high bone resorption markers (N-telopeptides of type 1 collagen [NTX] or C-telopeptides of type 1 collagen [CTX]) despite taking oral bisphosphonates; low 25(OH)-vitamin D levels or elevated PTH levels; elevated antibodies; or unexplained iron deficiency. However, the only way to definitively diagnose celiac disease is through a biopsy of the small bowel. For asymptomatic celiac patients at high risk of fracture, parenteral bisphosphonates, teriparatide, or denosumab are often required.

Bone Turnover Markers and Assessment of Response

The use of biochemical markers of bone turnover offer several advantages, including an integrated, dynamic assessment of skeletal metabolism and the ability to assess resorption and formation independently. In addition, bone turnover markers can be used to assess metabolism that is not affected by bone mass. Automated assays to conduct such assessments are widely available. However, measurements of bone turnover markers also have several drawbacks. For example, they cannot distinguish cancellous bone from cortical bone; there is a large degree of variability at different times of the day, so collections should always been done in the fasting state early in the morning; and there is poor quality control and cross-calibration among commercial laboratories. Thus, clinicians should use the same laboratory for repeated measurements and ensure that the same assay is used.[26]

When assessing causes of poor response to antiresorptive therapy, it is important to talk to the patient to get an accurate assessment of compliance to therapy.[13,27] A second workup to reassess potential causes of osteoporosis may also be warranted, and changes to therapy may need to be considered.

FGF-23

FGF-23 is a protein secreted by osteocytes that acts in the renal tubules to decrease reabsorption of phosphate. Excess circulating FGF-23 or gain-of-function mutations in the FGF-23 gene have been linked to urinary phosphate wasting and hypophosphatemia. FGF-23 also induces degradation of 1,25$(OH)_2$-vitamin D.[28] Commercial assays for FGF-23 are available and can be informative in some situations. I recommend an FGF-23 assay for patients with (1) unexplained and persistent hypophosphatemia and any phosphaturia, (2) unexplained elevations in bone-specific alkaline phosphatase, (3) unexplained osteomalacia as determined by histomorphometry, or (4) normal 25(OH)-vitamin D_3 and low 1,25$(OH)_2$-vitamin D_3 levels in the absence of stage 4 or stage 5 CKD. FGF-23 assays are also valuable for monitoring the success of surgical removal of mesenchymal tumors in patients with oncogenic osteomalacia.

Put It Into Practice

- When considering osteoporosis treatment on the basis of hypercalciuria, take into account other patient-specific factors, such as a history of renal stones. Do not just rely on treatment thresholds.
- Make sure that the patient is well hydrated when collecting for 24-hour urine testing.
- When screening for CKD, use the MDRD equation for calculating eGFR.
- Use the same laboratory and same assay equipment for all measurements of bone turnover markers.

Drug Therapy to Prevent Osteoporosis: Is It Ever Appropriate?

Michael McClung, MD

In most of the 1980s, osteoporosis was diagnosed only in postmenopausal women after a hip or spine fracture. But in 1989, osteoporosis was redefined as a systemic skeletal disorder that was a risk factor for fracture. In 1994, the World Health Organization (WHO) defined osteoporosis in postmenopausal women solely on the basis of BMD: a T-score by DXA of -2.5 or lower. This change in diagnostic definition left us with a dilemma regarding what it means to *prevent* osteoporosis. Originally, treatment to prevent osteoporosis meant therapy to prevent fractures. We now think of preventing osteoporosis as therapy to preserve bone mass in patients without osteoporosis, thereby preventing a risk factor for fracture. Old treatment guidelines endorsed the notion of using drugs to prevent bone loss in young menopausal women with low bone density but no other risk factors

for fracture, and several drugs received United States Food and Drug Administration (FDA) approval for the prevention of osteoporosis.

However, the main purpose of pharmacologic therapy is to reduce the risk of fractures. Clinical efficacy has been documented in postmenopausal women with osteoporosis, usually at high fracture risk, but fracture reduction is modest and very difficult to document in patients at low risk for fracture. As a consequence, we have very little data that show women who do not have osteoporosis obtain benefit from treatment in terms of reduction in fracture risk, the only exception being the Women's Health Initiative study of estrogen.[29]

We recognize that there are women without osteoporosis who are at moderate or even high risk for fracture, and that most fractures related to skeletal fragility or loss of bone mass occur in women who do not meet the diagnostic threshold for osteoporosis.[30] The FRAX fracture prediction tool was developed to aid in the recognition of women without osteoporosis but who are at high fracture risk and, thus, candidates for treatment. Current guidelines now recommend therapy only for patients at high fracture risk based on FRAX results, in addition to patients with osteoporosis based on prior fracture or T-score.[13]

The corollary to the updated treatment guidelines is that patients with low BMD, but not low enough to be diagnosed as osteoporosis, and who have no other risk factors are not appropriate candidates for pharmacologic therapy to prevent osteoporosis. This new thinking challenges long-held beliefs about the importance of preventative therapy and raises the question of whether the use of drugs to prevent bone loss and osteoporosis is ever justified in low-risk patients.

Bone mass declines during menopause, but there is good evidence that it does not continue declining at the same rate once the menopausal transition is complete. Rather, bone mass declines for 5 years to 6 years around the time of menopause, with a total loss of approximately 10% to 15% in the spine. After the menopausal transition, bone mass plateaus to a relatively stable level for a number of years, during which there is a much slower rate of bone loss.[31-33] Fracture rates, however, do not increase substantially until many years after menopause. A question faced by clinicians caring for young menopausal women is whether (and when) to use osteoporosis drugs to prevent bone loss in early menopause or upon discontinuation of estrogen therapy.

Attempts to reduce or prevent perimenopausal bone loss using exercise, calcium intake, or vitamin D supplements have been largely unsuccessful since it is estrogen deficiency—not exercise or nutritional deficiency—that is responsible for the bone loss that occurs in early menopause. All women experience bone loss at menopause, although those with low body weight are at a higher risk for bone loss than are women with higher body weight.[33]

Women who enter menopause with below average BMD are likely to lose the same amount of bone mass as women with average BMD, and thus will reach the threshold for osteoporosis much earlier. In this situation, it is attractive to consider a brief course of treatment to blunt bone loss during the menopausal transition and to forestall the need for long-term therapy. Indeed, several studies, such as the PEPI Trial, have shown that estrogen therapy during early menopause can prevent bone loss and even increase BMD.[34] Unfortunately, when estrogen therapy is withdrawn, there is a rapid decline of bone mass, and fracture risk becomes indistinguishable from that of untreated patients within 5 years.[35] Bisphosphonates, such as alendronate, can also preserve or increase bone mass in early menopause and even restore some lost BMD in women a few years past menopause.[36] The benefits of alendronate persisted for much longer than the benefits of estrogen after the drug was withdrawn. In young postmenopausal women who received treatment with alendronate for 2 years, treatment benefit persisted for 4 years after treatment was stopped.[37] Recent evidence suggests that zoledronate provides a similar degree of prolonged protection after only 1 or 2 years of therapy.[37] In addition to reducing bone loss during natural menopause or after natural menopause, there is also evidence that alendronate or other bisphosphonates may stem the loss of bone after discontinuation of therapeutic estrogen.[38]

Together, these various findings suggest that there may be a role for bisphosphonate therapy in selected women undergoing natural menopause or discontinuing estrogen therapy. BMD testing is appropriate at the time of menopause or stopping estrogen therapy in women at risk for low bone mass. This includes women who (1) are in the lowest quartile of body weight, (2) have had a fragility fracture, or (3) have a family history of hip or spine fracture. Those found to have a BMD T-score equal to or below -1.5 may be candidates for alendronate or zoledronate therapy lasting at least 2 years. Accumulating evidence suggests that such a strategy may also be warranted in other patients about to experience rapid bone loss, such as premenopausal women undergoing chemotherapy that destroys ovarian function,[39] men using androgen deprivation therapy (in whom denosumab has been shown to prevent bone loss),[40] and patients with spinal cord injury.[41]

Put It Into Practice

- Take into account risk factors for low bone mass in women in early menopause, including low body weight, personal or family history of a fragility fracture or a hip or spine fracture, and perhaps smoking.
- Consider whether there is a role for brief bisphosphonate therapy in women who have low bone mass and are about to experience rapid bone loss due to menopause or other clinical situations.

Teriparatide and Fracture Repair: A Review

Robert Marcus, MD

A number of injury-related and patient-related factors can lead to delayed healing or nonunion of bone fractures, and a number of attempts have been made to develop treatments to accelerate the healing of fractures. One proven and approved method is the use of low-intensity ultrasound, which can shorten median healing time by several weeks.[42] Another strategy

approved for tibia fractures is the use of bone morphogenetic protein-2,[43] which must be either applied directly to the fracture area or injected near the site. Studies of bisphosphonates for fracture healing suggest that they affect the structure of the callus, but appear to offer no obvious advantage in terms of healing time and may actually delay healing in some situations.[44,45] However, the major trials of bisphosphonates for osteoporosis have reported no obvious increase in delayed healing or nonunion.

Teriparatide (TPTD; human parathyroid hormone [PTH 1-34]) is approved for use in men and postmenopausal women with osteoporosis and a high risk of bone fractures. Although it is not approved for use in treating fractures, there are biologic reasons and preclinical evidence to suggest it may be useful for that purpose, as well as some data from off-label uses in humans. Regarding biologic plausibility, TPTD can act as an anabolic agent with regard to bone; stimulate mesenchymal stem cell recruitment, osteoblast differentiation, and vascular endothelial growth factor expression; and work through signals similar to prostaglandin E2, which has well-established resorptive and anabolic effects in bone.[46-50]

Because of FDA restrictions on the design of clinical trials of TPTD for fracture repair, the first clinical trial to address this issue was conducted in postmenopausal women with Colles' fracture. Furthermore, the end point had to demonstrate a functional improvement, rather than simply showing a decrease in time-to-healing. This phase 2 trial was designed before metal fixation was the standard of care, and as that procedure became the standard of care, it became difficult to enroll patients into the trial. The trial enrolled 102 postmenopausal women with unilateral, dorsally angulated fracture of the distal radius within the preceding week, treated nonoperatively.[51] Patients were excluded for the recent use of oral or intravenous bisphosphonates. Patients were randomized to receive 8 weeks of placebo or 1 of 2 doses of TPTD (20 μcg/day or 40 μcg/day). The primary end point was time-to-radiographic healing (complete cortical bridging in 3 of 4 cortices) for 40 μcg TPTD versus placebo. The estimated median time from fracture to the primary end point was 9.1, 7.4, and 8.8 weeks in the placebo, 20 μcg TPTD, and 40 μcg TPTD groups, respectively. The primary end point (40 μcg vs placebo) was not statistically significant. However, a post-hoc analysis comparing the 20 μcg TPTD group with the placebo group was significant (P <.006). Although the primary end point was negative, the positive result for the 20 μcg group suggests that further study of TPTD for wound repair is warranted.[51]

In an observational cohort study of 145 patients with difficult-to-heal fractures, Bukata and colleagues[52] reported that 135 of 145 (93%) fractures achieved radigraphic and clinical union during treatment with TPTD, including several patients who experienced delayed union for several months before beginning TPTD therapy. Six patients (4%) had partial radiographic union, and 4 (3%) failed to achieve pain improvement or radiographic union. Clearly, this study was uncontrolled, but it also supports the further study of TPTD for the treatment of fracture.

Put It Into Practice

- Biologic, preclinical, and early-stage clinical studies support the further investigation of TPTD for use in speeding repair of nonunion fractures or difficult-to-treat fractures.

Controversies with Bisphosphonate Therapy

Nelson B. Watts, MD

Overview

A variety of drugs are now approved for the treatment or prevention of osteoporosis, especially in postmenopausal women. The bisphosphonates are somewhat unique (along with teriparatide) because 3 of them—alendronate, risedronate, and zoledronic acid—are also approved for the treatment of glucocorticoid-induced osteoporosis and for the treatment of osteoporosis in men. These same 3 bisphosphonates, and more recently denosumab, have shown evidence of broad-spectrum antifracture efficacy and of reducing vertebral, nonvertebral, and hip fractures, the latter being the most serious consequence of osteoporosis. Table 3 shows various drugs for fracture prevention and whether evidence is available to show efficacy in different settings.

As bisphosphonates developed, we gradually advanced our understanding of their mode of action. They are known to concentrate in bone and to be released by the action of osteoclasts. The bisphosphonates then enter the osteoclast and inhibit its resorptive activity by inhibiting farnesyl pyrophosphate synthase (FPPS), an enzyme in the mevalonate pathway.[53] The available bisphosphonates vary in terms of their affinity for bone and their affinity for binding to FPPS, and the rank order of these 2 affinities differ among the agents.[54-56] Although the bisphosphonates were initially classified as simple bisphosphonates and nitrogen-containing bisphosphonates, the nitrogen-containing agents are now subdivided into alkylamino agents, which have intermediate potency, and the heterocyclic agents, which have high potency and almost irreversible inhibition of FPPS.[55,57]

Duration of therapy

When considering biology-based therapies for osteoporosis (such as estrogen, raloxifene, or PTH-based agents), recognize that continued treatment is required for continued efficacy. However, there are definite reasons for limiting the duration of therapy using these agents, especially PTH-based therapies. In contrast, bisphosphonates reside in bone for prolonged durations. A modeling study has provided some evidence, however, that this reservoir is probably not a major safety concern.[58] These investigators found that patients who stopped taking alendronate after having received the drug at 10 mg per day for 10 years would have a circulating drug concentration due to release from bone equivalent to an oral dose of approximately 2.5 mg.[53] They concluded that long-term therapy was unlikely to be different than short-term therapy with regard to the accumulation of bisphosphonates in bone.

Established side effects

Oral bisphosphonates are known to be associated with esophageal irritation, and intravenous or high-dose oral administration can provoke an acute phase reaction, which is usually mild, transient, and limited to the first dose. Rarely, bisphosphonates can

Drug	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture
Calcitonin	✓		
Raloxifene	✓		
Ibandronate	✓		
Alendronate	✓	★	✓
Risedronate	✓	✓	★
Zoledronic acid	✓	✓	✓
Denosumab	✓	✓	✓
Teriparatide	✓	✓	

✓ FDA-approved indication
★ Evidence for efficacy, but not an FDA-approved indication

Table 3. **Evidence for fracture reduction for FDA-approved medications.**

be associated with hypocalcemia. Finally, the drugs are excreted by the kidneys and secreted by the kidney tubules, and, therefore, have the potential to cause kidney damage at high doses. At this time, we have limited data on their use in patients with limited kidney function.

Atrial fibrillation

The issue of atrial fibrillation (AF) as a potential side effect of bisphosphonates arose from the pivotal fracture trial of zoledronic acid.[59] In that trial, the rates of AF as an adverse event were comparable in the zoledronic acid and placebo arms (2.4% vs 1.9%, respectively), but rates of AF as a serious adverse event (leading to hospitalization, prolongation of hospitalization, or leading to disability) were higher in the zoledronic acid arm (50 patients [1.3%] vs 20 patients [0.5%]; $P < .01$). There was no relation between the occurrence of AF and the time of administration or cumulative dose. Furthermore, the overall incidence of AF was lower than expected for patients in the same age range. There was no difference in AF or serious AF rates in the trial of zoledronic acid for recurrent fracture[60] or in trials of the drug in cancer patients, some of whom use much more frequent administration of the drug (eg, 4 mg every 3 to 4 weeks in patients with bone metastases).[61-63] In light of the increased rate of serious adverse events in the trial of zoledronic acid for fracture prevention, retrospective reviews of alendronate and risedronate clinical trials were performed. There was a nonsignificant trend toward higher rates of AF in the pivotal trial of alendronate (1.5% vs 1% for placebo; $P = .07$)[64] and no difference versus placebo for risedronate.[65] Ultimately in 2008, the FDA issued an updated safety review regarding this issue and concluded that healthcare professionals should not alter their prescribing patterns for bisphosphonates, and patients should not stop taking their bisphosphonate medications.[66]

Osteonecrosis of the jaw

On June 2, 2006, *The New York Times* published an article entitled "Drug for Bones is Newly Linked to Jaw Disease," which alarmed many patients. In 2008, an expert panel representing the American Society for Bone and Mineral Research, the National Osteoporosis Foundation (NOF), and the International Society for Clinical Densitometry defined osteonecrosis of the jaw (ONJ) as "exposed necrotic bone in the maxillofacial region, not healing after 6–8 weeks, and in patients with no history of craniofacial radiation."[67] According to a study published in 2006, only approximately 4.1% of cases occur in patients receiving bisphosphonates for osteoporosis; approximately 94% of cases occur in patients receiving frequent doses of the drugs for bone metastases.[68] Several risk factors for ONJ have been identified, including dental extraction and other invasive dental procedures; dose, potency, and duration of bisphosphonate exposure; cancer; chemotherapy; and other factors.[67] Estimates of the incidence of ONJ among patients receiving bisphosphonates have varied widely, but range from 1 in 10,000 (0.01%) to 1 in 160,000 (0.000625%).[67] In comparison with hip fracture risk used to initiate bisphosphonate therapy (3%) and considering the severe consequences of hip fracture, the risk of ONJ is very low. Indeed, even the American Dental Association has concluded that "routine dental treatment generally should not be modified solely on the basis of oral bisphosphonate therapy."[69] Very good information is available from the American Dental Association (http://www.ada.org/3045.aspx) with which to counsel patients on this issue.

Subtrochanteric fracture of the femur

In July 2008, *The New York Times* published another article on bisphosphonates citing a series of case reports describing an "unusual fracture pattern" in people who used bisphosphonates for 5 years or more. This issue was revived again in March 2010 when ABC News televised a report on the same issue. Two days later, the FDA issued a press release stating that the case reports included too few patients to determine whether there was an association with bisphosphonates and patients should not stop taking bisphosphonates; that healthcare providers should be aware of the potential risk, but continue to follow the drug label when prescribing oral bisphosphonates. A review of data from a Danish registry on alendronate concluded that only 7% of these atypical fractures were in patients exposed to alendronate and that the percentage of patients with typical hip fractures was the same.[70] Furthermore, the authors concluded that the risk of fracture was reduced by high adherence to alendronate, and that subtrochanteric/diaphyseal femur fractures in patients treated with alendronate shared the characteristics of fractures caused by osteoporosis.[70]

Esophageal cancer

In January 2009, *The New England Journal of Medicine* published a letter to the editor from Diane Wysowski, an employee of the FDA, with a disclosure that the views contained in the letter did not necessarily

represent those of the FDA.[71] The letter described 23 patients in the United States diagnosed with esophageal cancer while taking alendronate between 1995 and 2008. Unfortunately, no comparative data were presented and no denominator was given with which the reader could gauge the percentage of alendronate patients this represented, the percentage of esophageal cancers, or how the rate compares with the rate of esophageal cancer in the general population or with patients receiving other drug therapies. Given that tens of millions of patients have taken bisphosphonates, the rates of esophageal cancer associated with the drugs are likely to be exceedingly low, if there is any association at all. Several follow-up letters published in April pointed out these issues, and one group analyzed a claims database and found no increase in esophageal cancer associated with bisphosphonates.[72-77] Unfortunately, these follow-up letters did not receive the same press coverage as the initial letter.

Musculoskeletal pain

In January 2008, the FDA issued an alert reminding healthcare providers about statements in the prescribing information for bisphosphonates relating to the potential for severe musculoskeletal pain in patients who take these drugs. These statements were based on another letter to the editor written by Dr. Wysowski in 2005.[78] The letter reported 118 cases of musculoskeletal pain associated with alendronate use and 6 with risedronate use between 1995 and 2002. As with the esophageal cancer letter, there were no comparative data given for the general population and no numbers given with which to assess the incidence of this effect. Although there is no obvious biological explanation for such an adverse event, there are anecdotal reports from patients consistent with a link between bisphosphonates and musculoskeletal pain.

Duration of Therapy: Reprise

Can there be safety problems associated with long-term use of bisphosphonates? The above discussions indicate that the answer to that question is probably yes. However, considering the millions of patients who receive these drugs, the likelihood of such problems is low. My opinion is that safety concerns should not drive the decision of the duration of use of bisphosphonates.

The Fracture Intervention Trial Long-term Extension (FLEX) trial randomized patients who had already used alendronate for 5 years to either discontinue or continue its use for another 5 years. At 10 years, there was no significant difference between the 2 groups in terms of nonvertebral or morphometric vertebral fractures. However, there was still a significant (55%) decrease in clinical vertebral fractures in patients who continued to take alendronate.[79] Furthermore, patients with femoral neck T-scores lower than -2.5 also had a significantly lower risk of nonvertebral fracture if they continued to take alendronate (relative risk = 0.5).[80] These data suggest that treatment for 10 years is more effective than 5 years of treatment in patients with more severe osteoporosis.

Another study examined fracture rates during a 1-year extension in patients who discontinued the use of risedronate after 3 years.[81] This study concluded that the fracture risk remained low during that year, even though bone turnover markers rebounded to levels seen in control patients. These data suggest that there is approximately 1 year to 2 years of residual benefit in patients who discontinue treatment after 3 years to 5 years.

In the absence of definitive data regarding the duration of therapy, I will share the current approaches I and some of my colleagues use. If patients do not need treatment in the first place, then I recommend stopping treatment. If patients have modestly low BMD and stable or increasing BMD by DXA, then a drug holiday can be considered at 5 years, and treatment restarted when BMD declines, bone turnover markers increase, or fracture occurs. In higher risk patients, such as those with a history of fracture, those using corticosteroids, or those with very low BMD, a drug holiday can be considered after 10 years of therapy, with treatment restarted after 1 or 2 years regardless of BMD or bone turnover markers. In selected patients about whom I am especially concerned, I will consider using teriparatide or raloxifene during their bisphosphonate holiday.

Put It Into Practice

- Although healthcare providers should be aware of the potential risk of ONJ with the use of oral bisphosphonates, the risk is markedly lower than the risk of hip fracture associated with untreated osteoporosis.
- Be aware of the potential risk for unusual subtrochanteric fractures of the femur, but continue following drug labels when prescribing oral bisphosphonates for osteoporosis.
- Dispel patient concerns about media-reported adverse events by providing good patient education and counseling.

New and Emerging Therapies for Osteoporosis

John P. Bilezikian, MD

New Therapies

The newest FDA-approved therapy for osteoporosis is denosumab, which was approved in June 2010. Denosumab interrupts the RANK/RANKL/OPG system (Figure 1) that is critical for intercellular bone signaling. Receptor activator of nuclear factor κB ligand (RANKL) is expressed by osteoblasts and binds to its receptor (RANK) on the surface of osteoclasts and osteoclast progenitor cells. By activating RANK, RANKL is a powerful stimulator of osteoclastogenesis and osteoclast action.[82] Osteoprotegerin (OPG) functions as an important regulator of this system by acting as a decoy receptor for RANKL, making it unavailable for binding to RANK.[83] The balance between RANKL and OPG is crucial for controlling bone remodeling. Denosumab acts in much the same way as OPG. Denosumab binds to RANKL and prevents it from binding to RANK, thereby reducing the activation and development of osteoclasts.

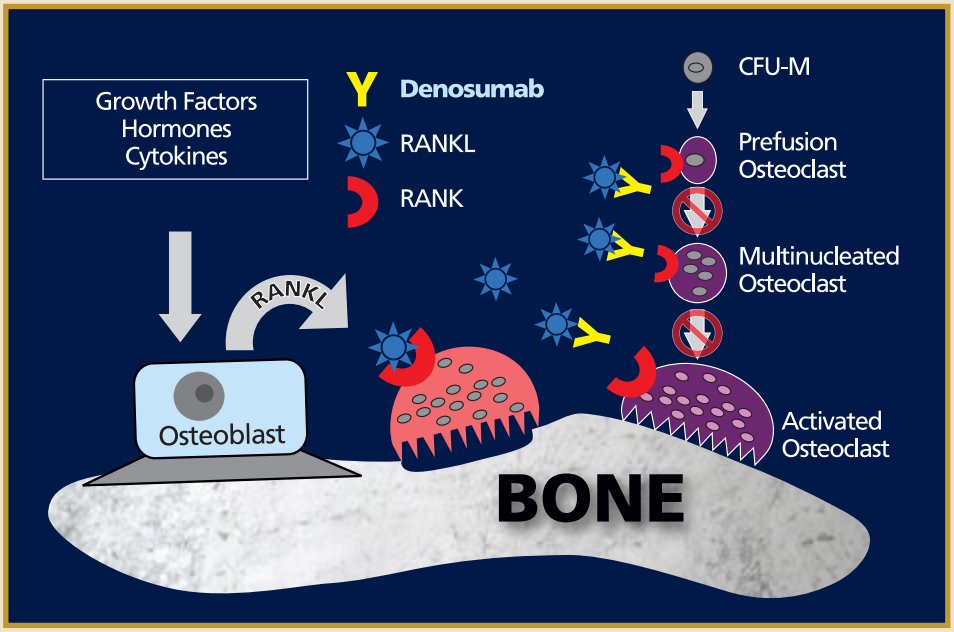
Phase 2 trials of denosumab demonstrated substantial and sustained increases in bone density in the spine, hip, and distal radius.[84,85] An interesting observation from these studies is that denosumab treatment was associated with transient increases in intact PTH levels, which lasted several months.[85] From this observation arises the paradox that primary hyperparathyroidism

is associated with a decrease in cortical BMD; whereas, increased PTH levels during denosumab treatment is associated with increases in cortical BMD. To explain this paradox, researchers have hypothesized that denosumab shifts the action of endogenous PTH from primarily catabolic action at cortical sites to a primarily anabolic action, which may involve favoring the inhibition of sclerostin by PTH.

The pivotal trial of denosumab was the FREEDOM Trial, in which 7808 postmenopausal women with osteoporosis were randomized to receive denosumab (60 mg) or placebo subcutaneously every 6 months for 36 months. The results demonstrated a significantly lower risk of vertebral fractures in the denosumab arm compared with the placebo arm (2.3% vs 7.2%; risk ratio = 0.32; 95% CI, 0.26-0.41; $P < .001$). Patients in the denosumab arm also experienced significantly lower rates of hip fracture (0.7% vs 1.2%; hazard ratio [HR] = 0.60; 95% CI, 0.37-0.97; $P = .04$) and nonvertebral fracture (6.5% vs 8.0%; HR = 0.80; 95% CI, 0.67-0.95; $P = .01$).[86] Denosumab is now FDA-approved with warnings about possible increases in the risk of skin infections and the possibility of "oversuppression" of bone turnover, which is not a clearly defined or understood concept for any osteoporosis treatment.

Emerging Therapies

Cathepsin K is an enzyme that is highly expressed in osteoclasts, is secreted during the process of bone resorption, and helps to excavate the resorption pits that become bone remodeling units.[87] Inhibition of cathepsin K or deletion of the cathepsin K gene lead to shallower resorption pits and greater bone mass in animal models; however, osteoclasts remain present and functional in other capacities, including signaling with osteoblasts.[88] Although several cathepsin K inhibitors were in development, only 1 so far, odanacatib, has advanced to pivotal clinical trials. Results of a phase 2 trial of odanacatib were consistent with observations from animal models, indicating that odanacatib inhibits bone resorption in a dose-dependent manner.[89] Furthermore, bone resorption was inhibited to a greater degree than bone formation, and bone formation was preserved to a greater degree than with bisphosphonates.[89] Phase 3 trials of odanacatib are ongoing.



IgG denotes immunoglobulin G; RANKL, nuclear factor κB ligand; RANK, receptor activator of nuclear factor κB; CFU-M, colony-forming unit-macrophage.

Figure 1. **Denosumab, a human IgG antibody to RANKL, controls osteoclast differentiation, activation, and survival.**

Future

An ideal osteoporosis treatment will have the ability to convert osteoporotic bone back into normal bone at macroscopic and microstructural levels. Drugs with this capability are known as osteoanabolic drugs, and the only drug in this class at this time is PTH, represented in the United States by TPTD. Traditionally, PTH is considered to be bad for bones. But when given at low doses in a pulsatile fashion, the activity of PTH is shifted to favor its anabolic activity.[90] Indeed, several clinical trials using either TPTD (PTH 1-34) or intact PTH (1-84) have shown beneficial effects in terms of reduced fracture rates at both vertebral and nonvertebral sites and in terms of bone microarchitecture.[90-94]

Drawbacks to the use of TPTD or PTH (1-84) include the need for daily injection, concerns from animal studies showing increased risk of osteosarcoma during prolonged treatment, and the expense of the drugs. Three approaches are being pursued in an attempt to improve the delivery of PTH or to take advantage of endogenous PTH secretory mechanisms. One approach relies on the use of inhibitors of the parathyroid cell calcium-sensing receptor by the drug ronacaleret. Inhibition of this receptor mimics hypocalcemia, leading to increased secretion of endogenous PTH. Unfortunately, recent studies of ronacaleret were disappointing in terms of improving BMD.[95]

Another approach for improving PTH-based therapy is the use of parathyroid-related protein (PTHrP) (1-36). PTHrP is an endogenous protein with sequence homology to PTH. It is secreted by numerous tissues in the body, including some cancer cells, and is implicated in hypercalcemia associated with malignancy.[96] One study found that PTHrP induced increases in bone formation markers and little or no change in bone resorption markers in postmenopausal women with osteoporosis.[97] A phase 2 study of an analog of PTHrP found a dose-dependent and duration-dependent increase in spine and hip BMD that exceeded increases seen with TPTD.[98] This study also showed that PTHrP increased bone formation markers, but eventually also increased bone resorption markers in a manner similar to PTH.

The third approach for improving delivery of PTH is the use of a transdermal patch. This approach was studied in a phase 2 trial of 165 postmenopausal women with osteoporosis.[99] The study found that transdermal administration of TPTD significantly

increased lumbar spine and total hip BMD more than either placebo or subcutaneous TPTD at 6 months. Importantly, transdermal administration produced a rapid peak of blood PTH levels that declined within a few hours, more quickly than subcutaneous TPTD.[99]

Combination and Sequential Administration

From advances in our understanding of PTH action, a kinetic model has arisen suggesting that there is a brief anabolic window lasting a few months, during which PTH increases bone formation markers without significantly increasing bone resorption markers. Eventually, bone resorption markers also increase. The increase in bone resorption markers signals a switch from a modeling-based to a remodeling-based mechanism of PTH action. It is currently thought that the osteoanabolic actions of PTH are 30% modeling based and 70% remodeling based. During the remodeling phase, bone formation exceeds bone resorption for the duration of the efficacy period of PTH action. The anabolic window concept has led to numerous studies of various strategies to combine bisphosphonates with PTH-based therapies, administering the drugs either concurrently or sequentially. Although these results are of interest, it is still not clear whether these approaches will lead to greater anabolic actions of PTH than using the anabolic agent alone.

The Wnt Signaling Pathway

The Wnt pathway is a complex and ubiquitous signaling pathway involved in numerous physiological processes, as well as embryogenesis, neurogenesis, and cancer. It is also a key pathway regulating the differentiation and activity of osteoblasts.[100] Activity of the Wnt pathway and, hence, bone formation are down-regulated by the protein sclerostin, which is secreted by osteocytes.[100] In this manner, sclerostin is thought to serve as an endogenous brake on bone formation.[101] Indeed, studies of osteoporosis in animal models have shown that an antibody against sclerostin increases bone formation and bone mass.[102] Drugs targeting other components of the Wnt pathway may also be attractive targets for osteoporosis therapy.

Serotonin

Serotonin is produced in the brain, as well as the gastrointestinal tract. There is evidence, however, that excess free serotonin in peripheral tissues, mostly derived from the gastrointestinal tract, reduces bone mass.[103] In 2008, Yadav and colleagues presented results from genetic studies suggesting that inhibition of gastrointestinal production of serotonin can promote activity of osteoblasts, leading to bone formation.[104] These findings have led to studies of LP533401, an inhibitor of tryptophan hydoxylase 1, the enzyme responsible for serotonin synthesis in the gastrointestinal tract (but not brain). In a proof-of-principle study in ovariectomized mice, LP533401 prevented and reversed osteoporosis and improved bone quality.[105]

In summary, the future looks bright for the treatment and prevention of osteoporosis with many new drug candidates, including several targeting novel mechanisms or signaling pathways. Many challenges remain, however, in the demonstration of efficacy and the maintenance of safety and bone specificity of these potential new therapies.

Put It Into Practice

- Consider newly approved denosumab for treatment of osteoporosis in postmenopausal women with advanced osteoporosis.
- Keep abreast of clinical trials studying pulsatile delivery of PTH analogs for osteoporosis.
- Consider novel pharmacologic approaches to the treatment of osteoporosis.

Hot Topics in Bone

Paul D. Miller, MD, and Discussion Panel

How do you counsel patients about calcium supplementation in light of the recent meta-analysis suggesting an increase in coronary events associated with calcium supplementation?

This meta-analysis included 15 randomized placebo-controlled trials of calcium supplements (at 500 mg/day for at least 1 year) in participants aged at least 40 years.[106] Only 5 trials had patient-level data. In those 5 trials, there was a 31% increase in the relative risk of myocardial infarction in patients who received calcium supplements versus those who received placebo (95% CI, 2%-67%; $P = .035$) without concurrent vitamin D supplements. There were nonsignificant increases in the risk of stroke, death, and in the combined end point of myocardial infarction, stroke, or sudden death. Similar results were found in the meta-analysis of trial-level data.[106]

There have been a number of trials of calcium supplements that found no increase in the risk of cardiovascular disease. Furthermore, even among the individual trials included in the meta-analysis, none showed a significant increase in risk of cardiovascular outcomes individually.[106] The meta-analysis also did not include a sensitivity analysis to determine how much the results of the meta-analysis were influenced by individual trials, especially the 1 trial conducted by the same group that found the highest relative risk (which was still not statistically significant).[107] There are also some reasons to suspect that selection bias may have accounted for some of the results of the meta-analysis.

Since the meta-analysis was published, results have become available from a formal randomized controlled trial of calcium carbonate supplements (1200 mg/day) versus placebo in 1460 older women (mean age = 75 years at enrollment).[108] The trial found no significant risk of death or first-time hospitalization for atherosclerotic vascular disease during the 5-year trial (HR = 0.938; 95% CI, 0.690-1.275) or during the additional 4.5 years of observation. Indeed, there was some evidence that calcium supplementation reduced the risk of hospitalization and mortality in women with preexisting atherosclerotic vascular disease.[108]

Members of this discussion panel generally agreed that moderation of calcium intake is a reasonable approach at this time. A common approach is to sum dietary calcium intake with supplemental calcium intake with the goal of achieving a total intake of 800 mg to 1200 mg per day. Values in the lower part of this range may be more

appropriate when appropriate vitamin D levels are maintained as they should be. Obtaining the bulk of calcium from dietary sources was advocated. Panel members were comfortable with target levels of serum 25(OH)-vitamin D of 30 ng/mL to 50 ng/mL. Vitamin D intake levels to achieve those target levels are typically 1000 IU per day to 2000 IU per day. Some patients require adjustment of those intake values on the basis of comedications, comorbidities, or other factors. The safety of serum 25(OH)-vitamin D levels above 60 ng/mL is unknown.

Do proton pump inhibitors interfere with calcium absorption or affect bone mass?

A very recent paper reported a thorough study of fractional calcium absorption in postmenopausal women who obtained calcium from dietary sources and were treated for 30 days with omeprazole.[109] The study concluded that calcium absorption was unrelated to serum omeprazole levels, gastric pH, adherence to omeprazole, or 25(OH)-vitamin D levels. Although proton pump inhibitors have been linked to increases in the risk of fracture in observational studies, this effect does not appear to be related to calcium absorption, and it is not clear that proton pump inhibitor use is the causative factor.

Put It Into Practice

- Aim for a total calcium intake (dietary sources plus supplements) of 800 mg to 1200 mg per day. The lower values are probably acceptable for patients with adequate serum 25(OH)-vitamin D levels.
- Encourage patients to obtain the bulk of their calcium intake from dietary sources.

Healthcare providers should consider FDA-approved medical therapies in postmenopausal women and men aged 50 years and older based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) AND a 10-year probability of a hip fracture ≥ 3% OR a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinician's judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Table 4. **The National Osteoporosis Foundation guidelines to the prevention and treatment of osteoporosis.**

FRAX: Practical Issues with Use in Daily Practice

Michael McClung, MD

The WHO FRAX tool and subsequent guidelines for osteoporosis treatment were not intended to be strict rules about whom to treat. Rather, they were intended to provide guidance for physicians and a platform from which to start the decision-making process regarding treatment for osteoporosis. Furthermore, both the FRAX tool and the guidelines are still in evolution. After briefly discussing the properties of the FRAX and the NOF guidelines for the United States, I will discuss several practical issues relating to the use of the FRAX and the NOF guidelines that require significant clinical judgment.

The FRAX tool is a robust model based on data from a very large number of diverse individuals on 4 continents, and it has been validated in other large cohorts. Although the purpose of the FRAX tool was to provide a basis for deciding who should be treated, the WHO did not define a threshold at which treatment is recommended. That decision must also incorporate patient-specific and country-specific factors, including health economic considerations. In the United States, country-specific factors have been assessed and compiled by the NOF on the basis of assumptions about cost of therapy, treatment duration and efficacy, patient adherence, and a cost-effectiveness threshold.[110,111] The updated NOF guidelines (Table 4) incorporate the concept of absolute fracture risk based on the FRAX tool. Pharmacologic therapy is recommended for postmenopausal women or men older than 50 years who have either the clinical or bone density diagnosis of osteoporosis. The guidelines also recommend treatment for patients who exceed thresholds of fracture risk even though they do not have osteoporosis. These recommendations serve as a starting point for the decision to treat patients for osteoporosis.[110]

Incorporation of the FRAX model into the NOF guidelines was an important adjustment to the previous NOF guidelines that were based primarily on BMD values. Treatment is now recommended for many high-risk patients who did not qualify under the old guidelines, while treatment is no longer suggested for younger patients who are at low risk for fracture even though they have low BMD.

Although FRAX is a very robust tool and several problems with earlier versions have been corrected, FRAX still has several limitations, some of which are by design. For example, the FRAX tool intentionally does not include falls and frailty as risk factors, even though these are known risk factors for fracture, since treatment with osteoporosis drugs was not shown to reduce fracture risk in patients selected on the basis of fall-related risk factors.[112] Other risk factors, such as bone turnover markers, vitamin D status, and exposure to many drugs that adversely affect bone health, are not included in FRAX since they were not available in the cohorts from which FRAX was derived. Additionally, FRAX treats some risk factors as categorical variables without considering degrees of risk; 2 prominent examples are fracture history (multiple fractures are not taken into account) and corticosteroid use (duration of use and dose are not considered). The FRAX tool also does not incorporate BMD measurement at locations other than the femoral neck, which may affect the risk of future fracture. The NOF guidelines also have limitations. Some of the assumptions used in the cost-effectiveness model

are already out of date, and, as was true for the old guidelines, therapy is recommended for some patients (those with low bone density who meet certain fracture thresholds) for whom we have limited evidence regarding the efficacy of treatment to prevent fracture.

The various limitations of the FRAX tool and the NOF guidelines emphasize the importance of clinical judgment in the decision to treat patients. The following cases will illustrate some practical aspects of this decision-making process.

Case 1. A healthy 68-year-old woman went through menopause at age 51 years and used estrogen therapy for 5 years. She has no personal or family history of fracture and her intake of calcium and vitamin D is adequate. Her femoral neck T-score is -0.8, but her lumbar spine T-score is -2.4. Her 10-year risks according to FRAX are well below the thresholds for treatment according to the NOF guidelines. However, because of her age and low spinal T-score, I would consider treating her.

Case 2. Two 60-year-old men have identical T-scores and other variables, except that 1 has taken prednisone 5 mg daily for asthma for many years, while the other recently began taking prednisone 60 mg daily for temporal arteritis. Because the FRAX model only considers corticosteroid use as a simple categorical variable, both have the same FRAX 10-year risk probabilities. Although treatment might be considered in both men, I would be more aggressive about treating the latter patient.

Case 3. A healthy 66-year-old woman had a wrist fracture at age 53 and a proximal humerus fracture at age 64. Her T-scores and FRAX 10-year probabilities are below NOF thresholds for treatment. However, because she has a history of multiple fractures, which is not accommodated in the FRAX model, I would seriously consider treating her. Of course, if 1 of her fractures had been a vertebral fracture, she would meet the criteria for treatment.

The NOF guidelines are most appropriate for otherwise healthy older adults whose skeletal status is stable. The FRAX model and the NOF guidelines do not, in my opinion, address whether to treat patients who are about to experience rapid bone loss (ie, women early in menopause, those who are stopping estrogen therapy or beginning hormone deprivation therapy, post organ transplant patients, or those with acute immobilization). The objectives of treatment are different in these patients, and appropriate clinical judgment is warranted.

Put It Into Practice

- Use the FRAX tool and NOF guidelines as a platform from which to begin the process of making decisions regarding the use of therapies for osteoporosis, but incorporate clinical judgment and individual patient characteristics into the final decision.
- Recognize both the strengths and the limitations of the FRAX model and the NOF guidelines, and take into account additional risk factors when deciding whether to prescribe medications to treat or prevent osteoporosis.

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Highlights from the 2010 Santa Fe Bone Symposium

E. Michael Lewiecki, MD, John P. Bilezikian, MD, Sundeep Khosla, MD, Robert Marcus, MD
Michael McClung, MD, Paul D. Miller, MD, Nelson B. Watts, MD

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POSTTEST

1. According to results from Sundeep Khosla's team, the primary mechanism for declines in bone volume:tissue volume (BV/TV) ratio during aging in women is loss of trabeculae in women. In men, the primary mechanism for decrease in BV/TV is:
   a) Also loss of trabeculae b) Trabecular thinning c) Increase in trabecular spacing d) Cortical thinning
2. Which of the following is a potential disadvantage to the use of bone turnover markers?
   a) They cannot distinguish between turnover of cancellous versus cortical bone b) They are associated with rapid changes during osteoporosis therapy c) They indicate bone resorption and formation independently d) Options a, b, and c
3. Which of the following FDA-approved treatments for postmenopausal osteoporosis is not approved for osteoporosis prevention?
   a) Raloxifene b) Zoledronate c) Calcitonin d) Options a, b, and c
4. Approximately what percentage of cases of postmenopausal osteoporosis are secondary to common disorders detectable by simple laboratory tests:
   a) 10% b) 25% c) 50% d) 80%
5. Which of the following is not a risk factor for bone loss in women during early menopause?
   a) Low body weight b) Race c) Smoking d) High bone turnover markers
6. In postmenopausal women who use estrogen therapy during early menopause then discontinue, BMD and fracture risk are essentially the same as never-users of estrogen after approximately:
   a) 1 year b) 2 years c) 5 years d) Never
7. In postmenopausal women who begin bisphosphonate therapy during early menopause and then discontinue, BMD and fracture risk are essentially the same as never-users of bisphosphonates after approximately:
   a) 1 year b) 2 years c) 5 years d) Never
8. In the FREEDOM trial of postmenopausal women with osteoporosis and high risk for fracture, treatment with denosumab (versus placebo):
   a) Reduced the risk of vertebral, hip and non-vertebral fractures b) Increased BMD and reduced bone turnover markers c) Was associated with significantly more adverse events d) Options a and b
9. To preserve gains in bone density achieved with PTH therapy after PTH is discontinued:
   a) Bisphosphonate therapy should precede PTH therapy b) A bisphosphonate should be co-administered with PTH c) A bisphosphonate should be initiated after discontinuation of PTH d) No action is required
10. In which of the following situations is the FRAX risk calculation tool not applicable or of limited applicability?
    a) Patients currently receiving bisphosphonate therapy b) Patients with chronic kidney disease c) Women in early menopause d) Options a, b, and c

A. EVALUATION

1. Please indicate the degree to which this activity may help you:

	Excellent	*Very Good*	*Good*	*Satisfactory*	*Poor*
a. Employ consistently the current guidelines for osteoporosis screening and assessment	❑	❑	❑	❑	❑
b. Make appropriate use of the FRAX tool to define fracture risk	❑	❑	❑	❑	❑
c. Describe age- and sex-related changes in bone microarchitecture and macroarchitecture, the pathogenesis of skeletal fragility, and the implications these have on clinical care	❑	❑	❑	❑	❑
d. Employ bone turnover markers to assess response to treatment and monitor patient compliance	❑	❑	❑	❑	❑
e. Discuss emerging data on the use of PTH levels in combination with other agents and in diverse settings	❑	❑	❑	❑	❑
f. Discuss with patients the benefits and risks of long-term bisphosphonate therapy	❑	❑	❑	❑	❑
g. Discuss current expert recommendations for drug holidays for patients taking long-term bisphosphonates	❑	❑	❑	❑	❑
h. Compare current and emerging therapies, including their mechanisms of action, efficacy, safety, and administration for patients with osteoporosis	❑	❑	❑	❑	❑
i. Consider options for timing and sequencing treatment using antiresorptive and anabolic agents to maximize their unique benefits, particularly in patients at highest fracture risk	❑	❑	❑	❑	❑
j. Apply current insights in treatment to optimize bone health in complex cases	❑	❑	❑	❑	❑

2. Fair balance and professional effectiveness

	Strongly Agree	*Agree*	*Disagree*	*Strongly Disagree*
a. Course was free from commercial bias	❑	❑	❑	❑
b. Content was fair-balanced	❑	❑	❑	❑
c. Activity is relevant to my practice	❑	❑	❑	❑
d. What I learned may help improve patient care	❑	❑	❑	❑

3. Outcomes *(Check all that apply)*

	The material covered under this topic was important to me:	*These are topics in which I still have questions:*	*I would consider making changes in my practice in the following areas:*
a. Use of the current guidelines for osteoporosis screening and assessment	❑	❑	❑
b. Use of the FRAX tool to assess fracture risk	❑	❑	❑
c. Age- and sex-related changes in bone microarchitecture and macroarchitecture and the pathogenesis of skeletal fragility when defining a course for individual patients	❑	❑	❑
d. Employing bone turnover markers to assess response to treatment and monitor patient compliance	❑	❑	❑
e. Using PTH in combination with other agents and in diverse settings	❑	❑	❑
f. Discussing with patients the benefits and risks of long-term bisphosphonate therapy	❑	❑	❑
g. Counseling patients taking long-term bisphosphonates about taking drug holidays	❑	❑	❑
h. Options for timing and sequencing treatment using antiresorptive and anabolic agents to maximize their unique benefit particularly in patients at highest fracture risk	❑	❑	❑
i. How to optimize bone health in complex cases	❑	❑	❑

4. Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity. *(Check all that apply)*

- ❑ Interdisciplinary teams
- ❑ Professionalism
- ❑ Quality improvement
- ❑ Interpersonal and communication skills
- ❑ Medical knowledge
- ❑ Evidence-based practice
- ❑ System-based practice
- ❑ Informatics usage
- ❑ Practice-based learning and improvement
- ❑ Patient care or patient-centered care

B. GENERAL NEEDS ASSESSMENT

1. Please indicate how important each of the following areas would be to you in future CME newsletters: *(1 = least important; 5 = most important)*

	1	*2*	*3*	*4*	*5*
a. New pharmacologic agents	❑	❑	❑	❑	❑
b. Approaches to common clinical challenges	❑	❑	❑	❑	❑
c. Implementing guidelines	❑	❑	❑	❑	❑
d. How to educate patients	❑	❑	❑	❑	❑
e. Practice management	❑	❑	❑	❑	❑
f. Medical-legal issues	❑	❑	❑	❑	❑

2. Please answer all questions.

a. Most of the patients I see have problems in the following areas, so I would be interested in CME on these topics.

b. I often don't have enough time to keep up with advances and published articles on the following topics, so I would be interested in CME on these topics.

c. I usually seek consultation for problems in the following areas, so I would be interested in CME on these topics.

d. List the 2 clinical problems related to osteoporosis that you most frequently encounter.

3. Please indicate the value of each component of this activity: *(1 = least valuable; 5 = most valuable)*

	1	*2*	*3*	*4*	*5*
a. Complete slide sets	❑	❑	❑	❑	❑
b. Practical recommendations	❑	❑	❑	❑	❑
c. Panel discussion	❑	❑	❑	❑	❑
d. Audio FAQs	❑	❑	❑	❑	❑
e. Published CME newsletter	❑	❑	❑	❑	❑

4. Would you agree to participate in a brief online outcomes survey within 6 months of this activity? ❑ Yes ❑ No

C. CERTIFICATION OF PARTICIPATION

1. I claim _____ credit(s) (*up to 3 AMA PRA Category 1 Credit(s)™*).
2. Please provide your signature: _____

References

1. Bailey DA, Wedge JH, McCulloch RG, et al. *J Bone Joint Surg Am*. 1989;71(8):1225-1231. 2. Laib A, Ruegsegger P. *Bone*. 1999;24(1):35-39. 3. MacNeil JA, Boyd SK. *Med Eng Phys*. 2007;29(10):1096-1105. 4. Pistoia W, van Rietbergen B, Lochmuller EM, et al. *Bone*. 2002;30(6):842-848. 5. Kirmani S, Christen D, van Lenthe GH, et al. *J Bone Miner Res*. 2009;24(6):1033-1042. 6. Parfitt AM. *Osteoporos Int*. 1994;4(6):382-398. 7. Wang Q, Wang XF, Iuliano-Burns S, et al. *J Bone Miner Res*. 2010;25(7):1521-1526. 8. Muller ME, Webber CE, Bouxsein ML. *Osteoporos Int*. 2003;14(4):345-352. 9. Khosla S, Riggs BL, Atkinson EJ, et al. *J Bone Miner Res*. 2006;21(1):124-131. 10. Silva MJ, Gibson LJ. *Bone*. 1997;21(2):191-199. 11. Melton LJ 3rd, Christen D, Riggs BL, et al. *Osteoporos Int*. 2010;21(7):1161-1169. 12. Melton LJ 3rd, Riggs BL, Keaveny TM, et al. *J Bone Miner Res*. 2010;25(9):1922-1930. 13. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2008. Available at: http://www.nof.org/professionals/pdfs/NOF_Clinicians_Guide%202008.pdf. 14. Hodgson SF, Watts NB, Bilezikian JP, et al. *Endocr Pract*. 2003;9(6):544-564. 15. Tannenbaum C, Clark J, Schwartzman K, et al. *J Clin Endocrinol Metab*. 2002;87(10):4431-4437. 16. Luckey MM, Tannenbaum C. *J Clin Endocrinol Metab*. 2003;88:1402-1405. 17. Vezzoli G, Rubinacci A, Bianchin C, et al. *Am J Kidney Dis*. 2003;42(6):1177-1183. 18. Jaeger P, Lippuner K, Casez JP, et al. *J Bone Miner Res*. 1994;9(10):1525-1532. 19. Coresh J, Astor BC, Greene T, et al. *Am J Kidney Dis*. 2003;41(1):1-12. 20. Levin A, Bakris GL, Molitch M, et al. *Kidney Int*. 2007;71(1):31-38. 21. Bida JP, Kyle RA, Therneau TM, et al. *Mayo Clin Proc*. 2009;84(8):685-693. 22. International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757. 23. Politou M, Terpos E, Anagnostopoulos A, et al. *Br J Haematol*. 2004;126(5):686-689. 24. Fasano A, Catassi C. *Gastroenterology*. 2001;120(3):636-651. 25. Delmas PD. *Osteoporos Int*. 2000;11(suppl 6):S66-S76. 26. Bergmann P, Body JJ, Boonen S, et al. *Int J Clin Pract*. 2009;63(1):19-26. 27. Clowes JA, Peel NF, Eastell R. *J Clin Endocrinol Metab*. 2004;89(3):1117-1123. 28. Razzaque MS. *Am J Physiol Renal Physiol*. 2009;296(3):F470-F476. 29. Cauley JA, Robbins J, Chen Z, et al. *JAMA*. 2003;290(13):1729-1738. 30. Wainwright SA, Marshall LM, Ensrud KE, et al. *J Clin Endocrinol Metab*. 2005;90(5):2787-2793. 31. Burger H, de Laet CE, van Daele PL, et al. *Am J Epidemiol*. 1998;147(9):871-879. 32. Finkelstein JS, Brockwell SE, Mehta V, et al. *J Clin Endocrinol Metab*. 2008;93(3):861-868. 33. Recker R, Lappe J, Davies K, et al. *J Bone Miner Res*. 2000;15(10):1965-1973. 34. The Writing Group for the PEPI. *JAMA*. 1996;276(17):1389-1396. 35. Wasnich RD, Bagger YZ, Hosking DJ, et al. *Menopause*. 2004;11(6 pt 1):622-630. 36. Ravn P, Weiss SR, Rodriguez-Portales JA, et al. *J Clin Endocrinol Metab*. 2000;85(4):1492-1497. 37. McClung M, Miller P, Recknor C, et al. *Obstet Gynecol*. 2009;114(5):999-1007. 38. Ascott-Evans BH, Guañabens N, Kivinen S, et al. *Arch Intern Med*. 2003;163(7):789-794. 39. Hershman DL, McMahon DJ, Crew KD, et al. *J Clin Oncol*. 2008;26(29):4739-4745. 40. Smith MR, Egerdie B, Hernández Toriz N, et al. *N Engl J Med*. 2009;361(8):745-755. 41. Gilchrist NL, Frampton CM, Acland RH, et al. *J Clin Endocrinol Metab*. 2007;92(4):1385-1390. 42. Pounder NM, Harrison AJ. *Ultrasonics*. 2008;48(4):330-338. 43. Govender S, Csimma C, Genant HK, et al. *J Bone Joint Surg Am*. 2002;84-A(12):2123-2134. 44. Alharbi M, Pinto G, Finidori G, et al. *Horm Res*. 2009;71(1):38-44. 45. Rozental TD, Vazquez MA, Chacko AT, et al. *J Hand Surg Am*. 2009;34(4):595-602. 46. O'Loughlin PF, Cunningham ME, Bukata SV, et al. *Spine (Phila Pa 1976)*. 2009;34(2):121-130. 47. Alkhiary YM, Gerstenfeld LC, Krall E, et al. *J Bone Joint Surg Am*. 2005;87(4):731-741. 48. Andreassen TT, Ejersted C, Oxlund H. *J Bone Miner Res*. 1999;14(6):960-968. 49. Whitfield JF, Morley P, Willick GE. *Treat Endocrinol*. 2002;1(3):175-190. 50. Blackwell KA, Raisz LG, Pilbeam CC. *Trends Endocrinol Metab*. 2010;21(5):294-301. 51. Aspenberg P, Genant HK, Johansson T, et al. *J Bone Miner Res*. 2010;25(2):404-414. 53. Susan V. Bukata, MD. Personal communication. 53. Luckman SP, Hughes DE, Coxon FP, et al. *J Bone Miner Res*. 2005;20(7):1265-1274. 54. Dunford JE, Thompson K, Coxon FP, et al. *J Pharmacol Exp Ther*. 2001;296(2):235-242. 55. Kavanagh KL, Guo K, Dunford JE, et al. *Proc Natl Acad Sci U S A*. 2006;103(20):7829-7834. 56. Nancollas GH, Tang R, Phipps RJ, et al. *Bone*. 2006;38(5):617-627. 57. Rondeau JM, Bitsch F, Bourgier E, et al. *ChemMedChem*. 2006;1(2):267-273. 58. Rodan G, Reszka A, Golub E, et al. *Curr Med Res Opin*. 2004;20(8):1291-1300. 59. Black DM, Delmas PD, Eastell R, et al. *N Engl J Med*. 2007;356(18):1809-1822. 60. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. *N Engl J Med*. 2007;357(18):1799-1809. 61. Cartenì G, Bordonaro R, Giotta F, et al. *Oncologist*. 2006;11(7):841-848. 62. Rosen LS, Gordon D, Tchekmedyian NS, et al. *Cancer*. 2004;100(12):2613-2621. 63. Rosen LS, Gordon D, Tchekmedyian S, et al. *J Clin Oncol*. 2003;21(16):3150-3157. 64. Cummings SR, Schwartz AV, Black DM. *N Engl J Med*. 2007;356(18):1895-1896. 65. Karam R, Camm J, McClung M. *N Engl J Med*. 2007;357(7):712-713. 66. U.S. Department of Health & Human Services. Update of Safety Review Follow-up to the October 1, 2007 Early Communication about the Ongoing Safety Review of Bisphosphonates. Food and Drug Administration 2008. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm136201.htm. 67. Silverman SL, Cummings SR, Watts NB, et al. *J Bone Miner Res*. 2008;23(1):159-165. 68. Woo SB, Hellstein JW, Kalmar JR. *Ann Intern Med*. 2006;144(10):753-761. 69. American Dental Association. Dental Management of Patients Receiving Oral Bisphosphonate Therapy—Expert Panel Recommendations. Report of the Council on Scientific Affairs. Available at: http://www.ada.org/sections/professionalResources/pdfs/topics_osteonecrosis_bisphosphonate_report.pdf. 70. Abrahamsen B, Eiken P, Eastell R. *J Bone Miner Res*. 2009;24(6):1095-1102. 71. Wysowski DK. *N Engl J Med*. 2009;360(1):89-90. 72. Shaheen NJ. *N Engl J Med*. 2009;360(17):1790-1791. 73. Solomon DH, Patrick A, Brookhart MA. *N Engl J Med*. 2009;360(17):1789-1790. 74. Hofbauer LC, Miehlke S. *N Engl J Med*. 2009 Apr 23;360(17):1791-1792. 75. Abrahamsen B, Eiken P, Eastell R. *N Engl J Med*. 2009;360(17):1789. 76. Siris ES, Oster MW, Bilezikian JP. *N Engl J Med*. 2009;360(17):1791. 77. Robins HI, Holen KD. *N Engl J Med*. 2009;360(17):1790. 78. Wysowski DK, Chang JT. *Arch Intern Med*. 2005;165(3):346-347. 79. Black DM, Schwartz AV, Ensrud KE, et al. *JAMA*. 2006;296(24):2927-2938. 80. Schwartz AV, Bauer DC, Cummings SR, et al. *J Bone Miner Res*. 2010;25(5):976-982. 81. Watts NB, Chines A, Olszynski WP, et al. *Osteoporos Int*. 2008;19(3):365-372. 82. Boyle WJ, Simonet WS, Lacey DL. *Nature*. 2003;423(6937):337-342. 83. Vega D, Maalouf NM, Sakhaee K. *J Clin Endocrinol Metab*. 2007;92(12):4514-4521. 84. Lewiecki EM, Miller PD, McClung MR, et al. *J Bone Miner Res*. 2007;22(12):1832-1841. 85. McClung MR, Lewiecki EM, Cohen SB, et al. *N Engl J Med*. 2006;354(8):821-831. 86. Cummings SR, San Martin J, McClung MR, et al. *N Engl J Med*. 2009;361(8):756-765. 87. Stoch SA, Wagner JA. *Clin Pharmacol Ther*. 2008;83(1):172-176. 88. Pennypacker B, Shea M, Liu Q, et al. *Bone*. 2009;44(2):199-207. 89. McClung M, Eisman JA, Bone HG, et al. *Bone*. 2009;44(suppl 2):S438. 90. Dobnig H, Turner RT. *Endocrinology*. 1997;138(11):4607-4612. 91. Gallagher JC, Genant HK, Crans GG, et al. *J Clin Endocrinol Metab*. 2005;90(3):1583-1587. 92. McClung MR, San Martin J, Miller PD, et al. *Arch Intern Med*. 2005;165(15):1762-1768. 93. Chen P, Miller PD, Delmas PD, et al. *J Bone Miner Res*. 2006;21(11):1785-1790. 94. Greenspan SL, Bone HG, Ettinger MP, et al. *Ann Intern Med*. 2007;146(5):326-339. 95. Fitzpatrick L, Brennan E, Kumar S, et al. *J Bone Min Res*.2008;23:Abstract 1174. 96. Rankin W, Grill V, Martin TJ. *Cancer*. 1997;80(suppl 8):1564-1571. 97. Horwitz MJ, Tedesco MB, Garcia-Ocana A, et al. *J Clin Endocrinol Metab*. 2010;95(3):1279-1287. 98. O'Dea, et al, Presented at International Congress of Endocrinology, March 2010 (Kyoto, Japan). Abstract. 99. Cosman F, Lane NE, Bolognese MA, et al. *J Clin Endocrinol Metab*. 2010;95(1):151-158. 100. Kubota T, Michigami T, Ozono K. *J Bone Miner Metab*. 2009;27(3):265-271. 101. Hoeppner LH, Secreto FJ, Westendorf JJ. *Expert Opin Ther Targets*. 2009;13(4):485-496. 102. Li X, Ominsky MS, Warmington KS, et al. *J Bone Miner Res*. 2009;24(4):578-588. 103. Richards JB, Papaioannou A, Adachi JD, et al. *Arch Intern Med*. 2007;167(2):188-194. 104. Yadav VK, Ryu JH, Suda N, et al. *Cell*. 2008;135(5):825-837. 105. Yadav VK, Balaji S, Suresh PS, et al. *Nat Med*. 2010;16(3):308-312. 106. Bolland MJ, Avenell A, Baron JA, et al. *BMJ*. 2010;341:c3691. 107. Reid IR, Mason B, Horne A, et al. *Am J Med*. 2006;119(9):777-785. 108. Lewis JR, Calver J, Zhu K, et al. *J Bone Miner Res*. 2010 Jul 7. [Epub ahead of print.] 109. Hansen KE, Jones AN, Lindstrom MJ, et al. *J Bone Miner Res*. 2010 Jun 24. [Epub ahead of print.] 110. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2010. Available at: http://www.nof.org/professionals/pdfs/NOF_ClinicianGuide2009_v7.pdf. 111. Tosteson AN, Melton LJ 3rd, Dawson-Hughes B, et al. *Osteoporos Int*. 2008;19(4):437-447. 112. McClung MR, Geusens P, Miller PD, et al. *N Engl J Med*. 2001;344:333-340.

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