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Review Article

Proceedings of the 2017 Santa Fe Bone Symposium: Insights and Emerging Concepts in the Management of Osteoporosis

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Abstract

The 18th Annual Santa Fe Bone Symposium was held on August 4–5, 2017, in Santa Fe, New Mexico, USA. The symposium convenes health-care providers and clinical researchers to present and discuss clinical applications of recent advances in research of skeletal diseases. The program includes lectures, oral presentations by endocrinology fellows, case-based panel discussions, and breakout sessions on topics of interest, with emphasis on participation and interaction of all participants. Topics included the evaluation and treatment of adult survivors with pediatric bone diseases, risk assessment and management of atypical femur fractures, nonpharmacologic strategies in the care of osteoporosis, and skeletal effects of parathyroid hormone with opportunities for therapeutic intervention. Management of skeletal complications of rheumatic diseases was discussed. Insights into sequential and combined use of antiresorptive agents were presented. Individualization of patient treatment decisions when clinical practice guidelines may not be applicable was covered. Challenges and opportunities with osteoporosis drug development were discussed. There was an update on progress of Bone Health TeleECHO (Bone Health Extension for Community Healthcare Outcomes),

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a teleconferencing strategy for sharing knowledge and expanding capacity to deliver best-practice skeletal health care.

Key Words: Anabolic; atypical femur fracture; Bone Health ECHO; parathyroid; pediatric.

Introduction

The Santa Fe Bone Symposium is an annual meeting of scientists, researchers, physicians, and other health-care professionals to share information about the latest advances in basic bone science and clinical research. All discussions are focused on clinical implications and relevance for patient care. The 18th Santa Bone Symposium was held on August 4–5, 2017, in Santa Fe, New Mexico, USA. This is a highly interactive meeting with numerous opportunities for participants to collaborate with colleagues. Plenary presentations are followed by lively discussions of a broad range of issues. There is a session with oral presentations of abstracts by endocrinology fellows, as well as case-based open-topic panel discussions. Progress of Bone Health TeleECHO (Extension for Community Healthcare Outcomes; http://echo.unm.edu/) program was also presented.

Highlights of past Santa Fe Bone Symposia have been presented in peer-reviewed journals *(1–11)*, monographs in print and electronic formats *(12–16)*, online slide presentations *(17–19)*, and audiovisual webcasts. This is a summary of clinical insights from presentations and discussions at the 18th Santa Fe Bone Symposium.

Skeletal Effects of Parathyroid Hormone and Opportunities for Therapeutic Intervention

John P. Bilezikian, MD, PhD(Hon)

Disorders of parathyroid function are simply categorized as parathyroid gland hyperfunction leading to hyperparathyroidism or hypofunction leading to hypoparathyroidism. This presentation focuses on new insights into both disorders and how therapeutic opportunities for the use of parathyroid hormone (PTH) evolved into clinically important options. The premise is that understanding the disorders of PTH excess or deficiency has led to therapeutic opportunities in the management of disorders of calcium homeostasis.

Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a disorder of excessive secretion of PTH from one or more of the 4 parathyroid glands. Hypercalcemia and elevated or inappropriately normal PTH levels are biochemical hallmarks of the disease. PHPT is used to be characterized as a disease of "bones, stones and groans" in the days of Fuller Albright, but over the past 50 years, 2 other clinical phenotypes have been recognized. The most widely recognized form of PHPT is described as asymptomatic PHPT *(20)*. It is discovered in countries where biochemical screening testing is routine and in which the serum calcium is an integral component. These patients do not have the classical clinical features of PHPT. The third and most recent presentation of PHPT is seen in individuals whose serum calcium is virtually always normal but in whom the PTH is consistently elevated, in the absence of a secondary cause *(21)*. Although these 3 clinical presentations of PHPT evolved chronologically over time, with symptomatic disease being the first, it is now appreciated that all 3 forms of PHPT are seen concurrently in the world today. Several factors determine which of these disorders is more likely to be present in a given region of the world. If severe vitamin D deficiency is present, the disease is likely to be symptomatic. In countries where routine biochemical screening is employed, the asymptomatic form predominates. In metabolic bone diseases units where PTH is commonly measured, even if the serum calcium is normal, normocalcemic PHPT is seen. The point is that although chronology defined these 3 presentations of PHPT, over a period of 75 years, these 3 forms are concurrent throughout the world today.

Advances in noninvasive imaging technology, such as high-resolution peripheral computed tomography (HRpQCT), have given insights that were not readily discerned by routine skeletal imaging such as dual-energy X-ray absorptiometry (DXA). By DXA, a characteristic densitometric pattern is recognized in which the lumbar spine, a site of mostly trabecular bone, is relatively well preserved, whereas the distal 1/3 radius, a site of mostly cortical bone, is preferentially reduced *(22)*. Because DXA is a powerful risk factor for fracture, this observation gave rise to the notion that the nonvertebral skeleton would be at greater risk of fracture, whereas the vertebral spine would not. This observation, however, was at odds with epidemiologic observations that demonstrated as early as the late 1990s that in PHPT, both nonvertebral and vertebral fracture risk are increased *(23,24)*. By HRpQCT and trabecular bone score, it is now evident that in PHPT microstructural abnormalities can be demonstrated in trabecular bone and cortical bone *(25–29)*. These and other advances have led to revised guidelines for the management of PHPT *(30)*.

PTH for the Treatment of Osteoporosis

Although it seemed paradoxical that a hormone known for its devastating potential to destroy the skeleton could be used as a therapeutic agent to build bone, the historical roots for this concept are not new but extend to the days of Fuller Albright. However, the insight that low-dose, intermittent administration of PTH could lead to an osteoanabolic effect in rats *(31)* paved the way to the development of teriparatide [PTH *(1–34)*] as an osteoanabolic therapy for osteoporosis *(32)*. The time course of the

teriparatide anabolic effect demonstrates an initial stimulation of bone formation, thought to be a modeling effect, followed by a stimulation of bone resorption, a remodeling effect. The kinetics of these actions gave rise to the notion of an anabolic window of time when the osteoanabolic effects of PTH would be optimized *(33)*. Building on this idea, it seemed possible to develop an analog of PTH that would give an even wider anabolic window and, thus, be even more anabolic. To this end, the PTH-related protein molecule, which shares intense sequence homology with PTH from amino acid residues 1–15, was altered by the insertion of strategically placed residues between positions 22 and 34. The end result of this search was abaloparatide, a drug that has been successfully developed for the treatment of osteoporosis. Used at a daily subcutaneous dose that is 4 times higher than teriparatide (80 μg vs 20 μg), abaloparatide reduces vertebral and nonvertebral fractures with a time course that suggests a rapid effect *(34)*. Moreover, in keeping with the notion of greater anabolic activity, abaloparatide is associated with a lower incidence of hypercalcemia than is teriparatide.

PTH for the Treatment of Hypoparathyroidism

Different from the development of PTH analog to treat osteoporosis, the development of PTH *(1–84)* for the treatment of hypoparathyroidism was more logical. However, until PTH *(1–84)* was successfully developed, hypoparathyroidism was the last classical endocrine deficiency disease for which the missing hormone was not available. One reason for the delay in developing PTH as a therapy for hypoparathyroidism is because it is a rare disease *(35)*. Recent data from the United States place the incidence of hypoparathyroidism at less than 200,000, establishing it unequivocally as an orphan disease *(36)*. The pivotal clinical trial compared daily dosing of recombinant human PTH *(1–84)* [rhPTH *(1–84)*] with placebo in reducing the needs for supplemental calcium and active vitamin D by 50% while maintaining a stable calcium concentration. This primary endpoint was met, along with a major effect of rhPTH *(1–84)*, to eliminate the need for active vitamin D completely and to reduce supplemental calcium needs to 500 mg or less *(37)*, in comparison with the placebo arm. Data on long-term use of rhPTH *(1–84)* in hypoparathyroidism continue to show efficacy and safety *(38,39)*. The acquisition of new data has led to guidelines for the management of hypoparathyroidism *(40,41)*.

Other Therapeutic Applications of PTH

After Extensive Thyroid Surgery

Hypocalcemia due to transient hypoparathyroidism is common after thyroid surgery. It can complicate the immediate postoperative course, including prolongation of hospitalization. Palermo et al recently compared teriparatide (20 μg every 12 hours) with placebo in those whose circulating PTH fell to <10 pg/mL within 4 hours after thyroid surgery *(42)*. In subjects who received PTH "rescue" therapy, the incidence of postoperative hypocalcemia was much lower (23% vs 85%) and hospitalization time was significantly reduced (2 days vs 3 days).

To Accelerate Fracture Healing

Animal studies have amply demonstrated that PTH accelerates fracture healing *(43)*. It has been more difficult to demonstrate that PTH accelerates fracture healing in human subjects. Some data are available with regard to the Colles' fractures and pelvic fractures that suggest that this might be the case *(44,45)*. Further studies are clearly needed to establish this potential clinical application of PTH.

Summary

The history of PTH over the past 80 years has given new insights into the diseases associated with its excess or deficiency as well as therapeutic applications that cover a broad clinical spectrum from osteoporosis to replacement therapy to more speculative applications such as its use after thyroid surgery and to accelerate fracture healing.

Insights Into the Use of Anti-Remodeling and Anabolic Agents for Osteoporosis: Developing a Long-Term Management Plan

Michael R. McClung, MD

Osteoporosis is a chronic condition of skeletal fragility that leads to fractures that can seriously alter physical function and general health. Although we have several classes of medications that significantly reduce the risk of hip and spine fracture, we do not yet have a cure for osteoporosis. Thus, prolonged therapy is required, making it important to develop a long-term management plan *(46)*. This is a review of the evidence for benefits and risks of long-term therapy, the effects of discontinuing bisphosphonate and non-bisphosphonate therapies and new information about efficacy of sequential therapy, and to consider a strategy for long-term management of patients with postmenopausal osteoporosis.

Efficacy of Long-Term Therapy

Bisphosphonates and the receptor activator of nuclear kappa-B ligand inhibitor denosumab are the 2 classes of drugs indicated for both first-line therapy and long-term treatment. Raloxifene reduces vertebral fracture risk and has a role in the treatment of young postmenopausal women at risk of spine fracture, especially if there is concern about breast cancer risk, which can be reduced with raloxifene therapy *(47)*. As patients become more at risk of hip fracture due to growing older or experiencing bone loss, raloxifene is changed to a drug known to reduce the risk of hip fracture. Teriparatide and abaloparatide are especially useful in patients at high risk of spine fracture but are approved only for 18–24 months of use *(48)*.

Bisphosphonates and denosumab are the currently available drugs that significantly reduce the risk of vertebral, hip, and nonspine fracture *(47,49)*. With both drug classes, fracture risk reduction occurs within the first few months of treatment, and the effects on bone mineral density (BMD) and fracture risk persist as long as treatment is administered, with no evidence of resistance to therapy *(50–54)*. There is even a suggestion that the effectiveness of denosumab on reducing nonvertebral fracture risk may improve with long-term therapy *(55)*, consistent with the progressive increase in total hip BMD over 8–10 years of treatment *(54)*, which is in contrast with the plateau in proximal femur BMD after 4–5 years with bisphosphonate therapy *(50,53)*.

In patients with osteoporosis who have received bisphosphonates for at least 1 year, switching to denosumab results in greater increase in hip BMD than is observed if they remain on a bisphosphonate *(56,57)*. Recent evidence, based on a meta-regression of large fracture endpoint trials, suggests that the effects of treatment on reducing hip fracture risk is significantly correlated with the gain in total hip BMD on treatment ($r^2 = 0.52$) *(58)*. In addition, in the extension of the denosumab fracture prevention trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months; FREEDOM), the risk of nonvertebral fracture in individual patients was correlated with the total hip BMD measured while on treatment *(59)*. This is the first evidence that the actual BMD level achieved on treatment predicts current fracture risk, providing justification for considering a BMD target toward which we should strive in all patients with osteoporosis *(60)*.

Safety of Long-Term Therapy

The safety of long-term osteoporosis treatments has been evaluated over 7–10 years in open-label treatment extensions of the original placebo-controlled trials *(50–54)*. The only adverse events of long-term bisphosphonate therapy clearly associated with duration of treatment are subtrochanteric or shaft fractures of the femur with atypical radiographic features *(61)*. From a background incidence of 1–2/100,000 patient-year, the risk of these uncommon fractures increases to about 1 per 1000 patient-year after 8–10 years of therapy. There is very modest evidence that discontinuing the bisphosphonate results in a rapid reduction in the risk of such fractures *(62)*. Very rare femoral fractures with atypical features were observed in the 10-year FREEDOM extension study, but there were too few events to determine whether the risk of these atypical fractures was associated with the duration of therapy *(54)*. In that study, no other adverse events became evident with long-term denosumab therapy that were not observed in the 3-year placebo-controlled trial.

Effects of Discontinuing Treatment

As with most drugs, the skeletal benefits of osteoporosis drugs are lost when treatment is stopped. With both estrogen and denosumab, BMD decreases substantially within the first year of stopping treatment, and protection from fragility fracture is quickly lost *(63–66)*. Switching from estrogen or denosumab to alendronate prevents this rapid bone loss, but the effect of such a strategy on fracture risk has not been evaluated *(67,68)*.

The pharmacology of bisphosphonates is unique. By binding to bone mineral, the drugs remain in the skeleton for many years, and the offset of the inhibition of bone remodeling and the loss of BMD occur gradually. However, partial loss of protection from vertebral and nonvertebral fracture occurs within 3–5 years of stopping these long acting bisphosphonates *(51,52,69,70)*. This gradual offset of protection from fragility fracture, coupled with the possibility of a reduction in the risk of fractures with atypical features upon stopping bisphosphonate therapy, provides the justification for the concept of a "bisphosphonate holiday" *(71)*. A task force of the American Society for Bone and Mineral Research (ASBMR) recently provided clear guidance about managing long-term bisphosphonate therapy *(70)*. For patients remaining at high risk of fracture after 3–5 years of therapy, continuing bisphosphonate treatment or changing to another osteoporosis drug is recommended. This includes patients with a history of hip or spine fracture or of multiple other fragility fractures before or during bisphosphonate therapy, with hip BMD values remaining in osteoporosis range (*T*-score less than or equal to −2.5), or who are at high risk of fracture due to other risk factors. This recommendation essentially suggests continuing treatment in patients who still meet the criteria for being on an osteoporosis drug. For the smaller number of patients who do not meet these criteria for being at high risk, interruption of treatment for 1–2 years can be considered (but not mandated) with plans to restart treatment if indications for therapy return *(46)*.

The concept of a "drug holiday" clearly does not pertain to patients on other osteoporosis drugs such as denosumab *(72)*. Reports of rapid loss of vertebral fracture protection upon stopping denosumab led the US Food and Drug Administration (FDA) to caution prescribers of this drug about this phenomenon and to recommend that switching to another anti-remodeling agent (e.g., a bisphosphonate) be considered if denosumab therapy is discontinued *(73)*.

An algorithm for the long-term management plan used in our clinic is presented in Fig. 1. Bisphosphonates and denosumab are the drugs recommended for long-term use. After 3–5 years of bisphosphonate therapy, patients at low risk are considered for a "bisphosphonate holiday." For patients remaining at high risk of fracture, switching to denosumab is the only strategy to improve the BMD further. Although there is no time limit for denosumab therapy, discontinuation at anytime should be followed by treatment with a bisphosphonate for at least 1–2 years.

Anabolic and Anti-Remodeling Drugs in Sequence

We can take advantage of the marked differences in the mechanisms of action of anabolic and anti-remodeling therapies by using them in sequence. Teriparatide therapy may

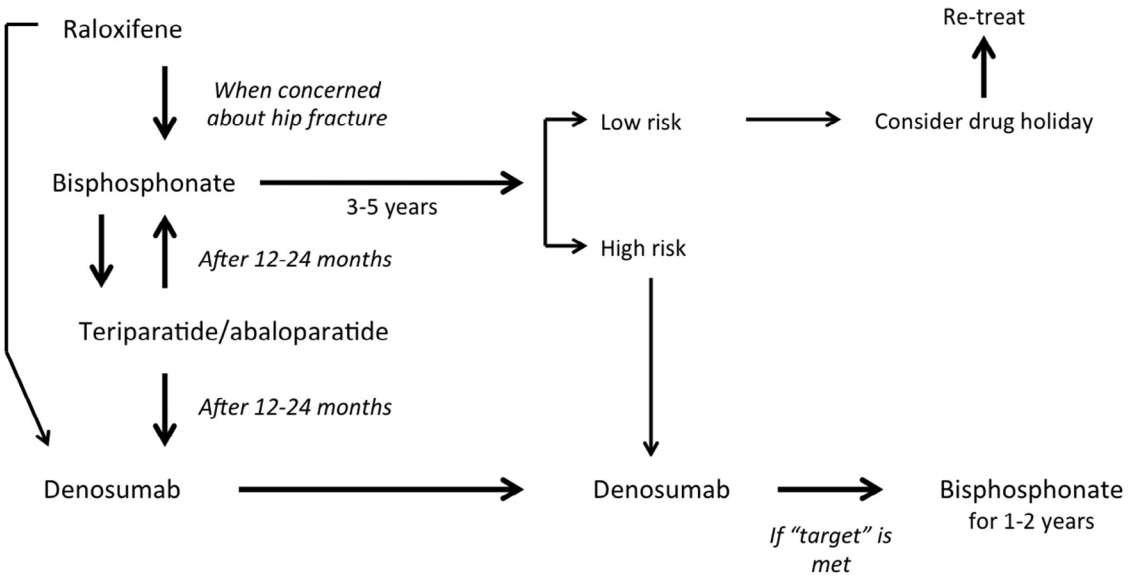

Fig. 1. Algorithm for long-term management of osteoporosis.

be considered in patients who have not achieved the desired gain in BMD or who have experienced fractures while taking an anti-remodeling agent. Additional gains in BMD at both the hip and the spine occur when bisphosphonate-treated patients transition to teriparatide *(74)*. Switching from denosumab to teriparatide results in a further increase in spine BMD but a transient decrease in bone density of the proximal femur *(75)*. If a patient on denosumab therapy is considered a candidate for teriparatide, adding the anabolic agent rather than discontinuing denosumab may be preferable *(76)*.

Following teriparatide with either a bisphosphonate or denosumab results in large additional increases in BMD *(75,76)*. The effectiveness of treatment with an anabolic agent followed by an anti-remodeling drug has been demonstrated in 2 recent phase 3 fracture endpoint studies. The substantial decrease in vertebral and nonvertebral fracture risk observed with abaloparatide was sustained during an additional 6 months of treatment with alendronate *(77)*. In patients who received romosozumab, an inhibitor of sclerostin, for 12 months, switching to denosumab for an additional 12 months resulted in large increases in BMD and additional reduction in vertebral fracture risk compared with patients who received a placebo for 12 months followed by denosumab *(78)*. These results are the first clear evidence that beginning an anabolic agent followed by an anti-remodeling drug is more effective in reducing fracture risk than is starting with the anti-remodeling drug. The primary endpoints in both the abaloparatide and the romosozumab studies included fracture risk reduction with this sequence. These studies provide both evidence and probable regulatory approval for the use of an anabolic drug as first-line treatment in patients with high or imminent risk of fracture to be followed by a potent anti-remodeling agent *(48)*.

Summary

The availability of multiple effective treatments with different mechanisms of action provides us with both the opportunity and the challenge of using the drugs most effectively. Decisions about therapy must be individualized. For patients at high risk of fracture, anabolic therapy, followed by an anti-remodeling agent, should and will become the accepted treatment strategy.

Skeletal Complications of Rheumatic Diseases

John J. Carey, MBBChBAO, MS

Rheumatic diseases commonly affect bone, joints, and other body tissues. Bone changes include new bone formation, osteophytes, painful osteitis and osteosclerosis, tendon, vessel and nerve impingement, bone loss, painful erosions and osteolysis, fractures, and loss of joint function (Table 1). Most medical students and doctors list heart, renal, and liver failure as causes of lower leg swelling, but they do not often think of joint failure or bone failure.

Table 1
Skeletal Complications of Rheumatic Diseases

Loss of bone	Gain of bone	Alteration of bone
Focal erosions	Osteosclerosis	Osteonecrosis
Periarticular bone loss	Osteophytes	Fracture
Generalised bone loss/ osteoporosis	Osteitis	Dysplasia
Osteolysis	Exostosis	Ankylosis
Cysts	Heterotopic ossification	Osteomalacia

Osteoarthritis, the most common disease in the world today, is associated with bone changes before and after the onset of disease symptoms (79,80). These include osteosclerosis, osteophytosis, microcracks, and microfractures (79,80). Early bone changes can be seen on scintigraphy (81) and magnetic resonance imaging (MRI) scans (82), which indicate a more rapidly progressive disease. Pharmacologic approaches for the treatment of skeletal lesions of osteoarthritis have been disappointing, as results from clinical trials of bisphosphonates and strontium have shown little or no benefit (83,84), and studies with glucosamine remain controversial (85,86).

Patients with inflammatory arthritis may suffer skeletal complications that include focal bone erosions and generalized bone loss resulting in joint damage, fractures, and disability (80,87). Treatment with disease-modifying medications can slow or halt the progression of bone loss (87,88), but does not repair it. The rate of progression depends on disease activity (89), yet to be identified patient factors, time to intervention, and the choice of arthritis therapy (87,88,90,91). Although glucocorticoids reduce symptoms and progression of erosions (92), they accelerate generalized bone loss and increase the risk of fracture (93,94). Combinations of disease-modifying therapy are more effective than monotherapy for preventing skeletal complications in most patients (88,90,91,95). The selection of therapeutic agent for treating or preventing adverse skeletal effects of chronic inflammatory diseases is confounded by differential effects of treatment options depending on the outcomes being evaluated (96).

Bone erosions, cartilage loss, and joint damage can result in end-stage joint disease. For many patients, joint replacement therapy is a valuable option to relieve pain. Although widely accepted and of great benefit for many patients, recent evidence shows the risks are not trivial (97); elective knee and hip replacement surgery has the highest mortality rate for noncardiac elective surgery in older men and women (98). Where possible, prevention of arthritis is key. Today, in rheumatology clinic patients, crutches and wheelchairs are uncommon.

Generalized bone loss and loss of joint function, muscle strength, and gait all result in a greater propensity to fracture among populations with inflammatory arthritis (99–101). Patients with rheumatoid arthritis have a higher risk of all types of fracture (99,101), whereas the risk of ankylosing spondylitis is specific to the vertebrae (100). The risk of osteoarthritis is more controversial, but recent evidence suggests a small increase (101). A large case-control study demonstrates patients with all types of rheumatic disease may be at significantly higher risk of fracture (102). Atypical fractures of the hip and other long bones can occur in patients with active chronic rheumatic disease. Strategies for effective control of rheumatoid arthritis include effective disease control, early use of disease-modifying medications, minimizing glucocorticoid use, and recognizing and treating coexisting illnesses (103), which should be applied to all rheumatic diseases.

Effective fracture prevention strategies are similar to patients without arthritis. Assessment of fall risk, bone strength by DXA, diet, exercise, and other modifiable risk factors is essential. Minimizing glucocorticoid use and maximizing disease control are critical as well (103). Finally, osteoporosis medications may be indicated in patients with rheumatic diseases, in particular those receiving oral glucocorticoid therapy (104–106). Experimental evidence suggests osteoporosis therapies may have a role in preventing focal bone erosions, although more evidence is needed before definite conclusions can be reached.

Other skeletal complications of rheumatic diseases are common, but receive less attention, including hyperostosis, osteitis, sclerosis, osteonecrosis, and ankylosis. Osteonecrosis in particular can be very problematic for patients and occurs spontaneously in some patients, but has also been associated with rheumatoid arthritis, vasculitis, systemic lupus erythematosus, and patients on glucocorticoids. Robust evidence for effective treatment is lacking. A strong clinical suspicious is warranted. Patients with osteonecrosis of the jaw need expert dental and oral surgery care, whereas patients with osteonecrosis of the hip, knee, or other sites benefit from rest, non–weight-bearing, and analgesia. Limited evidence suggests more severe cases may benefit from more specific medical or surgical intervention.

Identification of skeletal complications should prompt clinicians to evaluate and treat patients aggressively for their underlying disorder. Studies show management of the primary disease reduces the risk of skeletal complications. Some manifestations require specific therapy. Evidence for treatments that specifically target skeletal complications is emerging but limited to date. Osteoporosis medications appear to reduce the risk of fracture, particularly among patients on glucocorticoid therapy.

Pediatric Bone Disease in Children and Survivors to Adulthood

Catherine M. Gordon, MD, MSc

The foundation of adult bone health is built during the childhood and teenage years (107,108). Peak bone mass is established by the third decade, a compromise of which may be associated with an increased lifetime risk of osteoporosis and fractures (109). Numerous childhood diseases and pharmaceutical interventions can result in bone loss, suboptimal accrual of bone mass, or a combination of both (108). Therefore, clinicians have sought to identify the diagnostic testing that most optimally enables an accurate evaluation of bone health in young children and adolescents. The goal of bone densitometry in pediatrics is to identify individuals at risk of skeletal fragility, to determine the magnitude of compromised bone mass in children with established bone fragility, and to guide and monitor treatment. Although the rationale for densitometry is the same in children as adults, performing and

interpreting bone density results is much more complex in young, growing patients whose bone maps may represent a "moving target" *(108,109)*.

DXA is the most commonly used densitometric technique for children throughout the world, preferred over other modalities because of its speed, precision, safety, low cost, and widespread availability *(108,109)*. However, for a given patient, the clinician must consider the need for a bone density evaluation, including both the duration and the severity of the chronic illness, and/or frequency and nature of fractures. There are significant knowledge gaps in this area, such as the paucity of large representative normative databases from healthy youth, especially for certain ethnic groups, and the need for validated adjustment methods that are needed to interpret densitometric tests in children with abnormal growth or maturity patterns *(110–114)*. Adjustments for height *(110)* and in select cases bone age *(108)* lead to the most accurate interpretations of BMD *Z*-score. There is also debate over the issue of whether it is appropriate to compare the bone density of a child with chronic disease with data obtained from healthy youth; the need for disease-specific reference databases has been questioned.

In 2013, the International Society for Clinical Densitometry convened its second Pediatric Position Development Conference *(115)*. Pediatric experts from around the world were assigned to task forces focused on the following topics: (1) fracture prediction and definition of osteoporosis, (2) DXA assessment in children and adolescents with diseases that may affect the skeleton, (3) DXA interpretation and reporting in children and adolescents, (4) use of QCT and pQCT in children and adolescents, and (5) infant densitometry. The group endorsed the whole body and spine as the preferred skeletal assessment sites for growing children and adolescents. Of note, measurements of the hip are not recommended as the bony landmarks are not well-developed in a child to enable reliable replication of measurements, among other limitations. The lateral distal femur was an alternate site discussed for bone health assessments for children and adolescents with movement disorders, cerebral palsy, and other neuromuscular disorders. Reference data are also available for this site. However, there is not sufficient evidence at this time to support full endorsement of measurements from this skeletal site throughout all clinical centers.

The pediatric bone health field is moving toward alternate modalities to evaluate bone health in children and adolescents. Axial QCT and pQCT have emerged as techniques that warrant careful consideration *(115)*. Studies are underway examining the utility of both standard pQCT and high resolution or HRpQCT, the latter of which affords an assessment of bone microarchitecture. Use of pQCT led to confirmation of the components of a skeletal dysplasia in young children with the rare disease, progeria *(116)*. This bone assessment tool enables investigators to understand changes in both bone density and structure that are present in children with this disease.

Atypical Femur Fracture Update

Richard M. Dell, MD

The following observations are commonly overlooked in discussions of atypical femur fractures (AFFs).

1. AFFs can occur in patients with no exposure to antiresorptive medications such as bisphosphonates and/or denosumab *(117)*.
2. It remains uncertain whether there are causative links between bisphosphonates and other antiresorptive medications and AFFs, although there are now quite a few studies strongly suggesting associative links *(70,117)*.
3. There are about 162 fragility fractures prevented with bisphosphonate treatment for every 1 AFF that occurs *(70)*.
4. The incidence of AFFs appears to decrease when clinicians follow rather simple policies on the use of antiresorptive medications concerning criteria for initiating treatment, duration of treatment, and correct workup, and treatments are done when an incomplete or complete AFF has occurred *(118)*.
5. There is no standardized risk stratification tool for assessing the risk of AFF *(118)*.
6. Genetic testing to assess risk is still lacking, although some recent studies suggest some associations *(119)*.

Over the last 10 years, knowledge concerning AFFs has grown tremendously, but many questions still remain. The most pressing clinical questions deal with balancing ways to reduce the risk of osteoporosis-related fragility fractures yet at the same time decrease the rate of AFFs. What follows are recommendations developed from analysis of over 600 AFFs managed in the Kaiser Permanente Healthcare System and a review of the published literature on AFFs, presented in categories of phases of care.

Initial Decision to Treat With an Anti-Osteoporosis Medication

Essentially every osteoporosis or fracture prevention guideline has a bisphosphonate as the initial drug of choice because of the low cost and low risk of adverse effects. The risk of AFFs can be decreased by carefully selecting patients for treatment based on these accepted guidelines. Bisphosphonates should be used only in patients with risk of fragility fractures above set criteria in each country (Fig. 2).

Bisphosphonate Holiday

After 3–5 years of treatment with a bisphosphonate, fracture risk should be reassessed for every patient to determine subsequent treatment strategies. Depending on the level of risk, continuing the same treatment or switching to anabolic therapy may be appropriate, or a bisphosphonate holiday may be considered *(69)*. No randomized clinical trials are available to determine which patients fit the criteria

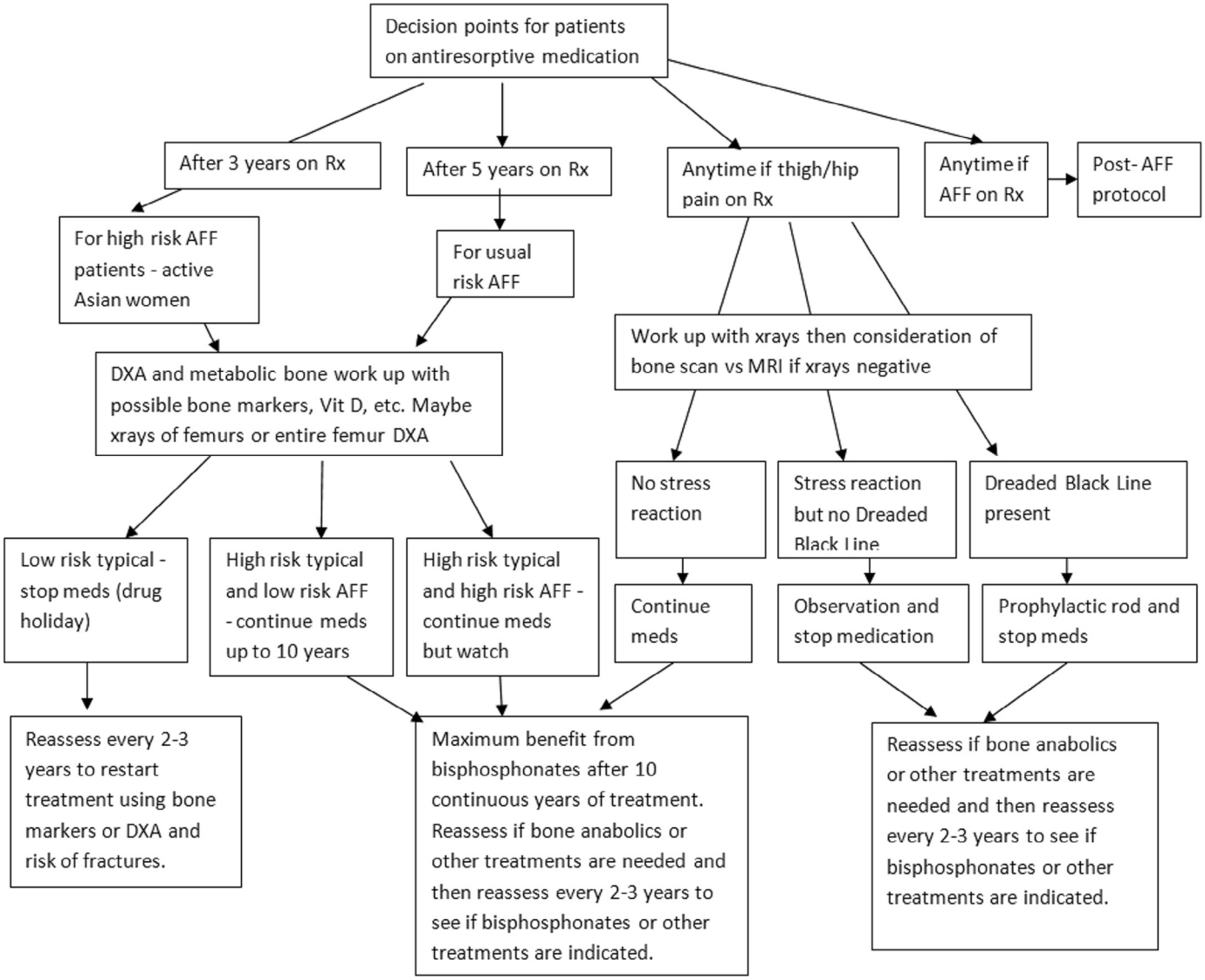

Fig. 2. Decision points for patients on an antiresorptive medication. This figure represents the decision points for patients on an antiresorptive medication such as a bisphosphonate. Patients at high risk of AFF should be evaluated after 3 years on treatment with a DXA scan and metabolic bone workup to see if further treatment is justified. Currently, no AFF risk calculator has been published but groups at high risk of AFF have been identified such as younger Asian women. Regardless of duration of treatment, patients with thigh or hip pain on antiresorptive medication should be considered as possibly having a stress reaction or incomplete AFF and an appropriate workup should be considered. The considerations for a drug holiday and when to restart antiresorptive medication are also outlined and discussed in the paper. AFF, atypical femur fracture; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; Rx, treatment.

for a bisphosphonate holiday, but in general if reassessment suggests a reduction risk below accept treatment thresholds, then the bisphosphonate should be temporarily discontinued.

Thigh or Hip Pain While on Bisphosphonates or Denosumab

If thigh or hip pain occurs while on antiresorptive treatment, then the possibility of a stress reaction or incomplete AFF should be considered. Evaluation usually begins with imaging with conventional radiography followed by MRI and/or bone scan if there is suspicion of a stress fracture or a stress reaction is visible. At this time, laboratory tests have not been found to be helpful in most cases.

Incomplete AFF

If a stress reaction (local and/or generalized lateral cortex thickening in the setting of thigh and/or hip pain) is seen

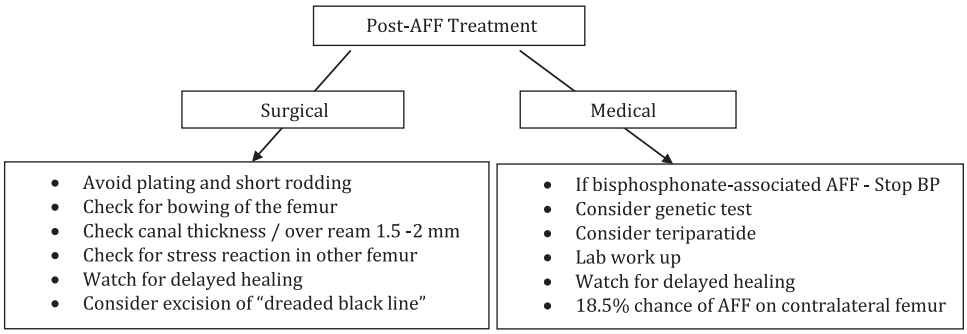

Fig. 3. Proposed guidelines for management of patients on with an atypical femoral fracture, adapted from multiple sources. AFF, atypical femur fracture; BP, bisphosphonate.

with skeletal imaging, then it is important to evaluate for the presence of a lucent line ("dreaded black line"). This finding suggests high risk of progression to a complete fracture *(120)*.

Complete AFF

The workup and management of a complete AFF have been discussed by Donnelly et al *(121)*, as adapted in Fig. 3.

Osteoporosis Treatment After an AFF

Continuing antiresorptive therapy after the index AFF may increase the risk of AFF in the contralateral femur. That risk of a contralateral AFF is 18.5% when the bisphosphonate is continued for less than 1 year but over 50% if the bisphosphonate in continued for 3 years or longer after the index AFF *(122)*.

Treatment of Osteoporosis in Special Circumstances

Paul D. Miller, MD

Not all bones are alike and not all patients with low trauma fractures have osteoporosis. The 5 cases presented here illustrate some of the challenges in managing patients with low trauma fractures when the *T*-score by DXA is greater than –2.5, not meeting the World Health Organization criterion for a densitometric diagnosis of osteoporosis.

Case 1

A 28-year-old Caucasian male with type 1 diabetes since the age of 8 years experiences the acute onset of low back pain without trauma. Vertebral fracture assessment by DXA revealed a Grade 3 vertebral fracture at L1 that was confirmed with lateral spine X-ray. MRI of the spine showed no evidence of malignancy. Evaluation for secondary causes of osteoporosis was unrevealing. BMD testing by DXA showed L2-L4 *T*-score = 1.2, femoral neck *T*-score = 0.4, total hip *T*-score = 0.2, and 1/3 radius *T*-score = 0.2.

It is now well recognized that many patients with fragility fractures have *T*-scores better than –2.5, classified as "osteopenia" or "normal" *(123)*. Why do patients with normal or slightly low BMD have fragility fractures? The answer lies in recognizing that about one-half of the bone strength is due to "bone quality." The microarchitectural arrangement in cancellous bone and the porosity of cortical bone can deteriorate with age or in specific disease states (such as diabetes mellitus), explaining why older bone (aging) and the bone of diabetics have greater risk of fracture independently of BMD. The National Institutes of Health (NIH) original definition of osteoporosis, published in 1991, is still relevant now, as it gives credence to the importance of bone quality in determining bone strength *(124)*.

Bone quality cannot be measured in clinical practice at this time. In research, bone quality can be measured by micro-MRI, HRpQCT, and in part, clinically by trabecular bone score *(125)*. In clinical practice, one has to assume that patients who have low trauma fractures with normal *T*-scores must have some impairment in bone quality and manage them accordingly with agents that improve bone quality, such as anabolic therapy with teriparatide or abaloparatide *(126)*.

Case 2

The patient is a healthy 24-year-old premenopausal woman who recently graduated from college. She has no history of eating disorder and no weight change in the past 5 years. She is physically active, running about 2 miles daily. While doing a daily run, she experience sudden sharp pain in her right thigh. X-rays at a local hospital showed a "stress" fracture in the lateral femoral cortex. While walking 3 days later, she felt a "snap" in her thigh and fell to the ground with her right femur angulated at about 30 degrees. Her evaluation for factors contributing to skeletal fragility was unremarkable except for a very high serum sclerostin level. Her double tetracycline-labeled bone biopsy showed nearly no tetracycline staining, indicating low bone formation. Her femur fracture was treated with placement

of rod and treatment was started with an anabolic agent, teriparatide.

Midshaft femur fractures in otherwise normal and healthy premenopausal women have been carefully studied by Cohen et al *(127)*. The mechanism whereby these patients develop low bone formation and fracture is uncertain but may be related to the elevated sclerostin seen in these individuals.

Case 3

A 45-year-old male has bilateral low trauma midshaft femur fractures treated with bilateral rods. A previous DXA study showed femoral neck and total hip *T*-scores = –4.0. Serum total alkaline phosphatase = 18 IU/L (normal > 40). He was diagnosed with hypophosphatasia (HPP).

HPP in adults is a rare but increasingly genetic metabolic bone disease with clinical manifestations that include atypical femur fractures, recurrent metatarsal fractures, and/or poor dentition *(128)*. Adults with HPP may be mistakenly diagnosed with osteoporosis because of having low *T*-scores. The key to recognizing this disorder is the finding of a low age-adjusted total serum alkaline phosphatase (<40 IU/L). Other conditions have been associated with a low total serum alkaline phosphatase, including antiresorptive therapy for osteoporosis, renal adynamic bone disease, hypoparathyroidism, vitamin D intoxication, celiac disease, cardiac bypass surgery, clofibrate, Cushing syndrome, massive blood transfusions, milk alkali syndrome, vitamin C deficiency, and Wilson disease. However, most of these conditions are already known or easily recognized. The finding of an elevated serum vitamin B6, a substrate for alkaline phosphate, provides clinical confirmation of HPP. Abnormal genetic testing is also confirmatory, although some patients with HPP may have mutations that are not detected. Enzyme replacement therapy with asfotase alfa is now available, and teriparatide has been shown in case reports to help mineralize the bone in these patients *(129)*. The indications for treatment of adult HPP patients and the duration of treatment, if started, are not well established.

Case 4

A 41-year-old Caucasian male with stage 5D chronic kidney disease has been on hemodialysis for 20 years. Over the past 8 years, he sustained a nontraumatic pelvic fracture, wrist fracture, and hip fracture. Metabolic testing show high serum calcium levels in the range of 11.0–11.5 mg/dL, high serum intact PTH = 170–280 pg/mL, and low serum bone-specific alkaline phosphatase = 10 IU/L. He was treated with nasal calcitonin, vitamin D3, calcitriol, and teriparatide, with transiliac bone biopsies performed before and 12 months after starting teriparatide. Bone histomorphometry showed substantial improvement in bone microarchitecture and dynamic parameters of bone remodeling, such as an increase in the mineralizing surface or bone surface, the best indicator by bone biopsy of an increase in osteoblast activity.

Patients with chronic kidney disease who have low bone remodeling may have fractures, low BMD, and serum alkaline phosphatase and intact PTH in the lower quartile of the normal range (PTH < 150 pg/mL), as distinguished from iatrogenic disease due to excessive suppression of PTH by vitamin D analogs or cinacalcet). Although there is no approved therapy for these patients, an anabolic agent seems logical. Because these patients often have elevated serum sclerostin levels, anti-sclerostin therapy, if approved, may offer clinical benefit *(130)*.

Case 5

A 51-year-old female has breast cancer with skeletal metastases treated for 4 years with monthly intravenous zoledronic acid and frequent radiation. She was losing weight, with difficulty eating and in severe distress due to osteonecrosis of the jaw (Fig. 4A). After extensive discussions with her family and other medical specialists, it was decided to treat off-label with teriparatide in an effort to stimulate bone healing in the jaw. Within 6 months of starting teriparatide, her osteonecrosis of the jaw (ONJ) was completely healed (Fig. 4B). ONJ did not recur despite continuing monthly zoledronic acid for 4 more years. She

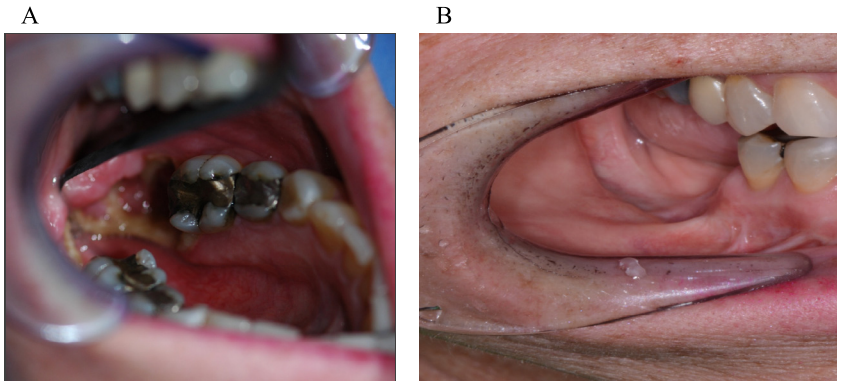

Fig. 4. (**A**) Osteonecrosis of the jaw in a patient with high bisphosphonate therapy for metastatic cancer. (**B**) Healing after 6 months of treatment with teriparatide.

also gained weight and had no further jaw pain until she ultimately succumbed to metastatic cancer.

These cases represent unusual situations where patients appear to have osteoporosis, but do not, or have conditions that may benefit from treatments that are not typically used. Low *T*-scores and/or fragility fractures may represent other metabolic bone diseases that require special expertise to diagnose and treat. Off-label use of pharmacologic agents, after full transparency and discussions with the patient and families, was based on knowledge of the pathogenesis of disease and drug mechanism of action.

Challenges in Osteoporosis Drug Development: Where Do We Go From Here?

Michael Rosenblatt, MD

A series of events and developments, arising both from within and outside the osteoporosis field over the last 2 decades, have converged to create a highly unusual situation in modern medicine. A public health-scale disorder, with relatively effective, safe, and often inexpensive medicines widely available for treatment and prevention *(131–133)*, is increasingly going undiagnosed and untreated *(134)*. The impact on patients and the US population are substantial. At the same time, comparative success in other fields of medicine leads to declining effort and investment to invent new drugs for osteoporosis by the research-driven biopharmaceutical industry. All this is occurring at a time when the population is increasing both in numbers and in age: the number of women and men with osteoporosis is growing. In the period 2000–2011, more than 5 million women over the age of 55 were hospitalized for osteoporotic fractures; this number is greater than the number hospitalized for stroke, myocardial infarction, or breast cancer.

Just as statins (combined with other health measures) decreased cardiovascular mortality in the United States by 40% over the last 3 decades, the introduction of bisphosphonates has been accompanied by a 40% decline in osteoporotic fractures in the United States. By several parameters of comparison, bisphosphonates are to osteoporosis what statins are to coronary artery disease. It is not surprising that the bisphosphonates are considered by physicians to be among the most transformative drugs of the last 25 years *(135)*.

So why is there a crisis in clinical practice around osteoporosis *(136)*? There are several reasons:

1. The consequences of osteoporosis, namely, fractures and resulting morbidity and mortality are not well understood by patients and physicians. There is no simple message to them, such as "broken bones and "nursing homes."
2. Osteoporosis drugs are associated with rare, but serious side effects, such as ONJ and AFF. Although benefit-risk ratio is clearly favorable for treatment with osteoporosis drugs *(137)*, this has not been successfully communicated to patients and physicians.
3. Because the putative side effects are fractures, and patients are placed on osteoporosis therapy specifically to avoid fractures, the media have focused on this ironic situation *(138)*. As a result, many patients who should be treated are too fearful to take prescribed drugs.
4. Other diseases, such as hypertension, diabetes, or lipid disorders, are diagnosed and monitored by a single simple measurement such as blood pressure, hemoglobin A1c (HgbA1c), or low-density lipoprotein cholesterol. For osteoporosis, primary care doctors are uncertain about: How to make the diagnosis of osteoporosis? Who and when to treat? Treat to what goal? And treat for how long? BMD is not universally accepted as a predictive measure. A fracture risk assessment algorithm, such as FRAX, may be more highly predictive of risk, but it is not as simple as a single measurement.
5. Osteoporosis diagnosis and treatment is not part of "quality of care" metrics in many health systems.
6. BMD testing has experienced a major decline in reimbursement.
7. Promotion of osteoporosis drugs to physicians and direct-to-consumer advertising by pharmaceutical companies has ceased.
8. Insurance companies do not actively promote "prevention" because most fractures occur after patients have "graduated" from their plan to Medicare. The result is that prescriptions for osteoporosis drugs have fallen by 50% since 2008 and the previously steady decline in fractures has now leveled off (are we heading toward a reversal, namely, an increase in fractures in the US population?). Treatment rates in the United States are abysmal: in 2003, only 15% of patients who experienced a hip fracture were placed on a bisphosphonate; in 2013, only 3% were placed on a bisphosphonate. Try to imagine US healthcare if these were the treatment rates for high blood pressure, elevated cholesterol, or diabetes.

The problem is compounded by recommendations from the FDA to discontinue treatment with bisphosphonates after 5 years. However, evidence of a benefit to discontinuation is lacking and guidance to practitioners on what to do if BMD declines is absent. Compounding the problem has been the view of experts that osteoporosis is overtreated in the United States because too many women with osteopenia received prescriptions in the past. This may be an issue, but the overriding public health problem is undertreatment of the "at risk" population, not overtreatment. The experts have contributed as well by focusing the field on rare putative side effects of drugs without communicating simultaneously favorable benefit-risk ratio.

The professional societies in our field have contributed inadvertently. They have not effectively explained the

seriousness of osteoporosis outside of the "bone" community. Also, their inexperience in dealing with the media led to failure to respond quickly and definitively to reporting about AFF. Instead, the ASPMR issued a scholarly 28-page statement that a task force took months to prepare. This is in contrast with handling of similar situations by the American Heart Association and American Diabetes Association.

How does the current context impact decision-making by biopharmaceutical companies? Inventing a drug is the longest, most expensive, most risky, most regulated process of product development. Factors that inhibit the undertaking of research and development in osteoporosis include:

1. Diagnostic criteria and approach to treatment are not clear or widely accepted.
2. The goal of treatment is ill-defined.
3. The presence of effective inexpensive oral medications sets the bar high for entry of novel therapies.
4. Clinical trials in the osteoporosis field are long, involve many patients to demonstrate safety and efficacy, pose patient recruitment challenges, are very expensive, and complex.
5. Fracture outcomes are required; a surrogate such as BMD is not acceptable.
6. Although the market is growing in theory, in reality, it is shrinking.
7. Consolidation of the industry through mergers and acquisitions has led to fewer large companies that can support an osteoporosis research and development initiative and franchise.
8. There is an "opportunity cost" to working in the bone field vs other fields (oncology, hepatitis C, orphan diseases), where the regulatory requirements are less daunting and the commercial opportunity is greater.

For these reasons, following the approval of abaloparatide and the possible approval of romosozumab, it is unlikely that any new drug for osteoporosis will be developed for another 10–20 years. To our knowledge, there are no major research and development efforts underway in osteoporosis.

The hope for new and better drugs in the future comes from genomics and precision medicine. These disciplines promise to identify subpopulations of patients for whom targeted agents might have greater efficacy and fewer side effects. In the meantime, what can we do to impact clinical practice? Here are a few suggestions:

1. Mobilize experts and professional societies to rectify the current situation regarding understanding of osteoporosis by patients and physicians and fear of medicines used for treatment of osteoporosis.
2. Work with patient advocacy groups.
3. Educate the media.
4. Professional societies should anticipate and prepare for incorrect or misleading media reports by having "off-the-shelf" responses ready to distribute.
5. Develop clear criteria for diagnosis that are "primary care-friendly." A single measure, such as BMD, would be ideal.
6. Develop clear goals for treatment.
7. Provide fracture liaison services.

There is hope, but we have a deep hole to dig out of.

Nonpharmacologic Therapy for Osteoporosis: Helpful or Harmful?

Steven T. Harris, MD

Since the mid-1990s, there has been great interest in the pharmacologic management of osteoporosis, both in prevention and in treatment. Accompanying that, however, has been a focus on nonpharmacologic options, often with the hope that such nonpharmacologic options would prove effective substitutes for drug management. Although diverse options have shown interesting effects on surrogate markers such as BMD or the biochemical markers of bone turnover, there is very little evidence that such alternatives reduce fracture risk, or even meaningfully impact the rate of bone loss over time in patients over age 50 years. It is the intent of this brief review to touch on selected aspects of nonpharmacologic management.

In assessing the impact of various interventions on osteoporosis, it is important to keep in mind that the ultimate metric by which intervention is judged is the prevention of fracture not the impact on surrogate markers. The assessment of every intervention, whether pharmacologic or nonpharmacologic, depends on an artful balancing of risks and benefits. The risk of any intervention can include economic cost, nuisance value, and possible adverse consequences ("side effects") of that intervention. In general, pharmacologic treatment options have proven effective in reducing fracture risk, with a relatively low risk of major complications such as osteonecrosis of the jaw and atypical femoral fracture. In the public forum, however, discussion of those relatively rare problems has dominated, leading many patients to seek nonpharmacologic options. Taken as a whole, those nonpharmacologic options are relatively inexpensive, with probable modest benefit, but the risks of those options are typically not explicitly discussed. Under any circumstance, nonpharmacologic options really should not be viewed as competitors to pharmacologic options, but rather complements. Fall prevention and the optimization of lifestyle, diet, and exercise should reasonably be considered adjuncts to any drug therapy of osteoporosis that is considered.

The latest iteration of the Clinician's Guide from the National Osteoporosis Foundation reasonably states: "Recommend regular weight-bearing and muscle-strengthening exercise to improve agility, strength, posture, and balance; maintain or improve bone strength; and reduce the risk of falls and fractures *(139)*." The guide goes on to highlight uncertainty, however, "Conclusions and remaining questions. . .What are the precise components (type, intensity,

duration, frequency) of an effective exercise program for osteoporosis prevention and treatment?"

In addressing the somewhat contentious issue of calcium and vitamin D supplementation, the guide suggests, "Advise on a diet that includes adequate amounts of total calcium intake (1000 mg/day for men 50–70, 1200 mg/day for women 51 and older and men 71 and older), incorporating dietary supplements if diet is insufficient." It also suggests, "Advise on vitamin D intake (800–1000 IU/day) including supplements if necessary for individuals 50 and older."

Long-term studies of isolated dietary constituents are challenging because free-living humans do not in fact maintain constant diets over time. Adding or subtracting a single dietary constituent in isolation can be challenging, and it is essentially impossible in long-term studies to distinguish between association and causation. Populations that differ in consumption of a particular dietary element may well differ in other respects that cannot be fully corrected by adjustment for known confounders.

The dietary supplement industry in the United States is a multibillion-dollar industry and operates under the auspices of the Dietary Supplement Health and Education Act of 1994 ("DSHEA") *(140)*. That legislation dictates that labeling for a supplement includes: ". . .prominently displayed and in boldface type, the following: 'This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease. . ..' A statement under this subparagraph may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases."

Dietary Protein

The role of dietary protein in bone health is complex. Sufficient dietary protein is necessary for the achievement of peak bone mass and for the maintenance of musculoskeletal health, including postfracture recovery *(141)*. It is also true, however, that the metabolism of sulfur-containing amino acids—particularly rich in animal protein—generates an "acid load" that must be excreted or buffered or neutralized in some way. The exposure of bone to an acid load enhances bone resorption and the liberation of base. Physiologically, the administration of an absorbable base such as potassium bicarbonate should then prove beneficial. Providing potassium bicarbonate (60–120 mmol per day) for 18 days in postmenopausal women on a high-protein diet largely neutralized endogenous acid production, improved calcium and phosphorus balance, and decreased markers of bone remodeling *(142)*. Despite these encouraging short-term observations, larger outpatient clinical trials with absorbable base have shown no consistent, clinically meaningful benefit on bone density. Generally, however, a diet with sufficient protein but rich in fresh fruits and vegetables is likely to be better for bone health than a diet centered on animal protein.

Caffeine

In the Framingham Study, consumption of at least 2.5 "units" of coffee each day increased the risk of hip fracture over 12 years. The authors cautioned, however, "Since caffeine use may be associated with other behaviors that are, themselves, risk factors for fracture, the association may be indirect *(143)*." Caffeine increases urinary and fecal calcium, producing a negative calcium balance—at least with a low calcium intake *(144)*. Calcium balance and epidemiologic data suggest, however, that a negative effect of caffeine can probably be offset by increasing calcium intake by 40 mg per 6-oz cup of coffee *(144,145)*.

Phytoestrogens

The term "phytoestrogen" is used to describe more than 20 compounds found in hundreds of plants, including herbs, grains, and fruits. Those compounds, including isoflavones, lignans and coumestans, exhibit estrogen-like effects in certain test systems. The biological relevance of phytoestrogens is largely supported by the prevention of bone loss in the ovariectomized rodent model, but is also supported by epidemiologic data showing that fracture rates tend to be lower in those populations in which dietary phytoestrogen intake is high, but there are multiple confounding variables. Small human studies have shown variable effects on markers of bone remodeling and BMD, and the studies have been too small to examine fracture rates as an outcome.

In addressing the role of isoflavones in particular, the North American Menopause Society offered the following position statement: "Clinical trial data do not support the use of isoflavones (a class of phytoestrogens found in rich supply in soybeans and soy products as well as in red clover) to prevent or treat osteoporosis. Although some data suggest that isoflavones may favorably affect bone health, accumulating data from several more recent studies indicate a lack of bone benefits from isoflavones, regardless of the source (i.e., extracted from red clover or soy or consumed in soy foods). Ipriflavone, a synthetic isoflavone available without a prescription in the United States and Canada, has not demonstrated a positive effect on bone density, bone turnover markers, or fracture risk in women with osteoporosis *(146)*."

Medical Food

The term medical food, as defined in Section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee [b] *(3)*) is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation *(147)*." The manufacturer of 1 medical food, Fosteum Plus, which is available by prescription, states

that, "The ingredients in Fosteum Plus are Generally Recognized As Safe (GRAS). This is the statutory safety standard that the US Food and Drug Administration (FDA) require [*sic*] of all ingredients added to food products. The standard for an ingredient to achieve GRAS status requires technical demonstration of nontoxicity and safety, general recognition of safety through widespread usage and agreement of that safety by experts in the field." Fosteum Plus is a proprietary mixture of calcium, phosphorus, the phytoestrogen genistein, zinc, vitamin K, and vitamin D.

Vitamin K

Vitamin K1 (phylloquinone) is the major dietary form of vitamin K and is found in plants and green vegetables. Vitamin K2 (menaquinone), in contrast, is produced normally by gut bacteria; MK-4 and MK-7 are distinguished by the length of the side chain.

Vitamin K promotes the carboxylation of osteocalcin, promotes osteoblast-to-osteocyte transition, and limits osteoclastogenesis. Serum vitamin K levels are positively associated with BMD and negatively associated with fracture risk *(148)*. Despite the described biology, the long-term use of a vitamin K antagonist such as warfarin has not consistently been linked to a change in BMD or fracture risk. MK-4 is approved for the treatment of osteoporosis in Japan, but in general, studies of supplementation with K1, K2, MK-4, and MK-7 have shown inconsistent results vis-à-vis biochemical markers, BMD, and fracture risk. Likely confounders in those studies include supplement formulation and dose, as well as patient-related variables such as age, gender, ethnicity, baseline BMD and vitamin K status.

Magnesium

Roughly 60% of the body's magnesium is in the skeleton, and that magnesium is important for normal crystal formation during bone mineralization. Magnesium deficiency leads to impaired PTH secretion—and end-organ resistance to the effects of PTH. Magnesium is found in green vegetables, nuts, seeds, unprocessed grains, and some legumes, but dietary magnesium intake is often less than the Recommended Dietary Allowance. Risk factors for magnesium deficiency include alcoholism, gastrointestinal malabsorption, and the use of various medications, including diuretics, antacids, proton pump inhibitors, and the aminoglycoside antibiotics *(149)*. High magnesium intake may adversely affect crystal formation and bone mineralization. In a large epidemiologic study, the Women's Health Initiative Observational Study, women in the highest quintile of magnesium intakes (>422.5 mg/day) had hip and total BMD 2%–3% higher than women in the lowest quintile (<206.5 mg/day). Nevertheless, total fractures and hip fractures did not differ between the 2 groups. Lower arm and wrist fractures were increased in women with the highest intake, but those women were more active and had more falls *(150)*. Magnesium is a laxative, which can prove problematic. There is no convincing evidence that magnesium supplements reduce fracture risk, or that magnesium must be administered in a critical ratio to calcium in a supplement to optimize bone health.

Strontium Ranelate

The oral administration of strontium, in the form of strontium ranelate, increases BMD due in large part to the strontium itself being incorporated into bone. Studies have demonstrated small changes in biochemical markers of bone turnover—an increase in bone formation and a decrease in bone resorption—but without histologic evidence for an anabolic, bone building effect. Those same studies demonstrated a reduction in vertebral and nonvertebral fracture risk in postmenopausal women with osteoporosis, leading to regulatory approval in Europe. No strontium preparation has been approved for administration in the United States, but various strontium salts are available as dietary supplements, unsupported by any clinical studies showing either efficacy or safety *(151)*.

Boron

There is no Recommended Daily Allowance for boron. Raisins and nuts are particularly rich dietary sources of boron, and a high-boron diet would include approx 3.25 mg daily. A low-boron diet would include roughly 0.25 mg daily. In a clinical study, 12 postmenopausal women between the ages of 48 and 82 were fed a low-boron diet for 119 days. Boron supplementation was then given at a daily dose of 3 mg. That supplementation decreased urinary calcium excretion, raised total serum estradiol from 15.5 to 38.0 pg/mL, and raised serum testosterone from 3.8 to 6.5 ng/dL *(152)*. In rats, boron deprivation impaired cortical bone strength and decreased trabecular bone volume *(153)*. Boron seems to have interesting effects on bone, but it is not clear with what frequency biologically relevant boron deficiency is present in a population likely to use supplementation. There are no studies showing the impact of boron supplementation on the clinically relevant human endpoint of fracture (or even clinically interesting surrogate endpoints). If one were to use a boron supplement, 3 mg/day would be a reasonable choice *(154)*.

Exercise

Weight-bearing and muscle-strengthening exercises are often advocated to increase BMD. The maximum effect of exercise on BMD is seen in children, but the effect on density in mature adults seems to be on the order of 1%–2%. That effect is both site-specific, the density increases only in the part of the skeleton being mechanically loaded, and transient; the density decreases again if the exercise regimen in interrupted. Even though the effect of exercise on bone density is small, regular exercise reduces the

loss of muscle mass with aging and may reduce the risk of falling by improving muscle strength and balance. Although certain commercial exercise devices have been promoted as uniquely beneficial, there are no controlled clinical trials demonstrating that such devices have unique effects on BMD or fracture risk.

Summary

Taken as a whole, nonpharmacologic options seem to be relatively inexpensive, and modestly effective, but the risks and benefits of the options are not typically explicitly discussed. Exercise in particular has other health benefits, although the same is likely to be true for diet optimization; in adults, the effect of exercise on BMD *per se* is quite small. Fall prevention and the optimization of lifestyle, diet, and exercise should be viewed as important adjuncts to the treatment of osteoporotic patients. There is no convincing evidence, however, that such adjuncts will prevent all bone loss, or adequately substitute for pharmacologic treatment.

Bone Health TeleECHO

E. Michael Lewiecki, MD

There are not enough osteoporosis specialists to care for the patients who need them. The osteoporosis treatment gap is large and worsening *(155)*. The crisis in osteoporosis care *(136)* has generated a call to action for measures to reduce the treatment gap *(156)*. One approach out of many that have been suggested is to use teleconferencing technologies to mentor interested health-care providers in underserved communities to achieve advanced levels of knowledge about skeletal diseases. Bone Health TeleECHO has been conducting weekly teleconferences since October 2015, linking osteoporosis experts and learners to share knowledge through discussion of real but de-identified patient cases. This is much the same learning method as occurs in medical training programs, but is often lost in real-world medical practice settings. Developed through a collaboration of the ECHO Institute at the University of New Mexico Health Sciences Center and the Osteoporosis Foundation of New Mexico, Bone Health TeleECHO offers relief of professional isolation and the opportunity for local providers to eventually develop centers of excellence for bone care. Patients benefit by receiving better care, closer to home, with greater convenience and lower cost *(157,158)*. By moving knowledge rather than patients, ECHO learners (e.g., physicians, nurse practitioners, physician assistants) can provide better care closer to home at greater convenience and lower cost than referral to a specialty center. The ECHO model of learning aims to reduce health disparities and expand capacity to deliver best-practice osteoporosis care. During the first 21 months of Bone Health TeleECHO, 263 health-care professionals registered to participate, representing a wide range of medical specialties and geographic diversity. Favorable outcomes were demonstrated with self-efficacy questionnaires. Other Bone Health TeleECHO programs have been launched and more are expected to follow.

References

1. Lewiecki EM. 2006 Proceedings of the Santa Fe Bone Symposium 2006. Womens Health 2:825–828.
2. Lewiecki EM, Bilezikian JP, Cooper C, et al. 2008 Proceedings of the Eighth Annual Santa Fe Bone Symposium, August 3–4, 2007. J Clin Densitom 11:313–324.
3. Lewiecki EM, Baim S, Bilezikian JP, et al. 2009 2008 Santa Fe Bone Symposium: update on osteoporosis. J Clin Densitom 12:135–157.
4. Lewiecki EM, Bilezikian JP, Laster AJ, et al. 2010 2009 Santa Fe Bone Symposium. J Clin Densitom 13:1–9.
5. Lewiecki EM, Bilezikian JP, Khosla S, et al. 2010 Osteoporosis update from the 2010 Santa Fe Bone Symposium. J Clin Densitom 14:1–21.
6. Lewiecki EM, Bilezikian JP, Jankowski LG, et al. 2012 Proceedings of the 2011 Santa Fe Bone Symposium. J Clin Densitom 15:1–20.
7. Lewiecki EM, Adler RA, Bilezikian JP, et al. 2013 Osteoporosis update from the 2012 Santa Fe Bone Symposium. J Clin Densitom 16:584–600.
8. Lewiecki EM, Bilezikian JP, Bonewald L, et al. 2014 Osteoporosis update: proceedings of the 2013 Santa Fe Bone Symposium. J Clin Densitom 17:330–343.
9. Lewiecki EM, Bilezikian JP, Binkley N, et al. 2015 Update on osteoporosis from the 2014 Santa Fe Bone Symposium. Endocr Res 40:106–119.
10. Lewiecki EM, Baron R, Bilezikian JP, et al. 2016 Proceedings of the 2015 Santa Fe Bone Symposium: clinical applications of scientific advances in osteoporosis and metabolic bone disease. J Clin Densitom 19:102–116.
11. Lewiecki EM, Bilezikian JP, Bukata SV, et al. 2017 Proceedings of the 2016 Santa Fe Bone Symposium: new concepts in the management of osteoporosis and metabolic bone diseases. J Clin Densitom 20:134–152.
12. Lewiecki EM, Bilezikian JP, Miller PD, et al. 2009 Highlights from the 2009 Santa Fe Bone Symposium. Available at: http://www.2009santafebonesymposium.com/downloads/2009-Santa-Fe-Bone-Newsletter.pdf. Accessed: August 25, 2011.
13. Lewiecki EM, Bilezikian JP, Khosla S, et al. 2010 Highlights from the 2010 Santa Fe Bone Symposium. Available at: http://santafebonesymposium.squarespace.com/storage/assets/2010_Santa_Fe_Bone.pdf. Accessed: August 25, 2011.
14. Lewiecki EM, Bilezikian JP, McCloskey EV, et al. 2011 Highlights of the 2011 Santa Fe Bone Symposium. Available at: http://www.2011santafebonesymposium.com/2011-Santa-Fe-Bone-Newsletter.pdf. Accessed: January 19, 2012.
15. Lewiecki EM, Bilezikian JP, Bonewald LF, et al. 2013 2013 Santa Fe Bone Symposium Highlights. Available at: http://2013santafebonesymposium.com. Accessed: September 6, 2015.
16. Lewiecki EM, Bilezikian JP, Binkley N, et al. 2014 2014 Santa Fe Bone Symposium Highlights. Available at: http://www.2014santafebonesymposium.com/. Accessed: September 6, 2015.
17. Lewiecki EM, Bilezikian JP, Khosla S, et al. 2010 2010 Santa Fe Bone Symposium. Available at: http://www.2010santafebonesymposium.com/. Accessed: August 25, 2011.

18. Lewiecki EM, Bilezikian JP, Miller PD, et al. 2009 2009 Santa Fe Bone Symposium. Available at: http://www.2009santafebonesymposium.com/. Accessed: August 25, 2011.
19. Lewiecki EM, Bilezikian JP, Jankowski LG, et al. 2011 2011 Santa Fe Bone Symposium Highlights. Available at: http://www.2011santafebonesymposium.com/presentations.html. Accessed: September 15, 2012.
20. Silverberg SJ, Clarke BL, Peacock M, et al. 2014 Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 99:3580–3594.
21. Cusano NE, Silverberg SJ, Bilezikian JP. 2015 Normocalcemic PHPT. In: The Parathyroids. Bilezikian JP, ed. San Diego, CA: Elsevier, 331–339.
22. Silverberg SJ, Shane E, de la Cruz L, et al. 1989 Skeletal disease in primary hyperparathyroidism. J Bone Miner Res 4:283–291.
23. Khosla S, Melton LJ III, Wermers RA, et al. 1999 Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Miner Res 14:1700–1707.
24. Vignali E, Viccica G, Diacinti D, et al. 2009 Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab 94:2306–2312.
25. Hansen S, Beck Jensen JE, Rasmussen L, et al. 2010 Effects on bone geometry, density, and microarchitecture in the distal radius but not the tibia in women with primary hyperparathyroidism: a case-control study using HR-pQCT. J Bone Miner Res 25:1941–1947.
26. Stein EM, Silva BC, Boutroy S, et al. 2013 Primary hyperparathyroidism is associated with abnormal cortical and trabecular microstructure and reduced bone stiffness in postmenopausal women. J Bone Miner Res 28:1029–1040.
27. Silva BC, Boutroy S, Zhang C, et al. 2013 Trabecular bone score (TBS)—a novel method to evaluate bone microarchitectural texture in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 98:1963–1970.
28. Romagnoli E, Cipriani C, Nofroni I, et al. 2013 "Trabecular Bone Score" (TBS): an indirect measure of bone microarchitecture in postmenopausal patients with primary hyperparathyroidism. Bone 53:154–159.
29. Eller-Vainicher C, Filopanti M, Palmieri S, et al. 2013 Bone quality, as measured by trabecular bone score, in patients with primary hyperparathyroidism. Eur J Endocrinol 169:155–162.
30. Bilezikian JP, Brandi ML, Eastell R, et al. 2015 Guidelines for the management of asymptomatic primary hyperparathyroidism. In: The Parathyroids. Bilezikian JP, ed. San Diego, CA: Elsevier, 489–497.
31. Dobnig H, Turner RT. 1997 The effects of programmed administration of human parathyroid hormone fragment (1–34) on bone histomorphometry and serum chemistry in rats. Endocrinology 138:4607–4612.
32. Neer RM, Arnaud CD, Zanchetta JR, et al. 2001 Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441.
33. Bilezikian JP, Rubin MR, Finkelstein JS. 2005 Parathyroid hormone as an anabolic therapy for women and men. J Endocrinol Invest 28:41–49.
34. Miller PD, Hattersley G, Riis BJ, et al. 2016 Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 316:722–733.
35. Bilezikian JP, Khan A, Potts JT Jr, et al. 2011 Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res 26:2317–2337.
36. Clarke BL, Brown EM, Collins MT, et al. 2016 Epidemiology and diagnosis of hypoparathyroidism. J Clin Endocrinol Metab 101:2284–2299.
37. Mannstadt M, Clarke BL, Vokes T, et al. 2013 Efficacy and safety of recombinant human parathyroid hormone (1–84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol 1:275–283.
38. Cusano NE, Rubin MR, McMahon DJ, et al. 2014 PTH(1–84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. J Clin Endocrinol Metab 99:3694–3699.
39. Rubin MR, Cusano NE, Fan WW, et al. 2016 Therapy of hypoparathyroidism with PTH(1–84): a prospective six year investigation of efficacy and safety. J Clin Endocrinol Metab 101:2742–2750.
40. Bollerslev J, Rejnmark L, Marcocci C, et al. 2015 European Society of Endocrinology clinical guideline: treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol 173:G1–G20.
41. Brandi ML, Bilezikian JP, Shoback D, et al. 2016 Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab 101:2273–2283.
42. Palermo A, Mangiameli G, Tabacco G, et al. 2016 PTH(1–34) for the primary prevention of postthyroidectomy hypocalcemia: the THYPOS trial. J Clin Endocrinol Metab 101:4039–4045.
43. Silverman SL, Kupperman ES, Bukata SV, Members of IOFFWG. 2016 Fracture healing: a consensus report from the International Osteoporosis Foundation Fracture Working Group. Osteoporos Int 27:2197–2206.
44. Aspenberg P, Genant HK, Johansson T, et al. 2010 Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res 25:404–414.
45. Peichl P, Holzer LA, Maier R, Holzer G. 2011 Parathyroid hormone 1–84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am 93:1583–1587.
46. Hanley DA, McClung MR, Davison KS, et al. 2017 Western osteoporosis alliance clinical practice series: evaluating the balance of benefits and risks of long-term osteoporosis therapies. Am J Med 130(862):e861–862 e867.
47. Lewiecki EM, Miller PD, Harris ST, et al. 2014 Understanding and communicating the benefits and risks of denosumab, raloxifene, and teriparatide for the treatment of osteoporosis. J Clin Densitom 17:490–495.
48. McClung MR. 2017 Using osteoporosis therapies in combination. Curr Osteoporos Rep 15:343–352.
49. McClung M, Harris ST, Miller PD, et al. 2013 Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med 126:13–20.
50. Bone HG, Hosking D, Devogelaer JP, et al. 2004 Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189–1199.
51. Black DM, Schwartz AV, Ensrud KE, et al. 2006 Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 296:2927–2938.

52. Black DM, Reid IR, Boonen S, et al. 2012 The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 27:243–254.
53. Black DM, Reid IR, Cauley JA, et al. 2015 The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 30:934–944.
54. Bone HG, Wagman RB, Brandi ML, et al. 2017 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 5:513–523.
55. Ferrari S, Adachi JD, Lippuner K, et al. 2015 Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. Osteoporos Int 26:2763–2771.
56. Kendler DL, Roux C, Benhamou CL, et al. 2010 Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res 25:72–81.
57. Miller PD, Pannacciulli N, Brown JP, et al. 2016 Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. J Clin Endocrinol Metab 101:3163–3170.
58. Black DM, Vittinghoff E, Eastell R, et al. 2015 Hip BMD by DXA can reliably estimate reduction in hip risk in osteoporosis trials: a meta-regression. J Bone Miner Res 30:S49.
59. Ferrari S, Libanati C, Lin CJF, et al. 2015 Relationship between total hip BMD T-score and incidence of nonvertebral fracture with up to 8 years of denosumab treatment. J Bone Miner Res 30:S49.
60. Cummings SR, Cosman F, Eastell R, et al. 2013 Goal-directed treatment of osteoporosis. J Bone Miner Res 28:433–438.
61. Dell RM, Adams AL, Greene DF, et al. 2012 Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res 27:2544–2550.
62. Schilcher J, Michaelsson K, Aspenberg P. 2011 Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 364:1728–1737.
63. Wasnich RD, Bagger YZ, Hosking DJ, et al. 2004 Changes in bone density and turnover after alendronate or estrogen withdrawal. Menopause 11:622–630.
64. Bone HG, Bolognese MA, Yuen CK, et al. 2011 Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab 96:972–980.
65. Heiss G, Wallace R, Anderson GL, et al. 2008 Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 299:1036–1045.
66. Anastasilakis AD, Polyzos SA, Makras P, et al. 2017 Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. J Bone Miner Res 32:1291–1296.
67. Ascott-Evans BH, Guanabens N, Kivinen S, et al. 2003 Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med 163:789–794.
68. Freemantle N, Satram-Hoang S, Tang ET, et al. 2012 Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 23:317–326.
69. Whitaker M, Guo J, Kehoe T, Benson G. 2012 Bisphosphonates for osteoporosis—where do we go from here? N Engl J Med 366:2048–2051.
70. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. 2016 Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 31:16–35.
71. Schwartz AV, Bauer DC, Cummings SR, et al. 2010 Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res 25:976–982.
72. McClung MR. 2016 Cancel the denosumab holiday. Osteoporos Int 27:1677–1682.
73. Amgen. 2017 Prolia prescribing information. Available at: http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/prolia/prolia_pi.pdf. Accessed: October 12, 2017.
74. Boonen S, Marin F, Obermayer-Pietsch B, et al. 2008 Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 93:852–860.
75. Leder BZ, Tsai JN, Uihlein AV, et al. 2015 Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 386:1147–1155.
76. Cosman F, Nieves JW, Dempster DW. 2017 Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res 32:198–202.
77. Cosman F, Hattersley G, Hu MY, et al. 2017 Effects of abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors. J Bone Miner Res 32:17–23.
78. Cosman F, Crittenden DB, Adachi JD, et al. 2016 Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 375:1532–1543.
79. Burr DB, Radin EL. 2003 Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? Rheum Dis Clin North Am 29:675–685.
80. McGonagle D, Tan AL, Carey J, Benjamin M. 2010 The anatomical basis for a novel classification of osteoarthritis and allied disorders. J Anat 216:279–291.
81. Boegard T, Rudling O, Dahlstrom J, et al. 1999 Bone scintigraphy in chronic knee pain: comparison with magnetic resonance imaging. Ann Rheum Dis 58:20–26.
82. Felson DT, McLaughlin S, Goggins J, et al. 2003 Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 139:330–336.
83. Davis AJ, Smith TO, Hing CB, Sofat N. 2013 Are bisphosphonates effective in the treatment of osteoarthritis pain? A meta-analysis and systematic review. PLoS ONE 8:e72714.
84. Reginster JY, Badurski J, Bellamy N, et al. 2013 Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. Ann Rheum Dis 72:179–186.
85. Bruyere O, Pavelka K, Rovati LC, et al. 2008 Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients

from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage 16:254–260.
86. Vlad SC, LaValley MP, McAlindon TE, Felson DT. 2007 Glucosamine for pain in osteoarthritis: why do trial results differ? Arthritis Rheum 56:2267–2277.
87. Schett G, Gravallese E. 2012 Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol 8:656–664.
88. Hazlewood GS, Barnabe C, Tomlinson G, et al. 2016 Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: a network meta-analysis. Cochrane Database Syst Rev (8):CD010227.
89. Gough AK, Lilley J, Eyre S, et al. 1994 Generalised bone loss in patients with early rheumatoid arthritis. Lancet 344:23–27.
90. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. 2006 Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 24:S77–82.
91. Mottonen T, Hannonen P, Korpela M, et al. 2002 Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 46:894–898.
92. Kirwan JR. 1995 The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 333:142–146.
93. Laan RF, van Riel PL, van de Putte LB, et al. 1993 Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 119:963–968.
94. van Staa TP, Leufkens HGM, Abenhaim L, et al. 2000 Oral corticosteroids and fracture risk: relationship to daily and cumulative dosing. Rheumatology (Oxford) 39:1383–1389.
95. O'Dell JR, Haire CE, Erikson N, et al. 1996 Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 334:1287–1291.
96. Taylor PC, Keystone EC, van der Heijde D, et al. 2017 Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 376:652–662.
97. Skou ST, Roos EM, Laursen MB, et al. 2015 A randomized, controlled trial of total knee replacement. N Engl J Med 373:1597–1606.
98. McIsaac DI, Bryson GL, van Walraven C. 2016 Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: a population-based cohort study. JAMA Surg 151:538–545.
99. van Staa TP, Geusens P, Bijlsma JW, et al. 2006 Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum 54:3104–3112.
100. Vosse D, Landewe R, van der Heijde D, et al. 2009 Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. Ann Rheum Dis 68:1839–1842.
101. Wright NC, Lisse JR, Walitt BT, et al. 2011 Arthritis increases the risk for fractures—results from the Women's Health Initiative. J Rheumatol 38:1680–1688.
102. Weiss RJ, Wick MC, Ackermann PW, Montgomery SM. 2010 Increased fracture risk in patients with rheumatic disorders and other inflammatory diseases—a case-control study with 53,108 patients with fracture. J Rheumatol 37:2247–2250.
103. O'Dell JR. 2004 Therapeutic strategies for rheumatoid arthritis. N Engl J Med 350:2591–2602.
104. Amiche MA, Albaum JM, Tadrous M, et al. 2016 Efficacy of osteoporosis pharmacotherapies in preventing fracture among oral glucocorticoid users: a network meta-analysis. Osteoporos Int 27:1989–1998.
105. Saag KG, Zanchetta JR, Devogelaer JP, et al. 2009 Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 60:3346–3355.
106. Carey JJ, Palomo L. 2008 Bisphosphonates and osteonecrosis of the jaw: innocent association or significant risk? Cleve Clin J Med 75:871–879.
107. Gordon CM, Zemel BS, Wren TA, et al. 2017 The determinants of peak bone mass. J Pediatr 180:261–269.
108. Crabtree NJ, Arabi A, Bachrach LK, et al. 2014 Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD pediatric official positions. J Clin Densitom 17:225–242.
109. Hui SL, Slemenda CW, Johnston CC Jr. 1990 The contribution of bone loss to postmenopausal osteoporosis. Osteoporos Int 1:30–34.
110. Zemel BS, Leonard MB, Kelly A, et al. 2010 Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab 95:1265–1273.
111. Schoenau E, Neu CM, Mokov E, et al. 2000 Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. J Clin Endocrinol Metab 85:1095–1098.
112. Hogler W, Briody J, Woodhead HJ, et al. 2003 Importance of lean mass in the interpretation of total body densitometry in children and adolescents. J Pediatr 143:81–88.
113. Crabtree NJ, Kibirige MS, Fordham JN, et al. 2004 The relationship between lean body mass and bone mineral content in paediatric health and disease. Bone 35:965–972.
114. Pludowski P, Lebiedowski M, Olszaniecka M, et al. 2006 Idiopathic juvenile osteoporosis—an analysis of the muscle-bone relationship. Osteoporos Int 17:1681–1690.
115. Gordon CM, Leonard MB, Zemel BS, International Society for Clinical Densitometry. 2014 2013 Pediatric position development conference: executive summary and reflections. J Clin Densitom 17:219–224.
116. Gordon CM, Gordon LB, Snyder BD, et al. 2011 Hutchinson-Gilford progeria is a skeletal dysplasia. J Bone Miner Res 26:1670–1679.
117. Shane E, Burr D, Abrahamsen B, et al. 2014 Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 29:1–23.
118. Dell RM. 2017 Kaiser SCAL Healthy Bones Program.
119. Roca-Ayats N, Balcells S, Garcia-Giralt N, et al. 2017 GGPS1 mutation and atypical femoral fractures with bisphosphonates. N Engl J Med 376:1794–1795.
120. Koh JS, Goh SK, Png MA, et al. 2010 Femoral cortical stress lesions in long-term bisphosphonate therapy: a herald of impending fracture? J Orthop Trauma 24:75–81.
121. Donnelly E, Saleh A, Unnanuntana A, Lane JM. 2012 Atypical femoral fractures: epidemiology, etiology, and patient management. Curr Opin Support Palliat Care 6:348–354.
122. Dell RM, Greene D, Tran D. 2012 Stopping bisphosphonate treatment decreases the risk of having a second atypical

femoral fracture. Presented at the American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting.
123. Schuit SC, van der Klift M, Weel AE, et al. 2004 Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 34:195–202.
124. Conference CD. 1991 Prophylaxis and treatment of osteoporosis. Am J Med 90:107–110.
125. Silva BC, Broy SB, Boutroy S, et al. 2015 Fracture risk prediction by non-BMD DXA measures: the 2015 ISCD official positions part 2: trabecular bone score. J Clin Densitom 18:309–330.
126. Miller PD. 2016 Management of severe osteoporosis. Expert Opin Pharmacother 17:473–488.
127. Cohen A, Shane E. 2013 Evaluation and management of the premenopausal woman with low BMD. Curr Osteoporos Rep 11:276–285.
128. Whyte MP. 2017 Hypophosphatasia: an overview for 2017. Bone 102:15–25.
129. Whyte MP, Mumm S, Deal C. 2007 Adult hypophosphatasia treated with teriparatide. J Clin Endocrinol Metab 92:1203–1208.
130. Palcu P, Dion N, Ste-Marie LG, et al. 2015 Teriparatide and bone turnover and formation in a hemodialysis patient with low-turnover bone disease: a case report. Am J Kidney Dis 65:933–936.
131. Black DM, Rosen CJ. 2016 Postmenopausal osteoporosis. N Engl J Med 374:2096–2097.
132. Cummings SR, Eastell R. 2016 Risk and prevention of fracture in patients with major medical illnesses: a mini-review. J Bone Miner Res 31:2069–2072.
133. Eisman JA, Bogoch ER, Dell R, et al. 2012 Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. J Bone Miner Res 27:2039–2046.
134. Miller PD. 2016 Underdiagnosis and undertreatment of osteoporosis: the battle to be won. J Clin Endocrinol Metab 101:852–859.
135. Kesselheim AS, Avorn J. 2013 The most transformative drugs of the past 25 years: a survey of physicians. Nat Rev Drug Discov 12:425–431.
136. Khosla S, Shane E. 2016 A crisis in the treatment of osteoporosis. J Bone Miner Res 31:1485–1487.
137. Khosla S, Bilezikian JP, Dempster DW, et al. 2012 Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab 97:2272–2282.
138. Jha S, Wang Z, Laucis N, Bhattacharyya T. 2015 Trends in media reports, oral bisphosphonate prescriptions, and hip fractures 1996–2012: an ecological analysis. J Bone Miner Res 30:2179–2187.
139. Cosman F, de Beur SJ, LeBoff MS, et al. 2014 Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25:2359–2381.
140. National Institutes of Health. 1994 Dietary Supplement Health and Education Act of 1994; Public Law 103-417; 103rd Congress. Available at: https://ods.od.nih.gov/About/DSHEA_Wording.aspx. Accessed: October 23, 2017.
141. Rizzoli R, Stevenson JC, Bauer JM, et al. 2014 The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas 79:122–132.
142. Sebastian A, Harris ST, Ottaway JH, et al. 1994 Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med 330:1776–1781.
143. Kiel DP, Felson DT, Hannan MT, et al. 1990 Caffeine and the risk of hip fracture: the Framingham Study. Am J Epidemiol 132:675–684.
144. Barger-Lux MJ, Heaney RP. 1995 Caffeine and the calcium economy revisited. Osteoporos Int 5:97–102.
145. Barrett-Connor E, Chang JC, Edelstein SL. 1994 Coffee-associated osteoporosis offset by daily milk consumption: the Rancho Bernardo study. JAMA 271:280–283.
146. 2006 Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause 13:340–367.
147. US Food & Drug Administration. 2017 Medical foods guidance documents & regulatory information. Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/default.htm. Accessed: October 23, 2017.
148. Palermo A, Tuccinardi D, D'Onofrio L, et al. 2017 Vitamin K and osteoporosis: myth or reality? Metabolism 70:57–71.
149. Castiglioni S, Cazzaniga A, Albisetti W, Maier JA. 2013 Magnesium and osteoporosis: current state of knowledge and future research directions. Nutrients 5:3022–3033.
150. Orchard TS, Larson JC, Alghothani N, et al. 2014 Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Observational Study. Am J Clin Nutr 99:926–933.
151. O'Donnell S, Cranney A, Wells GA, et al. 2006 Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev (3):CD005326.
152. Nielsen FH, Hunt CD, Mullen LM, Hunt JR. 1987 Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women. FASEB J 1:394–397.
153. Nielsen FH, Stoecker BJ. 2009 Boron and fish oil have different beneficial effects on strength and trabecular microarchitecture of bone. J Trace Elem Med Biol 23:195–203.
154. Zofkova I, Nemcikova P, Matucha P. 2013 Trace elements and bone health. Clin Chem Lab Med 51:1555–1561.
155. Solomon DH, Johnston SS, Boytsov NN, et al. 2014 Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. J Bone Miner Res 29:1929–1937.
156. American Society for Bone and Mineral Research. 2016 Call to action to address the crisis in the treatment of osteoporosis. Available at: https://www.asbmr.org/call-to-action.aspx. Accessed: November 30, 2017.
157. Lewiecki EM, Bouchonville MF 2nd, Chafey DH, et al. 2016 Bone health ECHO: telementoring to improve osteoporosis care. Womens Health (Lond Engl) 12:79–81.
158. Lewiecki EM, Boyle JF, Arora S, et al. 2017 Telementoring: a novel approach to reducing the osteoporosis treatment gap. Osteoporos Int 28:407–411.