

Review Article

Osteoporosis Update From the 2010 Santa Fe Bone Symposium

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Abstract

The 11th Santa Fe Bone Symposium was held in Santa Fe, NM, USA, on August 6–7, 2010. This annual event addresses clinically relevant advances in the fields of osteoporosis and metabolic bone disease. The venue includes plenary presentations by internationally recognized experts, oral presentations of abstracts, and interactive panel discussions of challenging cases and controversial issues. Attendees are active participants throughout the symposium program. Topics for the 2010 symposium included potential applications of novel technologies for the assessment of skeletal health for research and clinical practice; new and emerging treatments for osteoporosis; appropriate use of pharmacological agents to prevent osteoporosis; controversies with bisphosphonate therapy; practical applications of the World Health Organization fracture risk assessment tool (FRAX; World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK); insights into the use of osteoanabolic agents to enhance fracture healing; and challenges in laboratory testing in the assessment of factors contributing to skeletal fragility. Concurrent sessions focused on critical thinking for technologists in the acquisition and analysis of data with dual-energy X-ray absorptiometry. The key messages from each presentation, including the best available medical evidence and potential current and future clinical applications, are provided here.

Key Words: Bisphosphonate; denosumab; emerging; fracture; osteoporosis.

Introduction

The Santa Fe Bone Symposium, sponsored annually by the Osteoporosis Foundation of New Mexico, is devoted to new and emerging scientific, social, political, and economic issues in the care of patients with osteoporosis and metabolic bone disease. Faculty members are leading experts who are selected according to their knowledge of basic science or clinical research and their translation to potential applications for patient care. Attendees represent diverse backgrounds that include clinicians, academicians, house staff, researchers, ancillary health care providers, and technologists. The 11th annual Santa Fe Bone Symposium was held August 6–7,

2010, in Santa Fe, NM, USA. Each presentation addressed issues of clinical relevance, with the goal of bridging the gap between medical evidence and clinical utility. Faculty and attendees were encouraged to present patient challenging cases and common clinical dilemmas, usually followed by lively and lengthy discussions. Bone densitometry technologists conducted concurrent sessions to address quality issues associated with bone density testing. Endocrinology fellows gave oral presentations of abstracts selected from an educational event held in the days preceding the bone symposium. Topics were identified through evaluations from previous programs and new developments in the field of skeletal health care. Areas of particular interest were new and emerging treatments for osteoporosis, safety concerns with bisphosphonate therapy, and laboratory testing for secondary causes of osteoporosis. Proceedings of previous Santa Fe Bone Symposia have been published elsewhere (1–4). This is

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a summary of the key clinical presentations of the 2010 Santa Fe Bone Symposium, consisting of the current best medical evidence and expert opinion regarding potential clinical applications. The topics and faculty are as follows:

New and Emerging Therapies for Osteoporosis—John P. Bilezikian, MD.

Assessing Bone Structure: Can We Do Better Than DXA?—Sundeep Khosla, MD.

Teriparatide and Acceleration of Fracture Repair—Robert Marcus, MD.

Drug Therapy to Prevent Osteoporosis: Is It Ever Appropriate?—Michael R. McClung, MD.

FRAX: Practical Issues With Use in Daily Practice—Michael R. McClung, MD.

Challenges in the Laboratory Testing for the Management of Postmenopausal Osteoporosis—Paul D. Miller, MD.

Controversies With Bisphosphonate Therapies—Nelson B. Watts, MD.

Case Report: A Patient on Long-Term Bisphosphonate Therapy With Bilateral Thigh Pain—Michael Maricic, MD.

New and Emerging Therapies for Osteoporosis

John P. Bilezikian, MD

Available Therapeutic Agents

Over the past 15 yr, options for the pharmacologic treatment of osteoporosis have been enriched by many safe and effective agents (5,6). The drugs that dominate the therapeutic landscape are the antiresorptives. Although mechanisms by which antiresorptive agents act to reduce fracture risk differ both between and within classes, they all feature, as a common denominator, an action to impair the activity of the bone-resorbing cell, the osteoclast (7). Indirectly, they are also associated with reduced activities of the bone-forming cell, the osteoblast. By inhibiting the osteoclast to a greater extent than the osteoblast, however, the bone remodeling unit is brought into better balance and bone mass accrues (8). US Food and Drug Administration (FDA)-approved drugs that belong to this group of drugs are estrogens, raloxifene, calcitonin, bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), and most recently, denosumab. Some of these agents provide global protection against vertebral, nonvertebral, and hip fractures (estrogen, alendronate, risedronate, zoledronic acid, denosumab), whereas for others the evidence, based on prospective clinical trial data, is limited to effects at vertebral sites. Teriparatide [parathyroid hormone (1-34), PTH(1-34), TPTD] (available in the United States and throughout the world) and the full length PTH molecule [PTH(1-84)] (not available in the US but in many other countries) belong to a different therapeutic class called osteoanabolics in which the primary therapeutic effect is to stimulate processes associated with bone formation (9). An initial action of osteoanabolics is to stimulate bone modeling followed thereafter by stimulation of bone resorption, the initial component of the bone remodeling cycle. An anabolic window of time is created by virtue of the effect of PTH to stimulate bone formation first and osteoclast-mediated

bone turnover later (10). TPTD reduces vertebral and nonvertebral fractures (11), whereas the evidence for PTH(1-84) is limited to reduction of vertebral fractures (12). Both forms of PTH improve skeletal microstructure (13).

Adverse events occur with each of these established agents for the treatment of osteoporosis but generally they are well tolerated and safe. When used in a program of nutritional maintenance (calcium and vitamin D), exercise, life-style optimization, and measures to prevent falls, fracture risk is reduced.

Combination Therapy

The rationale for combination therapy with antiresorptives and osteoanabolic agents is based on the fact that they work by different mechanisms and, thus together, should lead to an enhanced therapeutic effect. Various combinations that have been used are sequential with bisphosphonate (or other antiresorptive) preceding or following the use of PTH. When antiresorptives are used before PTH, the data suggest that agents with a powerful effect to reduce bone turnover may delay the subsequent actions of PTH to increase bone formation and bone mineral density (BMD) (14,15). When antiresorptives are used after PTH, they maintain the densitometric gains achieved during the period of PTH administration (16,17). In fact, a standard of care is to follow the period of PTH administration (generally 2 yr) with an antiresorptive, preferably a bisphosphonate. Studies involving simultaneous combination therapy with a bisphosphonate and PTH(1-84) or TPTD have generally shown that monotherapy with the osteoanabolic agent gives better results in terms of BMD and bone turnover markers (18,19). Deal et al (20) showed, however, that combination therapy with raloxifene, which does not reduce bone turnover to the same extent as bisphosphonates, and TPTD does lead to rapid increases in bone turnover marker and increased hip BMD. Cosman et al (21) showed that a single dose of zoledronic acid followed by TPTD leads to an early advantage in terms of gains in BMD.

Other permutations on this theme have been used such as using TPTD for 12–24 mo with or without a background of continuous bisphosphonate use (22–24). The results have been mixed but generally the second administration of TPTD is associated with an effect on BMD that is similar to the results following initial administration. Finally, Cosman et al (25) have tested a protocol in which patients are switched from bisphosphonate therapy to TPTD or TPTD is added to the bisphosphonate regimen. Greater changes in bone turnover markers are seen with the switch regimen but the anabolic window may be wider with the add regimen.

It should be noted that in none of the combination therapy approaches are there data beyond changes in bone turnover markers and BMD. There are no fracture endpoints available.

Emerging Therapies and New Therapeutic Concepts

Antiresorptive

Denosumab

The newest therapy to be approved by the FDA (June, 2010) is denosumab. The actions of this drug are based on an

important intercellular signaling pathway (26) known as RANKL (receptor activator of nuclear factor κ B ligand), RANK (the RANKL receptor), and OPG (osteoprotegerin). RANKL is a powerful stimulator of osteoclastogenesis and osteoclast action. OPG, the natural inhibitor of RANKL, was initially thought to have therapeutic potential, but it was succeeded by denosumab, a fully human antibody against RANKL (27). The phase 2 studies (27–29) in which the human dose of denosumab was established (60 mg subcutaneously every 6 mo) were followed by the pivotal phase 3 study of Cummings et al (30). This 3-yr, placebo-controlled, randomized clinical trial, known as FREEDOM (Fracture Reduction Evaluation of Denosumab Every 6 mo), showed that denosumab reduced vertebral, nonvertebral, and hip fractures significantly more than the placebo arm of the study. In approving denosumab, the FDA issued a warning about skin infections and suppression of bone turnover. In contrast to the bisphosphonates, when denosumab is discontinued, bone turnover markers rise rapidly and BMD falls (28).

Odanacatib

Cathepsin K, a cysteine protease secreted by the osteoclast, degrades the organic matrix of bone and, thus, helps to define the bone remodeling space (31,32). The cathepsin K inhibitor, odanacatib, renders the osteoclast dysfunctional in this regard but does not appear to impair other properties of the osteoclast, such as intercellular communication with the osteoblast (31). Animal studies have shown that the resorption pits, induced by osteoclasts, are more shallow under the influence of odanacatib and that osteoclasts remain present and numerous. In addition, bone formation does not appear to be reduced to the same extent as it is with bisphosphonates or denosumab. Clinical experience with this drug in phase 2 trials appears to bear out this observation by reductions in bone formation that are small relative to reductions in bone resorption (33). This observation suggests that with odanacatib, the functional properties of the osteoblast may be maintained to a greater extent than is typically seen with other classes of antiresorptives. Odanacatib is currently in phase 3 clinical trials.

Osteoanabolics

Parathyroid Hormone

TPTD and PTH(1-84) are administered by daily subcutaneous injection. Two alternative delivery systems to circumvent this inconvenient feature are being studied at this time. A transdermal delivery system administers TPTD through the skin (34). Cosman et al have shown that the pharmacokinetic profile of transdermal TPTD displays very favorable kinetics with rapid uptake and rapid disappearance from the circulation, features that are believed to be important for the osteoanabolic effects of the drug. Another approach to more facile administration of PTH is the use of oral agents that inhibit the calcium sensing receptor on the parathyroid cell. These so-called calcilytics lead to stimulation of the parathyroid cell to synthesize and secrete endogenous PTH. Preliminary reports with the calcilytic, ronacaleret, were promising (35) but more recent observations suggest that

the pharmacokinetic profile may not be ideal (36). Finally, parathyroid hormone-related protein is being studied as a potential PTH-like therapeutic agent (37).

Sclerostin Inhibition

Recent data suggest that one of the mechanisms by which PTH may be anabolic is by inhibiting sclerostin (38–41), a powerful inhibitor of the anabolic Wnt signaling pathway (42). This concept has led to the development of an antibody that inhibits sclerostin (43). Data by Li et al (43) have shown that the antisclerostin antibody is a powerful stimulator of periosteal and endocortical bone although it has little effect to stimulate osteoclast activity.

Serotonin Antagonism

There are 2 serotonin systems that are thought to regulate skeletal mass (44). In the central nervous system, serotonin is synthesized by the enzyme tryptophan synthase 2. It is associated with the stimulation of bone formation. In the gastrointestinal tract where most of the body's serotonin is made, the responsible enzyme is tryptophan synthase 1 (Tph1). It is associated with inhibition of bone formation (45). The 2 enzymes are specific to their locations and do not cross the blood-brain barrier. Similarly, serotonin does not cross the blood-brain barrier, in either direction. Animal studies using a specific Tph1 inhibitor have shown a remarkable effect to stimulate bone formation as powerfully as PTH in ovariectomized rats (46).

Summary

Newer molecules are being developed to improve on what we have, and to take advantage of bone cell pathways of activation and inhibition. In the course of exploring these new approaches, it is important to bear in mind the ever-present goals of providing specificity and safety along with efficacy.

Assessing Bone Structure: Can We Do Better Than Dual-Energy X-Ray Absorptiometry?

Sundeep Khosla, MD

In recent years, a number of new imaging tools have become available to assess not only bone mass/density, but also volumetric BMD, bone geometry, structure, and indices of bone strength using finite element models. We have used high-resolution peripheral quantitative computed tomography (HRpQCT) at the wrist and tibia to evaluate a number of these parameters during growth and senescence, and in fracture and control patients. With a voxel size of 82 μ m, this technique can define trabecular and cortical microstructure and correlates highly with *ex vivo* microCT (μ CT) (47). These data have provided new insights into bone structural changes across life and the possible role of these approaches in helping to identify patients at increased risk of fracture.

During adolescence, the most common site of fracture is the distal forearm, with peak incidence at the pubertal growth spurt (48). We have previously found that the incidence of forearm

fractures increased by 32% in boys and 56% in girls over the past 30 yr (49). Because 25–50% of adult bone mass is accumulated during the pubertal growth spurt, adolescents today may be at increased risk of osteoporotic fractures later in life. To identify potential structural changes in bone at the distal radius during puberty, we studied healthy 6–21-yr-old girls ($n = 66$) and boys ($n = 61$) using HRpQCT (voxel size, 82 μm) at the distal radius (50). Subjects were classified into 5 groups by bone age: group I (prepuberty, 6–8 yr), group II (early puberty, 9–11 yr), group III (midpuberty, 12–14 yr), group IV (late puberty, 15–17 yr), and group V (postpuberty, 18–21 yr). Compared with group I, trabecular parameters (bone volume [BV] fraction, trabecular number [TbN], and thickness) did not change in girls, but increased in boys from late puberty onwards. Cortical thickness and density decreased from pre- to midpuberty in girls, but were unchanged in boys, before rising to higher levels at the end of puberty in both sexes. Total bone strength, assessed using microfinite element models, increased linearly across bone age groups in both sexes, with boys showing greater bone strength than girls after midpuberty. The proportion of load borne by cortical bone and the ratio of cortical to trabecular BV decreased transiently during mid- to late puberty in both sexes, with apparent cortical porosity peaking during this time. This mirrors the incidence of distal forearm fractures in prior studies. These findings thus demonstrated that regional deficits in cortical bone may underlie the adolescent peak in forearm fractures. Whether these deficits are more severe in children who sustain forearm fractures or persist into later life warrants further investigation. In further studies, we also used HRpQCT to define, in a population-based sample of women and men spanning a broad age range (21–97 yr), sex, and age effects on bone microstructure at the wrist (51). Relative to young women (age 20–29 yr), young men had greater trabecular BV/tissue volume (TV) and trabecular thickness (TbTh) but similar values for TbN and trabecular separation (TbSp). Between ages 20 and 90 yr, cross-sectional decreases in BV/TV were similar in women (–27%) and in men (–26%), whereas women had significant decreases in TbN (–13%) and increases in TbSp (+24%), these parameters had little net change over life in men (+7% and –2% for TbN and TbSp, respectively, $p < 0.001$ vs women). However, TbTh decreased to a greater extent in men (–24%) than in women (–18%, $p = 0.010$ vs men). Thus, although decreases with age in trabecular BV/TV are similar in men and women, the structural basis for the decrease in trabecular volume is quite different between the sexes. Over life, women undergo loss of trabeculae with an increase in TbSp, whereas men begin young adult life with thicker trabeculae and primarily sustain trabecular thinning with no net change in TbN or TbSp. Because decreases in TbN have been shown to have a much greater impact on bone strength when compared with decreases in TbTh, these findings may help explain the lower life-long risk of fractures in men, and specifically, their virtual immunity to age-related increases in distal forearm fractures.

We have also applied HRpQCT and vertebral quantitative computed tomography (QCT) imaging to test whether these

techniques can differentiate either forearm (52) or vertebral (53) fracture patients from nonfracture patients better than dual-energy X-ray absorptiometry (DXA). In these studies, we also constructed finite element models of the wrist and vertebrae to estimate bone strength and to evaluate the utility of these models in fracture prediction. In general, although the magnitude of differences between fracture and control subjects using the HRpQCT or vertebral QCT parameters was greater than the DXA parameters, improvements in predictive ability (assessed using odds ratios or area under the receiver-operator curves) were modest using these approaches. For example, the area under the receiver-operator curve improved from 0.69 to 0.74 for differentiating vertebral fracture from control patients using femoral neck areal BMD when compared with finite element model-predicted bone strength at the vertebra (7). Nonetheless, these approaches remain promising, particularly as improvements in image analysis techniques and in the fidelity of the finite element models continue to occur. Moreover, it is possible that microstructural changes may be most important in the early phases of bone loss. Thus, further work using microstructural analysis and strength estimates of bone is clearly needed to obtain the maximal benefit from these approaches in assessing fracture risk.

TPTD and Acceleration of Fracture Repair

Robert Marcus, MD

The remarkable thing about fracture repair is that, given appropriate medical and/or surgical intervention, in the great majority of cases they repair beautifully, with full restitution of appearance and function. In these cases, it is difficult to argue that accelerated repair has any important clinical utility. However, instances in which the severity, nature, or location of the fracture predict a difficult outcome, a need for additional surgery, and delayed return to work or household duties, suggest the value of an agent that could accelerate the repair process.

Fracture repair can be differentiated into 3 separate phases. In the first, “inflammatory phase,” an organizing hematoma develops around the fracture site, creating a fibrin network upon which replacement tissue will be established. A series of growth factors and cytokines are released during this phase, which lasts for little more than a week. The next phase is “reparative,” during which callus is formed and subsequently calcified. This phase has a requirement for adequate cellular support, that is, osteoblasts and osteocytes. This phase determines the adequacy of clinical healing, and continues for several months. Finally, the “remodeling” phase, during which calcified cartilage is replaced by bone, continues to remodel for an extended period, even years.

When fracture repair does not proceed normally, the clinical terms “delayed union” and “nonunion” are applied. Causes for poor fracture repair can be related to the degree of trauma or to the characteristics of the patient. The intensity of impact, loss of critical vascular supply, the presence of bone fragments, or loss of periosteum are all related to the injury

itself. Patient-specific factors include age, nutritional state, presence of systemic disease, exposure to glucocorticoids or nonsteroidal anti-inflammatory agents, thermal or radiation injury, tobacco use, and obesity.

Although the focus of this presentation will be the PTH (1-34), or TPTD, other modalities have been FDA approved to accelerate fracture healing, albeit for a limited number of fracture types. These include low-intensity ultrasound for healing of distal radius and tibial fractures (54) and bone morphogenetic factor-2 (BMP-2) for use in poorly healing tibial fracture (55). In this case, the BMP-2 has been impregnated into a pledget, which is applied directly to the bone surface.

With respect to systemic, that is, pharmaceutical, agents, some attention has been paid to various bisphosphonates. In general, these antiresorptive drugs increase the volume of fracture callus by inhibiting its resorption. Although the strength of a given section of callus is reduced compared with a similar section of normal callus, the greater total callus volume leads to no deficit in overall tissue strength. In human osteoporosis trials using bisphosphonates, no signal for impaired fracture healing has emerged when assessing the experience of those participants who fractured during the trial. In patients with wrist fracture (56) or with osteogenesis imperfecta (57), bisphosphonate treatment has been associated with subtle prolongation in fracture healing. PTH and its fragment, TPTD, seem from first principles to be likely candidates to accelerate fracture repair. TPTD has an established role as an anabolic agent for the treatment of osteoporosis. It stimulates stem-cell recruitment and differentiation along the osteoblastic pathway. It promotes expression of vascular endothelial growth factor, and works through multiple signaling pathways. More than 15 animal studies have demonstrated that TPTD enhances external callus volume and quality, improves callus mineralization and overall biomechanical competence, and reduces time to fracture healing (58). TPTD has shown a powerful effect to promote fusion in a rabbit model of spinal fusion (59).

With respect to fracture healing in humans, a large body of anecdotal information has accrued over the past several years, much of it involving single cases, often in high-profile professional athletes. The best information to date comes from an industry-sponsored randomized controlled study and a moderately large observational study from University of Rochester.

In what was viewed as a proof of concept study, Eli Lilly & Co undertook a randomized controlled trial of TPTD in postmenopausal women with a unilateral, dorsally angulated, non-instrumented fracture of the distal radius (Colles' fracture) (60). Participants were randomized to receive 20 or 40 mcg/d TPTD or vehicle for 8 wk of intervention. Participants were required to complete screening and initiate therapy within 10 d of fracture. The primary objective of this study was to compare the effect treatments on time to radiographic fracture healing (cortical bridging). Secondary endpoints consisted of multiple functional assessments. Because, based on animal studies, it was considered likely that a larger dose than the clinically approved 20 mcg/d would be required, the statistical analysis was powered in a manner that established the effect at

40 mcg TPTD to be the primary analysis, and 20 mcg effects would not be considered unless the higher dose gave a statistically significant effect. Contrary to expectation, no significant effect was observed with the 40 mcg dose. However, in *post hoc* analysis, a clear reduction in time to healing was observed at the 20 mcg dose, which corresponds to all anecdotal reports of effective fracture healing in humans.

In an observational study of 145 patients with poor fracture healing at the University of Rochester, Bukata (Bukata SV, personal communication, 2010) reported that treatment TPTD at various doses and durations led to effective radiographic and clinical union in 93% of patients, partial union in an additional 4%, with only 4 individuals failing to achieve adequate fracture healing. Some of the most dramatic cases of success were in patients suffering long-standing nonunion of pelvic insufficiency fractures. In this particular series, some of these patients had nonunion related to previous radiation therapy. Because the label language for TPTD includes a warning based on the effect of TPTD to increase the incidence of osteosarcoma in Fisher 344 rats, patients with prior external beam ionizing radiation are not considered candidates for the use of this agent, so the efficacy of TPTD in patients with pelvic insufficiency fracture not related to radiation is not clear.

At present, it appears likely that TPTD can serve as an effective promoter of fracture healing in humans, but considerable additional work will be required before the validity of this concept, the optimal dose and duration of intervention, the particular types of fractures in which therapy might be useful, and the functional consequences of such an intervention can be understood.

Drug Therapy to Prevent Osteoporosis: Is It Ever Appropriate?

Michael R. McClung, MD

Since the mid-1990s, drugs have been approved for the treatment and prevention of osteoporosis in postmenopausal women, men, and patients receiving glucocorticoid therapy. The main purpose of pharmacological therapy for osteoporosis is to reduce the risk of fractures. Clinical efficacy has been documented in postmenopausal women with osteoporosis and patients receiving glucocorticoid therapy—patients at high fracture risk—but there is little evidence that treating low-risk patients reduces fracture risk. An exception is the Women's Health Initiative (WHI) estrogen study (61). Although reduction in spine and hip fractures was observed in the WHI, the absolute reduction in risk was very modest. Bisphosphonate therapy in patients with low bone mass but low fracture risk has not been shown to be cost effective (62). On the basis of these observations, recently updated guidelines now recommend therapy only for patients at high fracture risk (63).

We recognize that there are men and women without osteoporosis who are at high risk for fracture, and that most fractures related to skeletal fragility occur in patients who do not meet the diagnostic threshold for osteoporosis (64). To aid in the recognition of the individuals without osteoporosis but who were at high fracture risk and, thus, candidates for

treatment, the World Health Organization (WHO) fracture risk assessment tool (FRAX; World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK) was developed. Current guidelines now recommend therapy for patients with osteoporosis, based on prior fracture or T-score or with low bone mass at high fracture risk, based on FRAX results (63).

The corollary to the updated treatment guidelines is that patients with low BMD, but who have no other risk factors, are not appropriate candidates for pharmacological osteoporosis therapy. This new thinking challenges long-held beliefs about the importance of therapy to prevent osteoporosis and raises the question of whether the use of drugs to prevent bone loss and osteoporosis is ever justified in low-risk patients. The guidelines do not address the question of treating the several groups of patients who are about to experience rapid bone loss.

All women experience relatively rapid bone loss at menopause, but the interval of rapid bone loss is transient. Spinal bone mass declines at a rate of 2–3% per year for 5–6 yr around the time of menopause, with a total loss of about 1–2 T-score units (10–20%) in the spine (65,66). Fracture rates, however, do not increase substantially until many years after menopause. After the menopausal transition in otherwise healthy women, the rate of bone loss slows to almost imperceptible levels (65,66). The rate of perimenopausal bone loss varies only modestly among individual women, although low body weight may be a risk factor for somewhat greater loss. Thus, women who enter menopause with below average BMD will reach the threshold for osteoporosis much earlier. Attempts to reduce or prevent perimenopausal bone loss using exercise, calcium intake, or vitamin D supplements have been largely unsuccessful because it is estrogen deficiency—not exercise or nutritional deficiency—that is responsible for the bone loss.

Clinicians then face the question of whether or when to use osteoporosis drugs to prevent bone loss in early menopause or upon discontinuation of estrogen therapy, although the new treatment guidelines suggest not treating such patients unless they are at high risk for fracture. In my opinion, it is attractive to consider a brief course of treatment to blunt bone loss during the menopausal transition in women with low or low normal bone mass (T-score between -1.5 and -2.5) to postpone the need for long-term therapy.

Numerous studies, such as the Postmenopausal Estrogen/Progestin Interventions and Early Postmenopausal Intervention Cohort trials, have shown that estrogen therapy during early menopause can prevent bone loss and even increase BMD (67,68). 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 yr (69,70). Bisphosphonates can also preserve or increase bone mass in early menopause (71,72). In contrast to estrogen, the benefits of alendronate persisted for much longer after the drug was withdrawn compared with estrogen (70,73). In young postmenopausal women who received treatment with alendronate for 2 yr, treatment benefit persisted for 4 yr after treatment was stopped (70). A recent study demonstrates that a single intravenous dose of zoledronic acid

effectively prevents bone loss in early postmenopausal women for at least 2 yr (71). There is also evidence that alendronate stems the loss of bone after discontinuation of therapeutic estrogen (74).

Men and women beginning hormone deprivation therapy for management of breast and prostate cancer may also be candidates for treatment to prevent bone loss. Many of these patients experience rapid bone loss for 2–3 yr, and men receiving androgen therapy are at high risk for fracture during the initial years of treatment (75,76). Therapy with potent antiresorptive drugs prevent this bone loss, and in some studies have been shown to reduce fracture risk (77–81). Patients experiencing acute spinal cord injury (and probably other patients who are acutely immobilized) lose substantial bone mass from weight-bearing regions of the skeleton. Alendronate therapy effectively prevents bone loss in such patients (82).

Together, these various findings suggest that there may be a role for bisphosphonate therapy in selected patients at risk for short-term rapid bone loss. For some women undergoing natural or surgical menopause, discontinuing estrogen therapy or beginning aromatase inhibitor therapy, for most men beginning androgen replacement therapy, and patients with acute immobilization, bisphosphonate treatment for 2–3 yr seems appropriate. Drugs with a rapid offset of reducing bone turnover (estrogen, raloxifene, risedronate, ibandronate, and denosumab) would be much less attractive candidates for such therapy compared with alendronate and zoledronic acid that have persistent effects after stopping treatment. At the end of that treatment period, discontinuing treatment would be appropriate unless the patient meets the guidelines for therapy at that time.

In summary, treatment with osteoporosis drugs is recommended for patients at high risk of fracture to reduce that risk. However, there is a justification for therapy with alendronate or zoledronic acid in patients anticipated to experience rapid bone loss in an effort to prevent the development of osteoporosis and to forestall the need for long-term treatment.

FRAX: Practical Issues With Use in Daily Practice

Michael R. McClung, MD

Effective treatments now exist to reduce fracture risk in patients with osteoporosis. Clinical trials leading to approval of these drugs evaluated treatment response in postmenopausal women with osteoporosis—based on a history of previous vertebral fracture or BMD values consistent with osteoporosis. However, most fractures associated with osteoporosis, including hip fracture, occur in patients who do not have osteoporosis by these criteria (64). This has led to efforts to identify patients who would be appropriate for treatment but who do not have osteoporosis. Early guidelines recommended treatment for patients with T-score values of -1.5 or lower and one of the several risk factors (83). This guideline captured most patients at high risk for fracture but enfranchised treatment for many younger postmenopausal women who were not at high risk for fracture.

To address the issue of deciding which patients without osteoporosis to treat, the WHO developed FRAX (84). This risk calculator incorporates femoral neck BMD and other important clinical risk factors and provides estimates, for individual patients, of the 10-yr probability (risk) of developing a hip fracture or a major fracture (hip, wrist, proximal humerus, or symptomatic spine fracture) (85).

The FRAX tool has many strengths. It integrates easily assessed risk factors, can be used with or without BMD in regions with limited access to DXA, and is based on very strong epidemiological evidence. Almost 250,000 patient years of follow-up of cohorts from various parts of the world were the basis for the computer-based algorithm. The important subtleties of the interplay among risk factors that are not totally independent are accounted for in the computer program. The accuracy of fracture risk prediction has been validated in several large cohorts of patients.

FRAX has been incorporated, in different ways, into treatment guidelines in many parts of the world. In the United States, the National Osteoporosis Foundation (NOF) updated their treatment guidelines and incorporated the use of the FRAX tool (Fig. 1) (63). These recommendations (not rules) for treatment are clinically intuitive, easy to use, and are based on solid cost-effective evidence. When uncertainty exists about whether pharmacological treatment is appropriate, the new guidelines provide clinicians with a useful starting point from which to make the decision.

Despite the strength of the FRAX model and the clarity of the NOF guidelines, there are challenges and limitations to their use in daily clinical practice. Several of those issues are discussed here.

1. Choice of BMD data to use with FRAX

Because ethnicity and gender are accounted for in the FRAX algorithm, it is not appropriate to enter T-score values determined using non-Caucasian or male databases into FRAX. This problem was initially resolved with the “FRAX Patch,”

developed by the Oregon Osteoporosis Center. This required entry of the femoral neck BMD value (in g/cm^2) and the brand of the DXA machine. This approach was subsequently incorporated into the FRAX calculator.

2. Treatment of risk factors with varying intensity as categorical variables

A history of previous fracture, glucocorticoid use, smoking, and excessive alcohol intake are treated as categorical variables. However, the type and recency of the fracture and the numbers of fractures a patient has experienced alter the risk accompanying a fracture history. (6) Similarly, patients who smoke or drink heavily are at higher risk than those who partake of these habits less often. Patients on current or high-dose glucocorticoid therapy are at higher risk than patients receiving low-dose treatment or who no longer take steroids.

Case example: A healthy 66-yr-old woman had a wrist fracture at age 53 yr and a proximal humerus fracture at age 64 yr. T-scores in the lumbar spine and femoral neck are -1.9 and -1.0 , respectively. FRAX 10-yr probabilities are 16% for major fracture and 2.8% for hip fracture. This patient does not meet the NOF thresholds for treatment.

Because this patient has had multiple fractures, she is probably at higher fracture risk than patients with a simple history of fragility fracture. Although there is no way to quantify the additional risk associated with multiple fractures, clinical judgment would dictate revising risk upward in such patients, making her, in my opinion, a candidate for therapy. In the same way, FRAX probably overestimates fracture probability in patients with a prior history of glucocorticoid use or on very low-dose therapy while likely underestimating risk in patients on current or high-dose therapy.

3. Choice of FRAX database

Because age-specific fracture incidence and mortality rates differ among American ethnic groups, separate

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, total hip 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 1 of the following:
 - A 10-year probability of a hip fracture $\geq 3\%$, or
 - A 10-year probability of a major osteoporosis-related fracture $\geq 20\%$ based on the US-adapted WHO algorithm

NOTE: Clinician's judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels.

Fig. 1. US treatment guidelines of the National Osteoporosis Foundation (63).

FRAX databases exist for American Caucasian, black, Asian, and Hispanic patients. Fracture probability will differ depending on which database is chosen.

Case example: A healthy, 66-yr-old woman has experienced a wrist fracture, and her father had a hip fracture at age 83 yr. Her femoral neck T-score is -2.0 . Her father is from Columbia, whereas her mother is Caucasian. Using the American Caucasian FRAX database, her 10-yr probabilities are 28% for major fracture and 3.4% for hip fracture—meeting recommendations for treatment. However, using the American Hispanic database, she would not meet the treatment threshold (FRAX 10-yr probabilities of 16% for major fracture and 1.9% for hip fracture). There is no clear solution to the problem of choosing among the American ethnic databases in FRAX. In general, epidemiologists and sociologists have recommended that a patient's self-identified ethnicity be used in such situations.

4. Apparent discordance between the diagnosis of osteoporosis and fracture risk

Case example: A healthy, 56-yr-old woman experienced menopause at age 46 yr and did not take estrogen. She did not have a fracture and has no other risk factors. Her spine and femoral neck T-score values are -0.5 and -2.7 , respectively. Ten-year probabilities by FRAX are 9.9% for major fracture and 2.3% for hip fracture. Most patients who meet the BMD criteria for osteoporosis are at high fracture risk. However, younger postmenopausal women who have osteoporosis but no other risk factors may be at only moderate risk. This possibility was recognized by those who drafted the NOF guidelines, explaining the specific order in which the treatment recommendations are stated. If a patient meets the BMD criteria for osteoporosis, treatment is recommended, and FRAX is not necessary in the guidelines. I think that this is a case example of how knowing the patient's risk for fracture may influence how aggressively the clinician and patient may choose to be about osteoporosis treatment and/or could influence the choice of therapy.

5. Use of FRAX in patients receiving therapy

FRAX is not recommended for use in patients receiving fracture-preventing drugs because the calculator is not equipped to incorporate the reduction in fracture risk because of the treatment. Furthermore, FRAX was developed to help determine who should receive therapy and cannot be used to monitor treatment response. However, some patients began osteoporosis therapy several years ago and would not meet the updated treatment guidelines. Estimates of fracture probability by FRAX can be helpful, I believe, in making decisions about whether to continue or discontinue osteoporosis treatment.

6. Other issues

A. Exclusive use of femoral neck BMD in FRAX

The femoral neck BMD was the only bone density measurement available routinely in all of the databases upon which FRAX was calculated. There is no way to use lumbar spine BMD appropriately in

the FRAX calculator. The NOF guidelines partially solve the concern about patients with low spine BMD whose femoral neck value is not low, for if a patient's lumbar spine BMD value is -2.5 or less, treatment is recommended without the use of FRAX.

B. Exclusion of falls and other known risk factors for fracture from FRAX

The scientific basis for the development of the FRAX calculator required the availability of information about all risk factors incorporated into the model be present in the majority of the databases from which FRAX was calculated. History of falls, measurement of biochemical markers of bone turnover, assessment of vitamin D status, and the use of medicines that affect skeletal health were not available in those databases. As we did before FRAX and the guidelines were available, we must incorporate these additional clinical factors into our decision-making process.

The development of FRAX and the updated NOF guidelines have moved our field forward from BMD-based treatment guidelines. The strategy of basing treatment decisions on absolute fracture risk is a significant advance in our attempt to reduce the burden of fractures related to osteoporosis. The recommendations in the NOF guidelines are sound, scientifically strong, and clinically appropriate. The new guidelines are most useful for answering the question "Which patients who do not have osteoporosis should be treated?" However, no set of guidelines, no matter how strong, can address all the nuances of managing the wide variety of clinical situations that we encounter in our daily practice. Thus, although we recognize the limitations in FRAX and the current guidelines, those limitations do not undermine the usefulness of the tools in clinical practice. The guidelines are a useful platform from which to begin thinking about whether a patient should receive pharmacological therapy for osteoporosis. However, the guidelines are not meant to be rules but must, in many situations, be tempered with appropriate clinical judgment as we make decisions with our patients.

Challenges in the Laboratory Testing for the Management of Postmenopausal Osteoporosis

Paul D. Miller, MD

Although estrogen deficiency is the most common cause of osteoporosis in postmenopausal women, there are many other conditions that may accompany estrogen deficiency and contribute to the impairment of bone strength in this population. Laboratory evaluation to detect any secondary mechanisms leading to derangements in bone metabolism in postmenopausal patients includes tests that may be ordered as a standard of care at the primary care level, and more in-depth tests that are considered in complex patients. The NOF and others have published recommendations for the basic laboratory tests that should be considered to detect secondary causes of osteoporosis (Fig. 2) (63,86,87). The NOF also states that "targeted

- Careful history and physical examination for all
- Basic laboratory testing for all
 - Blood chemistries (calcium, phosphorus, alkaline phosphatase, liver function tests, creatinine, total protein)
 - Complete blood count
 - Serum 25-OH-vitamin D
 - 24-hour urine calcium
 - Serum thyroid stimulating hormone for patients on thyroxine
- Targeted laboratory testing based on individual patient circumstances
 - 24-hour urine calcium [repeated from above as explained in the text]
 - Serum intact parathyroid hormone
 - Serum celiac antibodies
 - Serum bone specific alkaline phosphatase
 - Bone turnover markers (urine, serum)
 - Fibroblast growth factor 23 (FGF 23)
 - Transiliac bone biopsy

Fig. 2. Evaluation for secondary causes of postmenopausal osteoporosis. Adapted from guidelines of the National Osteoporosis Foundation (63) and other recommendations (86,87).

laboratory testing based on individual patients” should be considered.

This review focuses on clinical issues related to 8 targeted laboratory tests (Fig. 2). Although 24-hr urine calcium is often considered to be a component of a “basic” evaluation for osteoporosis, this author has included this important test as “targeted” because it is inconsistently performed and commonly misinterpreted at the primary care level.

Hypercalciuria

The upper limit of normal for a 24-hr urine calcium has been identified as 4.0 mg/kg/d for women and 4.5 mg/kg/d for men (88). How were these upper limits established? The upper limit of the normal laboratory reference range was established in population studies showing that patients exceeding this level were often excreting more calcium than was absorbed, leading to a net loss of total body calcium (89,90), and evidence that hypercalciuric calcium renal stone formers were at a higher risk for fractures and/or loss of BMD than is seen in hypercalciuric nonstone formers (90–96). Because of the difference in skeletal-related outcomes of hypercalciuric patients who form stones and those who do not form stones, it may be helpful to obtain a noncontrast computed tomography scan of the kidneys in some hypercalciuric patients with no history of a clinical renal stone event; the finding of a “silent” radiographic stone may change clinical strategy toward consideration of intervention with a thiazide diuretic.

What is the origin of high urinary calcium? Although it has been suggested that there are 3 possible sources of elevated urinary calcium excretion (bone, renal, or gut) (97), it is exceedingly difficult to discriminate among these sources in clinical practice. Although elevated intact PTH or 1,25-dihydroxyvitamin D levels may suggest a renal “leak” or hyperabsorption from the gastrointestinal tract, clinical management may not differ as long as the clinician is certain that the patient does

not have primary hyperparathyroidism as a cause of an elevated PTH. Several normal serum calcium concentrations (rather than a single isolated normal value) may be necessary to exclude primary hyperparathyroidism. Restriction of calcium intake has been suggested in patients with gastrointestinal hyperabsorption as the mechanism for hypercalciuria. However, without strong evidence that this dietary calcium restriction consistently reduces the risk for renal stone formation, there is the potential negative trade-off of reducing bone mass in others whose source of hypercalciuria is renal or bone (98).

When should a clinician treat hypercalciuria? Should everyone identified with “hypercalciuria” be treated with agents, such as thiazide diuretics, that reduce urinary calcium excretion? In this author’s opinion: “No.” Some patients may have low BMD and hypercalciuria without a causal relationship. Patients with hypercalciuria and no renal stones may never have a clinical event associated with their hypercalciuria and in that regard could be considered to have “healthy” hypercalciuria. Interventions to lower urinary calcium should be aimed at treating those patients who have a negative clinical consequence, such as a renal stone or unexplained fracture, associated with the hypercalciuria (Fig. 3).

- Hypercalcemia
- Renal stone history
- Nephrocalcinosis
- Renal tubular acidosis
- Elevated serum bone specific alkaline phosphatase
- Suspected osteomalacia or metastatic cancer
- Unexplained fractures
- Unexplained bone loss

Fig. 3. Considerations in patients with hypercalciuria. The finding of any of these conditions in association with hypercalciuria may be the cause for further investigation and treatment.

Serum Intact PTH

Serum intact PTH should be ordered in patients with unexplained fragility fractures, unexplained loss of BMD on or off therapy, hypercalcemia, or nephrolithiasis. An elevated PTH can be of primary or secondary origin. Primary hyperparathyroidism is because of autonomous production of PTH by the parathyroid gland, usually resulting in hypercalcemia (99). A less common disorder that chemically may mimic primary hyperparathyroidism is familial hypercalcemia hypocalciuria, which is differentiated from primary hyperparathyroidism by the finding of a low urinary calcium to creatinine clearance (CCr) ratio (usually <0.01) (100,101). Secondary hyperparathyroidism is because of a process causing negative calcium balance, such as: vitamin D deficiency, malabsorption (including asymptomatic celiac disease), hypercalciuria; some medications (e.g., lithium, calcilytic agents), or chronic kidney disease (CKD). In patients with CKD, serum PTH levels may begin to increase when estimated glomerular filtration rate (eGFR) falls to <60 mL/min (102), with further increases as the GFR declines. Because of a recommendation of the National Kidney Foundation, the eGFR is now commonly included in commercial laboratory reports; therefore, it is likely that CKD will be recognized more often, with consideration of secondary hyperparathyroidism receiving broader consideration by clinicians. Management guidelines have recently been updated by the Kidney Disease Improving Global Outcomes (103).

Immunoelectrophoresis

The NOF recommendations for the basic evaluation of secondary causes of osteoporosis do not include serum protein electrophoresis. Yet, both multiple myeloma and monoclonal gamopathy of undetermined significance (MGUS) are not uncommon conditions leading to osteoporosis and fractures. If the immunoelectrophoresis shows a monoclonal protein, then the possibility of MGUS or myeloma must be considered. MGUS has been defined as a monoclonal protein with either no accompanying “M” protein or an “M” protein that is 3 g/dL or less; small amounts of monoclonal light chains in the urine; and the 10% or less amounts of plasma cells in the bone marrow in the absence of bone lesions, anemia, hypercalcemia, or renal failure related to MGUS (104). Osteoporotic fractures are higher than controls in MGUS, independently of its progression to myeloma. This latter observation may be because of an increase in the soluble osteoblast-derived RANK ligand. MGUS patients may later progress to multiple myeloma, with the risk proportional to the magnitude of the “M” protein level; those with a serum “M” protein <1.5 g/dL have a 5% 5-yr risk of multiple myeloma, whereas those with a level >1.5 g/dL have a 12–22% 5-yr risk (105). If there is doubt about the correct diagnosis or progression of disease, referral to an experienced hematologist/oncologist for bone marrow aspiration should be considered.

Celiac Disease

Celiac disease is a very prevalent disorder and is one of the most common secondary causes of osteoporosis. The loss of

small intestinal villa and accompanying pathophysiology leads to selective malabsorption of calcium (and iron) with a progressive negative calcium balance. Celiac disease laboratory detection is best accomplished by measuring serum antibodies to gluten, both the tissue transglutaminase (TT-IgA) antibody and the endomesial antibody (EmA). The sensitivity/specificity of these antibodies in patients with gastrointestinal symptoms is high: 87%/99% for TT-IgA and 87%/97% for EmA (106). However, the sensitivity/specificity of these antibodies in asymptomatic celiac disease is less clear, because there have been few robust studies of small bowel biopsies, the “gold standard” for diagnosis, in asymptomatic patients. The sensitivity/specificity of the antibodies are correlated with the severity of the histological findings—those with “partial” villous atrophy often have normal antibodies. From clinical experience, patients with osteoporosis who have no gastrointestinal symptoms and normal serum antibody levels should be considered for small bowel biopsies when there is a very low 24-hr urine calcium (<50 mg/d), unexplained secondary hyperparathyroidism, 25-hydroxyvitamin D deficiency, unexplained iron deficiency, or higher than expected bone turnover marker levels despite antiresorptive therapy.

Bone-Specific Alkaline Phosphatase

If the total alkaline phosphatase is elevated, then bone-specific alkaline phosphatase (BSAP), a biochemical marker of bone formation, should be ordered. Discussion of BSAP is presented separately from other bone turnover markers (to follow) because the imperative to investigate this commonly occurs when the total alkaline phosphatase elevation is detected as part of a routine panel of blood chemistries. An elevated BSAP may be because of a wide list of possible etiologies (Fig. 4), many of which can be determined clinically (107). If the cause of an elevated BSAP is not clear, a total body nuclear bone scan should be ordered for the detection of asymptomatic Paget’s disease of bone or metastatic cancer to bone. If the bone scan shows a “hot spot,” then an X-ray of that area should be performed. Magnetic resonance imaging (MRI) or positron emission tomography (PET) may be helpful in identifying metastatic cancer or recent fracture.

Bone Turnover Markers

Bone turnover markers are proteins that are derived from either an increase in osteoclast or osteoblast bone cell activity, generally representing the magnitude of bone resorption or formation, respectively. There have been many recent review articles examining their value in managing untreated or treated osteoporotic patients (107–111). Some of the currently available bone turnover markers are listed in Fig. 5. High bone resorption markers in the postmenopausal osteoporotic population are independent predictors of future fracture risk, but are not included in FRAX because they were unavailable when the population studies that validated risk factors for the FRAX model were initiated (112). The NOF recommends a baseline and repeat (3–4 mo after initiation of therapy) bone resorption marker as a method of monitoring for

- Paget's disease of bone
- Metastatic cancer to bone
- Osteomalacia
- Hyperthyroidism
- Hyperparathyroidism
- Recent bone fracture
- Chronic anticonvulsant therapy
- Immobilization
- Calcineurin anti-organ rejection therapy
- Severe vitamin D deficiency (serum 25-hydroxyvitamin D < 8 ng/ml)

Fig. 4. Differential diagnosis of elevated bone-specific alkaline phosphatase.

therapeutic effect with an antiresorptive agent (63). If the resorption marker does not change significantly, query the patient on compliance, proper adherence to dosing instructions, and reassess for secondary causes of poor response. The decline in resorption markers is greater with denosumab than oral bisphosphonates (27,28,113). In addition, on discontinuation of denosumab, the resorption marker, C-telopeptide, returns to normal and even above baseline within 6 mo after discontinuation, but then returns to baseline, an observation that at the current time remains unexplained. Monitoring of a bone resorption marker may provide value in assessing the long-term effects of bisphosphonates on discontinuation (e.g., "drug holiday") to evaluate when the bisphosphonate pharmacological effect might be dissipating (114). At the current time, there is no evidence that bone turnover markers are predictive of osteonecrosis of the jaw (ONJ) or atypical femur fractures (108,115). Bone formation markers increase with the anabolic agent TPTD, although the response is not linear, as observed with the 3-mo increase in the most sensitive anabolic marker, N-terminal propeptide of type 1 collagen propeptide (115,116).

Change of bone turnover marker levels in response to pharmacological therapy occur more rapidly and are greater than changes in BMD; these 2 methods of monitoring are considered complimentary in assessing therapeutic response (117,118). In untreated patients, high bone turnover marker

levels are predictive of a rapid rate of bone loss and greater risk for fracture. The cause of high bone marker levels is not always osteoporosis, but may be seen in other disease states (e.g., myeloma, metastatic cancer) also. If BMD remains stable with treatment, which is an acceptable efficacy endpoint, then a low bone resorption marker with antiresorptive therapy or a high formation marker with osteoanabolic therapy is reassuring evidence for a beneficial effect of therapy. Bone turnover markers may be helpful in the management of some patients with osteoporosis; as with other clinical tests, their interpretation is best made in the context of all other available clinical information.

Fibroblast Growth Factor 23

Fibroblast Growth Factor 23 (FGF 23), a protein secreted by osteocytes, regulates renal phosphate excretion and renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, and may have effects on tissue mineralization (119,120). FGF 23 is increased in patients with CKD, resulting in decreased renal tubular reabsorption of phosphorus even before a rise in PTH levels occurs. In clinical practice, measurement of serum FGF 23 should be considered in a variety of clinical situations (Fig. 6). In patients with oncogenic osteomalacia, an FGF 23-producing tumor induces the clinical syndrome of renal phosphate wasting,

- Bone formation markers (serum)
 - Osteocalcin (OC)
 - Bone specific alkaline phosphatase (BSAP)
 - N-terminal propeptide of type 1 procollagen (P1NP)
- Bone resorption markers (serum, urine), derived from bone collagen or osteoclast (TRAP5b)
 - Pyridinoline, deoxypyridinoline
 - N-telopeptide of type 1 collagen (NTX)
 - C-telopeptide of type 1 collagen (CTX)
 - Tartrate resistant acid phosphatase 5b (TRAP5b)

Fig. 5. Commonly available bone turnover markers.

- Patient with unexplained and persistent hypophosphatemia and renal phosphate wasting
- Patient with unexplained elevated serum bone specific alkaline phosphatase
- Patient with unexplained osteomalacia on bone biopsy
- Patient with normal serum 25-hydroxyvitamin D and low 1,25-dihydroxyvitamin D not in stage 4 or 5 chronic kidney disease
- Patient with humoral hypercalcemia of malignancy
- Patient with oncogenic osteomalacia after removal of tumor to evaluate for response

Fig. 6. Clinical situations when measurement of serum fibroblast growth factor 23 may be helpful.

hypophosphatemia, and osteomalacia; monitoring FGF 23 postoperatively may provide an assessment of the adequacy of tumor ablation.

Bone Biopsy

A double tetracycline-labeled transiliac bone biopsy with quantitative histomorphometry is the only known means of measuring bone dynamic aspects of bone remodeling—bone formation rates, osteoid (matrix) accumulation using well-established histomorphometric reference values (121). Although an operative procedure, a transiliac bone biopsy is associated with a low morbidity when performed by experienced operators. A bone biopsy should be considered in young patients with unexplained fragility fractures and in patients with stages 4–5 CKD having fragility fractures to assess the nature of the bone disease (122,123).

Conclusions

Specific laboratory testing may be necessary for complex patients with osteoporosis. As with all clinical laboratory tests, results must be interpreted in the context of all other available clinical information.

Controversies With Bisphosphonate Therapies

Nelson B. Watts, MD

Bisphosphonates have been available since the 1970s and widely used since the mid-1990s. Combined, alendronate, ibandronate, risedronate, and zoledronic acid are the most commonly prescribed medications for the treatment of osteoporosis. Bisphosphonates can be given intravenously or taken by mouth. About half of the absorbed drug binds to bone surfaces, mostly avidly at sites of active remodeling; the rest is excreted rapidly by the kidneys. Bisphosphonates are released locally from bone in the environment of acid and enzymes beneath active osteoclasts, entering the cell and causing loss of resorptive function and accelerating apoptosis. Bisphosphonates have been shown to prevent bone loss because of aging, estrogen deficiency, and glucocorticoid use, to prevent fractures in women with postmenopausal osteoporosis and women and men with glucocorticoid-induced osteoporosis. Three of the 4 bisphosphonates approved in the United States for use in osteoporosis—alendronate, risedronate, and zoledronate—have evidence for reducing the risk of hip fractures and nonvertebral fractures. It is this “broad-spectrum”

antifracture efficacy that has established bisphosphonates as the agents of choice for most patients with osteoporosis.

Side effects that emerged in clinical trials include esophageal irritation with oral administration and acute phase response in up to one third of patients treated with intravenous (IV) or high-dose oral drug (124–126), but these rarely recur with subsequent administration. Hypocalcemia is rare, usually mild, and not clinically recognized (127).

Ten-year data with alendronate and 8-yr data with risedronate indicated good tolerability and safety; however, uncommon events have been reported with postmarketing surveillance including ONJ, musculoskeletal complaints, atrial fibrillation (AF), esophageal cancer, and atypical fractures. The numbers of events are small and a clear cause-and-effect relationship between these events and bisphosphonate treatment has not been established.

Osteonecrosis of the Jaw

The first report linking bisphosphonate use with ONJ appeared in 2003 (128). High-dose bisphosphonate use for skeletal complications of cancer (approximately 10 times higher than the doses used to treat osteoporosis) was a common factor for all the 36 patients in this series. Subsequent reports (129,130) included patients receiving lower doses of bisphosphonates for treatment of osteoporosis, but well over 90% of reported cases have been in cancer patients. A Task Force of the American Society for Bone and Mineral Research has produced a comprehensive review (131). ONJ has received considerable public exposure in the lay press, resulting in misconceptions among medical and dental professionals and the public regarding the frequency and seriousness of this condition; many patients at high risk of fracture (and low risk of ONJ) decided to stop or not initiate bisphosphonate treatment. No cases of ONJ were identified prospectively in any of the bisphosphonate clinical trials. A retrospective review of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial (PFT) identified 2 cases of ONJ—one in the treatment group and one in the placebo group (132). Epidemiologic surveys suggest the risk of ONJ in oral bisphosphonate users is about 1:160,000. It is likely that there is a causal link between bisphosphonate use and ONJ, but this is not yet clearly established. ONJ has also been reported with denosumab, a nonbisphosphonate potent inhibitor of bone resorption, so oversuppression of bone turnover is the leading hypothesis.

Atrial Fibrillation

AF occurring as serious adverse events was reported more commonly in patients receiving IV zoledronic acid (1.3%) compared with placebo subjects (0.5%) in the HORIZON PFT (132). Cases did not cluster in the days or weeks following the infusion, did not increase with greater exposure, and did not appear to be related to the acute phase reaction or any electrolyte imbalance. No increase in the rate of AF seen in other trials of zoledronic acid or other bisphosphonates. Observational studies have given conflicting results but the majority show no increased risk of AF. After review of data for zoledronic acid and other bisphosphonates, the FDA recommends that physicians not alter their prescribing patterns for bisphosphonates although it continues to monitor postmarketing reports of AF in such patients (133). In view of the above and in the absence of more definitive data, the benefits of treatment for osteoporosis appear to outweigh the risks in the majority of patients from this perspective.

Esophageal Cancer

Although usually well-tolerated, orally administered bisphosphonates are known to cause esophageal irritation. A 2008 letter to the editor of the *New England Journal of Medicine*, written by an employee of the FDA reported 23 cases of esophageal cancer in the United States among patients receiving oral bisphosphonate therapy (134). However, this report did not have information about risk factors for esophageal cancer, the number of patients exposed, or the expected incidence of esophageal cancer in this age group (135). Two observational studies have shown no increased risk of esophageal cancer among patients receiving oral bisphosphonates compared with those who were not (136,137).

Musculoskeletal Pain

Musculoskeletal pain is listed as a possible side effect in the prescribing information for all bisphosphonates. In a 2005 letter to the editor of the *Archives of Internal Medicine*, written by the same FDA employee who reported the above cases of esophageal cancer, she notes that, between 1995 and 2005, the FDA received 117 reports of severe musculoskeletal pain in adults taking bisphosphonates (138). The onset of symptoms did not seem to be related to the duration of treatment. In some patients, symptoms improved promptly after discontinuation of the bisphosphonate, but most patients experienced a gradual or incomplete resolution of symptoms (138). The size of the at-risk population was not provided, nor the incidence of similar complaints among nonexposed subjects. Evidence supporting a causal relationship between musculoskeletal pain and bisphosphonate use is lacking. Musculoskeletal pain is a common problem in the age group being treated with bisphosphonates. The FDA recommends instructing patients to alert their physician if such symptoms occur for consideration of stopping the medication.

Renal Safety

In the doses used for treatment of osteoporosis, bisphosphonates have not been associated with renal adverse events in patients with CCrs above 30–35 mL/min, but the FDA-product labeling states recommends against the use of these medications in patients with a lower CCr because of the lack of experience in such patients (6,139). Retrospective analysis of subjects from the alendronate and risedronate trials suggests no difference in the incidence of adverse events in the treatment groups regardless of renal function, and therapy was as effective in terms of preservation of BMD and reduction of fractures (140,141). It is important to note that none of these patients had intrinsic kidney disease or a CCr < 15 mL/min.

In the IV bisphosphonate studies, both ibandronate and zoledronate appeared to be safe in patients with CCr above 30–35 mL/min if administered correctly (142–145). Transient changes in renal function may occur in postmenopausal women after receiving IV zoledronate but renal function usually returns to baseline in the long term (146). Adverse effects on renal function seem to be primarily related to the peak concentration, which is determined by the dose and the infusion rate.

Bisphosphonates appear to be safe and effective in individuals with modestly reduced renal function. However, there is insufficient data in patients with more severe CKD and in end-stage renal failure, where other forms of metabolic bone disease may be present (147). There are no data regarding the use of bisphosphonates in patients with stage 5 CKD (CCr < 15 mL/min).

“Atypical” Femoral Shaft Fractures

Numerous clinical trials and observational studies show reductions in fractures because of osteoporosis in patients who are compliant with bisphosphonate therapy. Recent reports in the lay press and some in peer-reviewed publications have suggested a link between bisphosphonate use and the development of “atypical” insufficiency fractures in the subtrochanteric region of the femur. This is postulated to be the result of long-term oversuppression of bone turnover leading to impaired bone remodeling, accumulation of microdamage in bone, and increased skeletal fragility (148–151). These fractures are typically associated with prodromal pain in the region of the fracture and are frequently bilateral. Radiographic findings include thick cortices, a straight transverse “chalk stick” fracture with a “spike” on the medial surface (152). Iliac crest biopsies are reported to show severely suppressed bone turnover (149–153), although we have seen a patient with 1 of these fractures whose bone biopsy was completely normal (NB Watts, personal communication). Retrospective studies have also suggested an association between bisphosphonate use and atypical fractures (154–156), although a register-based national cohort study showed that the ratio of classical to atypical hip fractures was identical in the alendronate-treated subjects compared with matched untreated controls (157), suggesting that these atypical

fractures were more likely because of osteoporosis rather than the treatment. A review of trial data with alendronate and zoledronic acid did not suggest an increased risk for atypical fractures (158); however, because of small numbers, an increased risk could not be excluded. A task force of the American Society for Bone and Mineral Research recently released a report on atypical femur fractures (159) and the FDA has added warnings about atypical fractures to the bisphosphonate class label. The number of cases remains small and a causal relationship has not been established.

Drug “Holidays?”

Because bisphosphonates accumulate in bone, they create a reservoir leading to continued release from bone for months or years after treatment is stopped. This may allow for a “drug holiday” after 5–10 yr of treatment. Registration trials for bisphosphonates in the United States included studies of 3- or 4-yr duration. Some of these studies were extended. Two alendronate cohorts have been followed for 10 yr (160,161) and risenedronate cohorts have been followed for 4 (162) and 7 yr (163). No new safety concerns were seen in these extension studies (ONJ, atypical fractures, etc.). Although there has been theoretical concern about possible oversuppression of bone turnover, iliac crest biopsies with up to 10 yr of treatment have not shown oversuppression.

The extension of the alendronate Fracture Intervention Trial (FLEX) enrolled subjects who had approximately 5 yr of alendronate treatment in the Fracture Intervention Trial into a second 5-yr study where some subjects continued alendronate and others were changed to placebo. At the end of the FLEX study, 5-yr fracture rates for new clinical vertebral fractures were reduced by 55% in the subjects who had 10 yr of treatment compared with those who had 5 yr on/5 yr off. Although the original report suggested no differences in radiographic vertebral fractures or nonvertebral fractures, a subsequent analysis indicates that, among subjects with T-scores of -2.5 or below, nonvertebral fracture risk was reduced by 50% (164).

The data suggest that, although there is some residual benefit in terms of fracture reduction for some time after a 3–5-yr course of bisphosphonate therapy, continuing treatment for 10 yr is better for patients at high risk of fracture. Although the risks of bisphosphonate therapy for osteoporosis are small, for patients at low risk of fracture, the risk/benefit ratio may be negative. For patients who were candidates for treatment, after a course of some years, treatment may be stopped for a “drug holiday.” Although there is difficult to find evidence to support the need for or clinical results of a course of treatment followed by a drug holiday (how long to treat, how long the holiday should be, when the holiday should be stopped, effectiveness of treatment after restarting), we believe there is logic to support the following clinical scenarios:

1. Mild risk of fracture: treat with bisphosphonate for 3–5 yr, then stop. The “drug holiday” can be continued until there is a significant loss of BMD (i.e., more than the least significant change as determined by the

testing center) or the patient has a fracture, whichever comes first.

2. Moderate risk of fracture: Treat with bisphosphonate for 5–10 yr, offer a “drug holiday” of 3–5 yr or until there is significant loss of BMD or the patient has a fracture, whichever comes first.
3. High risk of fracture: treat with bisphosphonate for 10 yr, offer a “drug holiday” of 1–2 yr, until there is significant loss of BMD or the patient has a fracture, whichever comes first. A nonbisphosphonate treatment (e.g., raloxifene, TPTD) may be offered during the “holiday” from the bisphosphonate.

It has been suggested that a decrease in BMD or increase in bone turnover marker level might be used to decide when to end a drug holiday, but the risenedronate study showed that fracture risk remained reduced despite what appeared to be unfavorable changes in these parameters (165). Conversely, there is no evidence that, off treatment, fracture risk is reduced if BMD is stable or bone turnover markers are low.

Summary

Bisphosphonates offer a safe and effective treatment to reduce fracture risk, with evidence for “broad spectrum” (i.e., spine, hip, and nonvertebral) fracture risk reduction not shown for other available agents. They can be administered orally (daily, weekly, or monthly) or intravenously (quarterly or yearly). Since their initial introduction in the United States in 1995, questions have been raised about their association with possible side effects (ONJ, musculoskeletal pain, AF, atypical fractures, esophageal cancer) that appear to be rare and may not be causally related. For most patients with osteoporosis, the benefits of treatment outweigh the risks.

Because bisphosphonates are avidly bound to bone, a reservoir of drug accumulates after years of treatment that is gradually released over months or years and appears to result in a lingering antifracture benefit for some time after therapy is stopped. This makes it possible to consider “drug holidays”—time off bisphosphonate therapy (but possibly on another agent)—and then resuming therapy. Although there is no strong science to guide us, we believe that some time off treatment should be offered to most patients on long-term bisphosphonate therapy. The duration of treatment and the length of the “holiday” should be tailored to individual patient circumstances, including the risk of fracture and the binding affinity of the particular bisphosphonate used.

Case Report: A Patient on Long-Term Bisphosphonate Therapy With Bilateral Thigh Pain

Michael Maricic, MD

The patient is a 66-yr-old white female with a history of osteoporosis, polymyositis, kidney stones, psoriasis, gastroesophageal reflux, hypothyroidism, and a history of breast and thyroid cancer. She presented for her yearly bone density

evaluation with a chief complaint of bilateral leg edema and bilateral thigh pain.

She was found to have polymyositis by muscle biopsy in 1970. She was treated first with high-dose corticosteroids and has remained ever since on prednisone 5 mg every other day. She has a diagnosis of severe osteoporosis with multiple vertebral compression fractures, treated with alendronate for over 10 yr.

She was diagnosed with lobular cancer of the right breast 15 yr ago, treated with radical mastectomy, cytoxan, methotrexate, and fluorouracil, followed by tamoxifen for 5 yr. She has been in remission for the past 15 yr. A MRI study of the left breast and right axilla was done 1 mo before this visit for right axillary pain and was negative.

She has had severe idiopathic lymphedema of both legs for the past 6 mo, treated with compression stockings and a daily lymphedema pump. She had a lymphangiogram performed recently, which was negative. She also has diffuse psoriasis on her arms and abdomen but no psoriatic arthritis.

She had thyroid cancer many years ago, which she believes was secondary to radiation of her tonsils as a child. She has had a total of 2 surgeries to remove her thyroid gland and is now on thyroid replacement. It is not known if her parathyroids were removed or damaged at the time of her surgeries.

For the past 6 mo, she has had bilateral midthigh pain, present only on standing and walking, not on sitting. She denies pain waking her up at night. She denied weight loss, fevers, or night sweats. In addition to prednisone and alendronate, her current medications include prednisone levothyroxine, atenolol, triamterene/hydrochlorothiazide, and famotidine. Her physical examination was unremarkable except for severe edema of both legs up to the hips and a psoriatic rash on the abdomen chest and near both elbows. Her motor strength was normal in all extremities and she was able to get out of a chair without pushing off. A DXA scan was performed at the time of the visit, which showed a T-score of -2.6 at L1–L4, -2.3 at the left femoral neck, and -2.0 at the left total hip. There was no significant change since the prior DXA scan 1 yr ago on the same instrument at the same facility.

Because of her bilateral thigh pain, she was sent for radiographs of both femurs (Figs. 7 and 8). These revealed bilateral cortical thickening on the lateral surface of the midshaft of both femurs. Linear lucencies representing insufficiency fractures were seen within both areas of thickening. Because of these findings, the patient was called and told to discontinue her alendronate. She was instructed to get a walker and wheelchair and not to ambulate except to go to the bathroom. An MRI of both femurs was scheduled for 3 d after the initial visit to look for additional insufficiency fractures, with plans for the patient then return for initiation of treatment with TPTD.

Laboratory studies showed a normal complete blood count and normal serum calcium, phosphorus, albumin, alkaline phosphatase, creatinine, and PTH. The serum 25-hydroxyvitamin D was 28.5 ng/mL and the 1,25-dihydroxyvitamin D was 79.7 pg/mL. The MRI of both femurs was consistent with metastatic cancer (Figs. 9 and 10), with abnormal bone



Fig. 7. Bilateral cortical thickening of the lateral aspects of the midfemurs.

marrow signal throughout both femora. There were also findings of diffuse pelvic metastatic disease.

The patient's oncologist was immediately contacted and within the next few days, she had a computed tomography studies of the chest, abdomen, and pelvis, all of which were negative. A technetium bone scan showed increased uptake only in the third to ninth ribs, felt to be traumatic in origin. A PET scan showed inhomogeneous densities at multiple ribs, compatible with old fractures. No other lesions were seen.

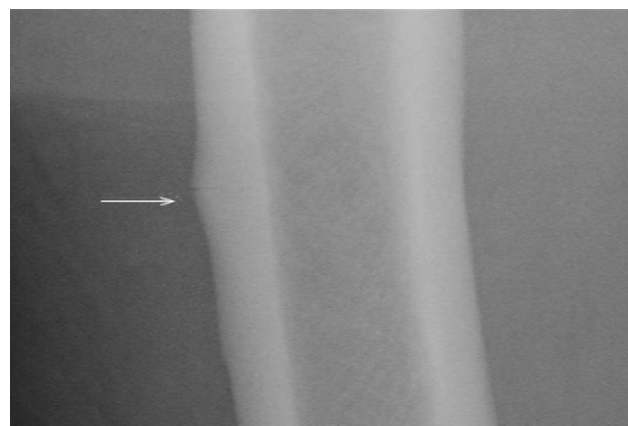


Fig. 8. Insufficiency fracture within area of cortical thickening.

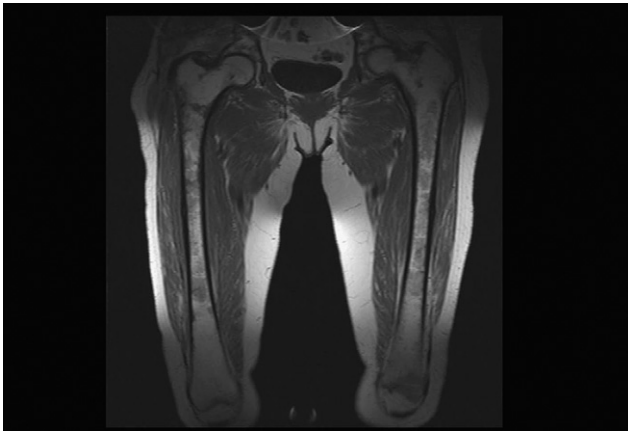


Fig. 9. Magnetic resonance imaging showing inhomogeneous infiltration of diaphyseal marrow by cancer.

A bone marrow biopsy of the femur was subsequently done, revealing lobular breast carcinoma with 60% cellularity; 90% of the cells were estrogen receptor positive and 100% were progesterone receptor positive. The cells were also HER-2-neu+.

The patient was then started on letrozole 2.5 mg per day and zoledronic acid 4 mg once monthly by her oncologist. Bilateral femoral rods were inserted by orthopedics to prevent pathological femoral fractures. Shortly after starting treatment, there was a marked reduction in her breast cancer serum markers carcinoma antigen (CA) 15.3 and CA 27.29, and a significant reduction in her bilateral leg edema.

Discussion

The occurrence of atypical subtrochanteric or diaphyseal femur fractures in patients on long-term bisphosphonates has been extensively discussed and reviewed (166). The incidence and pathophysiology are unknown at this time. The largest studies to date (157,158) suggest no increased incidence in patients on oral bisphosphonates compared with patients

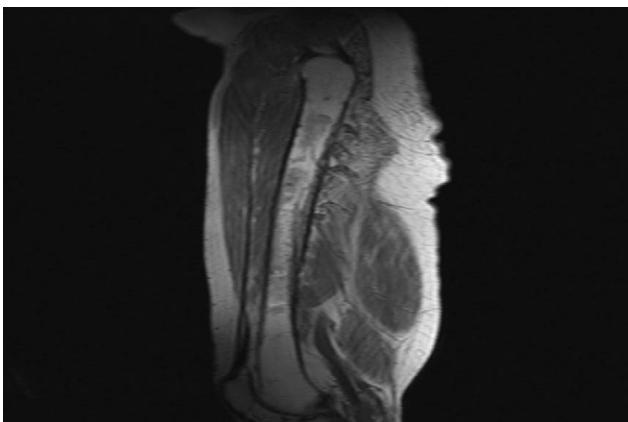


Fig. 10. Magnetic resonance imaging showing diaphyseal marrow infiltration by cancer.

with osteoporosis who have never received bisphosphonates; however, there are significant limitations to these studies, and the definitive answer is not known. It is thought that a mechanism for these fractures may be prolonged suppression or oversuppression of bone turnover, perhaps leading to an inability to repair microfractures, leading to complete pathological fractures (167).

Despite limited knowledge of the incidence and pathophysiology of atypical femur fractures, there is no doubt that these fractures are occurring and are of great concern to patients taking long-term oral bisphosphonates and the physicians treating them. This case illustrates a number of issues and questions concerning the diagnosis and management of these patients.

The most important aspect of diagnosis is to have a high index of suspicion for these fractures in patients taking long-term bisphosphonates who complain of lower extremity thigh pain. The pain is usually midthigh and worse on standing or weight bearing typical of an insufficiency fracture. In such patients, radiographs of the involved areas must be taken immediately, and if the radiograph is negative, further studies with MRI and/or technetium bone scans should be obtained to completely exclude fracture. If a fracture is found, imaging of the contralateral side should be undertaken, because 50–75% of these fractures can be bilateral.

Whether or not to obtain an MRI in a patient where there is radiographic confirmation of an insufficiency fracture to look for further fractures is unknown. An MRI was obtained in this case, leading to the fortuitous discovery of the patient's metastatic cancer. MRI should probably be performed in patients with known cancer or where there is a suspicion of recurrence.

In patients with atypical femur fractures without cancer, it is not clear whether or not elective or prophylactic rodding of the femurs should be undertaken in all cases. Certainly, avoidance of weight bearing as much as possible should be undertaken and an orthopedic consultation should be considered as these insufficiency fractures may suddenly progress to complete pathological fractures.

In general, further treatment with bisphosphonates or other potent antiresorptive agent would be contraindicated. Although TPTD is not FDA approved for the treatment of insufficiency fractures, small case reports suggest that it may be a reasonable option. In this patient with metastatic breast cancer, TPTD was relatively contraindicated and she was started on IV zoledronic acid 4 mg once monthly.

This patient will be observed very carefully for the development of worsening lower extremity pain. Although her femurs are protected by her bilateral femoral rods, she still may be at risk for pelvic and/or tibial insufficiency fractures if her femoral fractures were caused by the bisphosphonates. However, it is felt that monthly IV zoledronic acid is indicated because of her high risk for developing bone pain and fractures because of her metastatic breast cancer. It is not clear whether her femoral insufficiency fractures were caused by the bisphosphonates alone, by her metastatic cancer, or perhaps some combination of the 2.

Another potential problem in giving this patient IV bisphosphonates is that she has had both neck radiation and thyroid surgery. If her parathyroid glands had been damaged or removed during surgery in the past, this could have led to hypocalcemia because of subclinical hypoparathyroidism. This has been reported in similar types of patients in the past, and should be a concern to anyone administering IV bisphosphonates in patients with prior thyroid surgery or radiation (168).

Summary

In a patient receiving long-term oral bisphosphonate therapy who develops lower extremity pain suggestive of an insufficiency fracture, the bisphosphonate should be discontinued and a thorough workup for the cause of the symptoms to be undertaken. If a fracture is found, patient should be taken off all weight bearing and referred to orthopedics for consideration of prophylactic rodding. A complete history and physical and laboratory workup should be undertaken to look for underlying metabolic bone disease and other secondary conditions.

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