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Proceedings of the 2015 Santa Fe Bone Symposium: Clinical Applications of Scientific Advances in Osteoporosis and Metabolic Bone Disease

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Abstract

The 2015 Santa Fe Bone Symposium was a venue for healthcare professionals and clinical researchers to present and discuss the clinical relevance of recent advances in the science of skeletal disorders, with a focus on osteoporosis and metabolic bone disease. Symposium topics included new developments in the translation of basic bone science to improved patient care, osteoporosis treatment duration, pediatric bone disease, update of fracture risk assessment, cancer treatment-related bone loss, fracture liaison services, a review of the most significant studies of the past year, and the use of telementoring with Bone Health Extension for Community Healthcare Outcomes, a force multiplier to improve the care of osteoporosis in underserved communities.

Keywords

Bone Health ECHO; emerging; osteoporosis; Project ECHO; treatment

Introduction

The 16th annual Santa Fe Bone Symposium was held on August 7–8, 2015, in Santa Fe, New Mexico, USA. The symposium is a 2-day multidisciplinary event that provides an opportunity for basic bone scientists, clinical researchers, physicians, and other healthcare

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professionals to review and discuss the clinical implications of recent advances in knowledge of skeletal health and disease. The focus of the presentations and discussions was the application of evidence-based medicine to clinical practice, recognizing that clinical decisions are often necessary despite limited scientific evidence. Proceedings of previous symposia have been published in peer-reviewed journals (1–9).

Translation of Basic Bone Biology Into Improved Patient Care

Roland Baron, DDS, PhD

In the last 10–15 years, multiple discoveries have been made in the laboratory, most often as a consequence of the emergence of genetics and genomics, identifying novel mechanisms by which skeletal remodeling and homeostasis are ensured in both mice and humans. Some of these novel signaling pathways and/or potential therapeutic targets have been used to develop novel molecules to inhibit bone resorption (antiresorptives) or enhance bone formation (osteoanabolics) with the ultimate goal of restoring bone mass and microstructure in osteoporotic patients at risk of fragility fractures. This is a review of these therapeutic approaches and describes their mode of action.

A large part of skeletal homeostasis is accomplished through bone remodeling. This process is the result of crosstalk between 2 cellular lineages, the hematopoietic lineage, which gives rise to osteoclast precursors, and the mesenchymal lineage, which gives rise to osteoblast precursors (10). Osteoclasts are responsible for resorption of bone; these cells also communicate with cells of the osteoblast lineage through the process of “coupling,” thereby ensuring the recruitment of bone forming cells at the end of each resorption phase. In turn, cells of the osteoblast lineage (i.e., osteoblasts, osteocytes, and bone lining cells) are responsible for the activation of bone remodeling cycles by ensuring the differentiation of osteoclasts through the local secretion of receptor activator of nuclear factor kappa B ligand (RANKL) and for ensuring a balance between the amount of bone formed and the amount resorbed at each bone remodeling site. In the remodeling process, bone formation therefore occurs as a consequence of bone resorption (10). Logically, a purely antiresorptive drug should therefore decrease not only resorption but also bone formation and ultimately bone turnover.

This link between resorption and formation is well illustrated by the results of the phase 2 and phase 3 clinical trials of denosumab, a fully human monoclonal antibody that prevents the osteoclastogenic action of RANKL (11,12). In the phase 2 clinical trial, denosumab was compared with alendronate. Both treatments markedly decreased the bone resorption marker serum C-telopeptide and also, with a short lag in time, the bone formation marker serum procollagen type 1 N-terminal propeptide. The effect of denosumab on bone remodeling was confirmed in the phase 3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months trial, in which bone turnover markers (BTMs) and histomorphometric analysis of iliac crest biopsies were evaluated in a subset of patients (11–13). Denosumab drastically reduced osteoclast numbers as well as bone formation and remodeling activity in trabecular bone. Despite these effects on bone remodeling, bone density at all measured skeletal sites increased significantly with long-term use. Denosumab treatment for up to 8 years was associated with persistent reductions of BTMs, continued bone mineral density

(BMD) gains, and low fracture incidence (14). The increase in bone density cannot be entirely explained by the very low remodeling-based bone formation. In monkeys, denosumab allows the continuation of another type of bone formation: modeling-based bone formation, perhaps explaining the continued gains in bone mass in humans (15).

Attempts were then made to find novel antiresorptive drugs that could decrease resorption without having a negative impact on bone formation. The finding that deletion of cathepsin K (an osteoclast enzyme critical for bone resorption) blocks resorption but has a neutral or even positive effect on bone formation (16) opened the way. Mouse genetic studies have shown that, at least in part, this is due to an enhancement of the osteoclast-dependent coupling mechanism (17). In preclinical and clinical studies (16–18) with small molecules inhibiting cathepsin K, markers of bone resorption are decreased to a level comparable to alendronate, but bone formation markers are maintained close to normal levels. In all these models, the decrease in bone resorption occurs despite a normal or even increased number of osteoclasts (16–18), indicating that it does not affect osteoclast differentiation but rather decreases the resorbing activity of osteoclasts while maintaining the “coupling” activity (17). The phase 2 and phase 3 Long-term Odanacatib Fracture Trial clinical trials with odanacatib have established the ability of these once-a-week oral compounds to increase bone density over several years (19) and to decrease the number of fractures (20).

An alternative approach to increasing bone mass and strength is to increase bone formation with osteoanabolic drugs (21). The prototype of this more recent class of osteoporosis drugs is teriparatide, the N-terminal 1–34 amino acids of parathyroid hormone (PTH 1–34). Unlike antiresorptive agents, this drug targets cells of the osteoblast lineage and induces an increase in their numbers and activity, increasing overall bone formation and bone mass, ultimately reducing the number of fractures (22). A limitation of its use, however, is that PTH increases the local production of RANKL by osteoblasts and osteocytes and secondarily increases also osteoclast numbers and bone resorption, preventing further increases in bone density (22). Two approaches have recently been proposed to limit this secondary increase in bone resorption. The first one uses an analog of PTH-related peptide (PTHrP [1–34]), abaloparatide, instead of PTH (23). In this compound, several amino acids have been substituted, resulting in a limitation of the resorbing responses and favorable stability at room temperature (teriparatide must be kept refrigerated). In preclinical and clinical phase 2 (23) and phase 3 clinical trials and in a head-to-head comparison with teriparatide, abaloparatide was found to increase bone density at both trabecular and cortical sites and to reduce vertebral and nonvertebral fractures (24). Although teriparatide and abaloparatide affect the same receptors in cells of the osteoblast lineage, they differ in their affinities, possibly explaining the observed differences in skeletal responses. The second approach has been to combine the use of teriparatide and denosumab (25). As the PTH-induced increase in bone resorption is for the most part due to an increase in the local production of RANKL, adding denosumab to PTH is a logical choice. Indeed, the results of clinical trials have clearly demonstrated that this drug combination produced effects on BMD at various skeletal sites superior to either drug taken alone (25,26), confirming that the secondary increase in RANKL and bone resorption induced by teriparatide is limiting its ability to maximally increase bone density, in particular at cortical skeletal sites.

An ideal approach to treating osteoporosis would be with an osteoanabolic drug that increases bone formation without affecting bone resorption, or even better, one that decreases bone resorption. Although this seemed a far-fetched goal a few years ago, the discovery of the role of the Wnt (a term derived from a combination of the *Drosophila* gene *wingless* and the mouse gene *int*) signaling pathway in the regulation of skeletal homeostasis has made it reachable (10). Patients with a high bone mass have been identified in several cohorts and genetic analysis revealed that they had mutations in the Wnt receptor low-density lipoprotein receptor-related protein 5 (LRP5) (27,28). Further studies demonstrated that these mutations decreased the affinity of these receptors for a natural inhibitor of Wnt signaling, sclerostin, effectively increasing Wnt signaling activity in the bone microenvironment. At the same time, the causal mutation in sclerosteosis, a rare inherited disease in humans characterized by high bone mass, has been found to be a null mutation of the SOST gene (29,30). Homozygotes have very high bone mass associated with serious adverse effects, while heterozygote carriers have high bone mass but no apparent deleterious consequences of this increase in bone density (31). This suggests that a compound that partially inhibits sclerostin might be both effective and safe in treating patients with low bone mass; this is an approach followed by several drug companies. Importantly, multiple in vitro and animal studies established these findings and revealed that expression of sclerostin is restricted to osteocytes (32), such that its therapeutic inhibition would limit Wnt activation to the bone microenvironment, thereby avoiding off-target effects. Furthermore, sclerostin inhibition also increased osteoprotegerin (OPG), an endogenous RANKL receptor that inhibits osteoclastic bone resorption. Pre-clinical, phase 1, and phase 2 results with 2 monoclonal antibodies against sclerostin (romosozumab and blosozumab) have clearly established the strong ability of these compounds to increase bone density at all measured skeletal sites by increasing bone formation and decreasing bone resorption (33–35). The strong anabolic effect is, however, limited in time to the first 6 mo, whereas the antiresorptive effect, while modest, is prolonged over the entire 1-yr period of treatment, establishing a sufficiently positive bone balance to markedly and rapidly increase bone density at trabecular and cortical sites (34,35). A phase 3 trial is currently ongoing with romosozumab to evaluate its effects on fractures.

In summary, the discoveries of the RANKL, PTH, Wnt signaling pathways, and cathepsin K have allowed the development of excellent novel therapeutics (e.g., denosumab, teriparatide, abaloparatide, romosozumab, and odanacatib), some of which have proven efficacy and safety, with others in their final stages of clinical development. This is a true illustration of how laboratory discoveries can be translated into improved patient care.

Current Concepts in Therapy of Osteoporosis

John P. Bilezikian, MD

In the quest for improved therapies for osteoporosis, we recognize several desirable properties. In some cases, these properties have been considered to be goals of therapy being developed now or in the future. This presentation dwells on some of these features, pointing out that, in many instances, we already have achieved these goals in the therapies or in the context of therapies that are on the horizon.

Improvement in Cortical Bone—Because cortical bone comprises about 80% of the human skeleton, it is self-evident that our therapies ideally should have beneficial effects in this skeletal compartment. Abundant data from several studies have documented an effect of denosumab on cortical bone. These studies have focused upon the positive effect of this drug on the distal 1/3 radius (a skeletal site with predominantly cortical bone) (36), the long-term effect of denosumab on nonvertebral fractures (14), reduction in cortical porosity at the distal radius (37), computed tomography (CT) cortical mapping at the femur (38), and finite element analysis (FEA) of CT images of the hip (39). Besides these effects of denosumab, it should be noted, also, that teriparatide has been shown to improve cortical bone (40), and animal data have demonstrated the salutary effects of odanacatib, a cathepsin K inhibitor, on cortical bone in ovariectomized monkeys (41) and of romosozumab, an antisclerostin agent, on cortical envelopes in ovariectomized animals (42). Compared with bisphosphonates, treatment with denosumab is associated with greater increases in BMD at both trabecular and cortical skeletal sites (including the distal 1/3 radius), although it is unclear whether there is a clinically meaningful difference in fracture risk reduction (43).

Lightening Up on Effects of Antiresorptives to Reduce Bone Formation

Dynamics—Most of the available antiresorptive drugs reduce bone resorption and, concomitantly, reduce bone formation. Because bone resorption is generally inhibited to a greater extent than bone formation, improvement in bone balance is achieved, bone density increases, and fracture risk is reduced. The cathepsin K inhibitor, odanacatib, introduces a new class of antiresorptives that, by virtue of its effects to selectively inhibit a single osteoclast product, namely, cathepsin K, osteoclasts continue to be viable both in number and function (44). It is presumed that these viable osteoclasts continue to signal to osteoblasts in a positive way, not only maintaining their numbers but also their function (45).

Lightening Up on the Effects of Osteoanabolics to Stimulate Bone Resorption

Secondarily—The osteoanabolics represent a class of agents that help restore the disordered microarchitecture that is characteristic of osteoporosis. Teriparatide, the first member of this class, powerfully and rapidly stimulates bone formation with a later effect on bone resorption. The discordant kinetics between the effects of teriparatide to stimulate bone formation and bone resorption have been described as the anabolic window during which time teriparatide is maximally anabolic (46). Even though bone resorption is increased soon after bone formation is stimulated, these 2 processes from a mechanistic point of view argue that the initial effect of the drug is a modeling effect (bone formation on quiescent surfaces), whereas the secondary effect is a stimulation of bone turnover through the classical bone remodeling process. Increased bone resorption is important because it serves to limit the anabolic effect of the drug, as occurs with teriparatide treatment. It may be for this reason that the pharmacological effects of teriparatide have a built-in time course of efficacy. A new osteoanabolic medication is being developed that takes further advantage of these concepts. Abaloparatide is a PTHrP analog designed with empirically placed residues in the 22–34 region of the PTHrP molecule to maximize its anabolic effect (23). The effect of abaloparatide to stimulate bone formation, as tracked by bone formation markers, is very similar to the effect of teriparatide, but its ability to stimulate bone resorption, as seen through a rise in circulating C-terminal telopeptide (CTX), does not appear to be as

powerful. Thus, there may be a greater distinction between abaloparatide's actions to stimulate bone formation (strong) and later to stimulate bone resorption (weaker) than with teriparatide (23). The initial results from the pivotal phase 3 clinical trial indicate that abaloparatide reduces vertebral and nonvertebral fractures with a time course suggesting a faster onset of effect than with teriparatide (24).

Moving Toward a New Class of Osteoanabolic Therapy—One of the remarkable aspects of our field is the rapid translation of breakthroughs in bone biology to the clinical world of therapeutics. A prime example of this is the development of an antisclerostin agent for the treatment of osteoporosis. Sclerostin is one of the key regulators of the anabolic signaling pathway referred to as Wnt. Sclerostin prevents interactions between Wnt and its binding sites such as lipoprotein receptor-related protein 5/lipoprotein receptor-related protein 6, and thus inhibits a biochemical cascade that ultimately leads to the translocation of beta-catenin into the nucleus where transcriptional activation occurs (10). The antisclerostin molecule, known as romosozumab, is a powerful stimulator of bone accrual with increases in bone density over a relatively short period of time (34). Curiously, romosozumab has effects on BTMs that are surprisingly transient, with a burst in procollagen type 1 N-terminal propeptide activity, a marker of bone formation, that returns to baseline within 6 mos. CTX, the resorption marker, is initially suppressed by approximately 50%, returning toward baseline but then falling again. Studies on experimental animals suggest a powerful effect on bone modeling as a partial explanation for these dramatic osteoanabolic effects of romosozumab. Phase 3 trials are currently being conducted.

Combination Therapy With Teriparatide and Denosumab—Understanding the mechanisms of the aforementioned therapeutics led to a hypothesis that the simultaneous combination of denosumab and teriparatide might be particularly attractive. The underlying hypothesis is that teriparatide requires RANKL for its catabolic actions. As denosumab inhibits RANKL, the osteoanabolic potential of teriparatide would be more evidently realized if it were combined with denosumab. This hypothesis has been tested in a series of studies led by Leder et al in which the combination of denosumab and teriparatide was associated with greater accrual of bone density and improved microarchitectural indices than either agent alone (25,26).

While we aspire to drugs that have distinctive effects in ways that should lead to desirable properties vis-à-vis efficacy, in many instances we have, or appear to be on the verge of having, drugs that go far toward meeting these objectives. As this field continues to progress with new insights into basic principles of cellular and molecular bone biology, it is very likely, if not certain, that these advances will be rapidly translated into therapeutic paradigms that are uniquely effective.

Cancer Treatment-Related Bone Loss

Robert F. Gagel, MD

General Trends in Cancer Therapy—Several threads have run through cancer therapy during the past 50 yr. The first is the evolution of cancer treatment from cytotoxic

chemotherapy to more “targeted” forms of therapy. The first examples of targeted therapy occurred in breast and prostate cancer with the recognition that estrogen and androgen depletion therapy, either by reducing sex steroid concentrations or by blocking their effects on their cognate receptors, had profound effects on tumor growth and survival. This trend has continued with the recognition that a finite number of mutated genes play a disproportionate role in genesis and progression of cancer. The corollary of these observations is that targeting these molecular drivers can have profound effects on tumor growth and survival. The earliest example was the use of imatinib, a tyrosine kinase inhibitor, in the treatment of chronic myelogenous leukemia (47) and gastrointestinal stromal tumors (48). Treatment with these compounds resulted in dramatic effects on both malignancies. Over the past decade, there has been a proliferation of compounds with kinase inhibitor effects (49).

A second trend is the impact these new therapies have on outcomes in cancer. Since the 1990s, there has been a continuous and, for some malignancies, profound reduction in mortality caused by cancer (50). This trend appears to be accelerating with the introduction of targeted cancer therapies. A characteristic of these targeted therapies is that therapeutic effects often require the continued presence of the targeted therapy—the effects are static rather than tumoricidal. Thus, unlike earlier side effects that were limited to the period of therapy, many patients will remain on chronic targeted therapy for as long as the malignancy remains responsive to the therapy.

How Do These Newer Therapies Affect Bone?—A characteristic of many of the newer targeted therapies is that they target important molecular pathways involved in cell growth and differentiation. Unfortunately, these same pathways are also important for a variety of other cellular functions, some of which have profound effects on bone and mineral metabolism. For example, the use of aromatase inhibitors in the treatment of estrogen receptor-positive breast cancer provides a clear example of a drug class with great oncological benefit that adversely affects the skeletal system (51). Multiple studies have demonstrated that these agents, which block the conversion of testosterone or androstenedione to estradiol, are highly effective for reducing recurrence and death in estrogen receptor-positive breast cancer (52). However, the further lowering of estradiol levels in postmenopausal women causes an acceleration of bone loss; studies have demonstrated an increased fracture risk within 3–5 yr of initiating aromatase inhibitor therapy (53,54). There has been an evolution of thought about the management of these patients, with significant disagreement among members of the bone and oncological communities. Initial guidelines focused on treatment only when the *T*-score fell into the osteoporotic range; more recent guidelines, based on evidence that earlier intervention substantially reduces fracture risk, have adopted earlier intervention. Intravenous and oral bisphosphonates have proven efficacy (55). A recent study has demonstrated that certain RANKL and OPG polymorphisms are associated with altered RANKL/OPG ratios and higher rates of bone loss, suggesting that some of the risk is determined genetically and involves RANKL (56). A more recent study has demonstrated clear evidence that adjuvant treatment with denosumab, an antibody that binds to and neutralizes RANKL, lowers fractures in women treated with aromatase inhibitors. Thirty-four hundred patients with

estrogen receptor-positive breast cancer were randomized to receive either placebo or denosumab (60 mg every 6 mos) at the outset of aromatase inhibitor therapy in a blinded study. There were 176 fractures in the placebo arm compared with 92 in the treatment arm, a highly significant difference. During this 6-yr study, there were no cases of osteonecrosis of the jaw in either placebo or treatment arm. Perhaps the most striking finding of this study was the finding that 10% of the placebo group had a fracture after 3 yr of therapy, 16% at 5 yr, and a remarkable 26% at 7 yr (54). Although this high fracture rate seems surprising, it is consistent with high-resolution CT studies which have shown that changes in volumetric bone mineral density and cortical thickness in this patient population are underestimated by dual-energy X-ray absorptiometry (DXA) (57). The results of this prospective study of denosumab in patients treated with aromatase inhibitors have already modified thinking in the oncological community regarding this issue, particularly as these agents are now being routinely used for 5–10 yr.

Bone and Mineral Effects of Tyrosine Kinase Inhibitors—Other targeted therapies have profound effects on bone and mineral metabolism. For example, vandetanib and cabozantinib, agents that target RET (REarranged during Transfection) and vascular endothelial growth factor receptors and are approved for the treatment of medullary thyroid carcinoma, have profound effects on the absorption of calcium and vitamin D. In the phase II and III studies of these agents, a high percentage of patients developed hypocalcemia and vitamin D deficiency, necessitating supplementation with substantial doses of calcium and vitamin D to overcome the abnormalities (58,59). These profound abnormalities were identified because a high percentage of patients with metastatic thyroid cancer have had extensive neck surgery leading to partial or complete hypoparathyroidism. As this class of vascular endothelial growth factor receptors is among the most commonly used tyrosine kinase inhibitors (e.g., sunitinib, pazopanib), it is likely that similar malabsorptive changes occur in patients with intact parathyroid glands, resulting in profound secondary hyperparathyroidism. Although this may not be a problem during short-term use, the fact is that these agents are routinely continued for years and could lead to profound effects in the skeleton. Another example is imatinib. In a group of patients treated for chronic myelogenous leukemia or gastrointestinal stromal tumors, 25% developed profound hypophosphatemia, and these same individuals had hypocalcemia and clear evidence of vitamin D deficiency with secondary hyperparathyroidism (60). The mechanisms of these profound changes in calcium metabolism are unclear, although the finding of a reduction of bone resorption (N-telopeptide) and bone formation (serum osteocalcin) markers suggests the possibility that bone resorption is inhibited, leading to secondary hyperparathyroidism.

Current cancer investigational agents are focused on a broad spectrum of genes that are mutated in cancer but also have important roles in normal physiology. The challenge that we face with these compounds is that they will be used for long periods, even an entire lifetime, magnifying their detrimental effects. The number of these agents currently under investigation is large, hundreds to thousands, and it is likely that some will have important skeletal effects. It will be important to understand which of these agents affect the skeleton, to take steps to understand their mechanisms of action, and to take preventive action to protect skeletal health.

Bone Disease in Children and in Adult Survivors of Childhood Chronic Disease

Mary B. Leonard, MD

Growth and development are characterized by sex and maturation-specific increases in trabecular and cortical BMD and cortical thickness (61). Myriad childhood chronic diseases and their therapies pose threats to skeletal development. The impact may be immediate, resulting in fragility fractures during childhood (62–67), or delayed, due to suboptimal peak bone mass and consequent fractures in adulthood (68–70). Potential threats to bone accrual in childhood chronic diseases include malnutrition, mal-absorption, impaired muscle strength, decreased physical activity, systemic inflammation, delayed maturation, abnormalities in the growth hormone/insulin-like growth factor-1 axis, and glucocorticoid (GC) therapy (71). In addition, the underlying disease may impact skeletal development directly. For example, insulin is anabolic to bone and type 1 diabetes is associated with increased risk of fractures across the life span (70). Numerous DXA studies documented abnormal areal BMD in pediatric disorders; however, studies using quantitative computed tomography (QCT) have provided important insights into discrete disease and treatment effects on trabecular and cortical volumetric bone mineral density (vBMD) and structure.

GCs are the leading cause of secondary osteoporosis in adults and are widely prescribed for the treatment of a spectrum of childhood diseases. The growing skeleton may be especially vulnerable to adverse GC effects on multiple components of bone formation, including osteoblast proliferation, function, and life span (72,73). The majority of prior DXA studies in children treated with GCs were confounded by, first, the effects of GCs and the underlying disease to impair growth, resulting in underestimates of areal BMD for age (74) and, second, by the impact of the underlying inflammatory disease on bone. Inflammatory cytokines, such as tumor necrosis factor- α , have direct adverse effects on osteoblasts, compounding the effects of GCs to impair bone formation. Inflammatory cytokines also increase bone resorption (75).

A series of peripheral QCT studies examined trabecular and cortical vBMD and cortical structure in children and in young adults treated with GCs for inflammatory diseases, including nephrotic syndrome (76–78), inflammatory bowel disease (74,79–83), systemic lupus erythematosus (84), and juvenile idiopathic arthritis (85–88). Taken together, these studies suggested that both GCs and chronic inflammation were associated with decreased vBMD and periosteal circumference, consistent with effects to decrease bone formation. Crohn's disease was associated with increased endosteal circumference at diagnosis prior to GC therapy, suggesting that inflammation promotes endocortical resorption. The impact of inflammatory cytokines on bone is further illustrated in a cohort study of children and adolescents with Crohn's disease treated with antitumor necrosis factor- α biologics (e.g., infliximab) (89). The pediatric Crohn's disease activity index decreased markedly during the 10-wk induction, in association with subsequent gains in height, trabecular BMD, cortical area (due to dramatic recovery of endocortical bone), and muscle area over 12 mos. Bone-specific alkaline phosphatase levels, a biomarker of bone formation, increased by a median of 75% during induction, and predicted improvements in trabecular BMD and cortical area

over 1 yr, above and beyond the gains expected with age and growth. Younger age was associated with greater increases in trabecular BMD and greater linear growth with greater recovery of the cortical area. These data suggest a window of opportunity for the treatment of bone deficits in children and in adolescents. Of note, serum β -CTX, a biomarker of bone resorption, also increased significantly following initiation of infliximab therapy. This reflects robust skeletal modeling during growth and recovery, rather than an adverse effect—highlighting the challenges of interpreting bone biomarkers during growth (90).

Multiple recent advances in the use of DXA have improved the utility for the study of childhood chronic diseases, as summarized in the 2013 International Society for Clinical Densitometry Pediatric Official Positions (91–94). First, the National Institutes of Health-funded Bone Mineral Density in Childhood Study (BMDCS) obtained annual DXA scans in over 2000 healthy participants, ages 5–23 yr, and generated sex- and race-specific reference curves relative to age for bone mineral content and areal BMD of the total body, lumbar spine, hip, and forearm (95). These data were obtained with Hologic scanners (Hologic, Inc., Bedford, MA) and are also available as “GE equivalents” (GE Healthcare, Madison, WI) using the transformation equations developed by Shepherd et al (96). The study demonstrated that fracture risk decreased with higher DXA *Z*-scores, except in white boys, who had increased fracture risk with higher DXA *Z*-scores (97). Second, the BMDCS study addressed the confounding effect of short stature on areal BMD. Areal BMD (gram per square centimeter) is not a measure of volumetric density (gram per cubic centimeter) because it provides no information about bone depth. Bones of larger width and height are thicker. As bone depth is not factored into DXA results, reliance on areal BMD systematically underestimates bone density in shorter people. This limitation is critical in children and adolescents with chronic diseases complicated by poor growth. For example, in the evaluation of a child on GC therapy, one could falsely attribute the decreased areal BMD as evidence for skeletal fragility, rather than a GC-induced reduction in height. Accordingly, the BMDCS investigators published prediction equations to adjust DXA bone mineral content and BMD *Z*-scores for height *Z*-scores and demonstrated that this approach is not subject to the biases introduced by alternative strategies, such as assessing bone outcomes relative to height age (98).

The multicenter Steroid-Associated Osteoporosis in the Pediatric Population study conducted in Canada was the first prospective study to demonstrate that spine DXA BMD *Z*-scores predicted incident vertebral compression fractures in children and adolescents treated with GCs (64,65). Vertebral morphometry was carried out by the Genant semiquantitative method. Children and adolescents with acute lymphoblastic leukemia suffered a cumulative incidence of vertebral fractures of 26% over 4 yr. Incident fractures were associated with greater GC exposure, younger age, and lower lumbar spine BMD *Z*-scores, compared to those without fractures. Each 1.0 unit reduction in lumbar spine BMD *Z*-score at baseline was associated with 80% greater odds of incident vertebral fracture at 12 mo (64). Similarly, in children treated with GCs for rheumatological disorders, greater GC exposure and decreases in lumbar spine BMD *Z*-scores over the first 6 mo of GC therapy were associated with increased risk of incident vertebral fractures (65).

In summary, recent years have seen important advances in the assessment bone health in children and adults with childhood-onset chronic disease. The challenge in the coming years is to identify anabolic strategies to promote bone accrual in these high-risk populations.

Advances in Risk Assessment

William D. Leslie, MD, MSc, FRCPC, CCD

With the advent of DXA, quantitative assessment of fracture risk became possible. The seminal meta-analysis by Marshall et al (99) showed that each standard deviation reduction in BMD was associated with an approximately 1.5-fold increase in fracture risk, but for prediction of hip fractures this gradient of risk increased to 2.6-fold for hip BMD measurements. Suboptimal performance of BMD as the sole predictor of fracture risk led to the development of risk prediction algorithms for estimating absolute fracture probability from multiple risk factors (100). The most widely used, the World Health Organization Fracture Risk Assessment algorithm (FRAX), estimates fracture probability over the subsequent 10 yr and is calibrated for rates of fracture and mortality in the target population (101). Currently, more than 60 such tools have been developed for different countries around the world. Despite many successes, limitations to applying FRAX in clinical practice are acknowledged (102): specific risk factors that are not included in FRAX (e.g., falls), lack of dose response in clinical risk factors (e.g., 1 prior fracture vs multiple fractures), and unresponsiveness of FRAX to pharmacologic intervention (e.g., unable to support a treat-to-target strategy). The only skeletal parameter considered by FRAX is femoral neck BMD. Although strongly associated with fracture risk, many other skeletal parameters can be derived from DXA and non-DXA methodologies. The 2015 Position Development Conference (PDC) held by the International Society for Clinical Densitometry (ISCD) addressed the clinical utility of several of these skeletal measures (103).

Lumbar spine trabecular bone score (TBS) was developed as a texture measurement derived from DXA images that could provide an assessment of skeletal “quality” independent of BMD. TBS evolved into a commercial product (Medimaps Group, Geneva, Switzerland) and in 2013 was cleared for clinical use in the United States. A review by Silva et al (104) summarizes the preclinical and clinical data that have contributed to the evidence-based supporting interest in TBS as a clinical tool. Most recently, a method for adjusting FRAX probability measurements based upon lumbar spine TBS has been derived (105). TBS can now be entered directly into the FRAX website for automated calculation of fracture probability that incorporates TBS into the risk calculation. The 2015 ISCD Official Positions now endorse the use of TBS for fracture risk assessment, but not for monitoring individuals on bisphosphonate therapy (106). There was insufficient evidence to determine whether TBS could be used as a measure of antifracture efficacy with other classes of therapeutic agents. Lumbar spine TBS may be particularly helpful in type 2 diabetes where BMD measurements and FRAX without TBS input do not adequately capture diabetes-associated fracture risk (107,108).

Since the early 1990s, it became possible to derive basic geometric and biomechanical measurements from DXA images (109). The 2015 ISCD PDC reviewed the available data and found that most of these parameters were strongly correlated with BMD but did not

significantly enhance risk assessment when adjusted for BMD (110). A single exception was hip axis length (HAL), defined as the distance from the inner pelvic brim along the femoral neck axis to the lateral border of the trochanter, where data in postmenopausal women consistently demonstrate that longer HAL is associated with increased hip fracture risk (110). HAL remained a significant predictor of hip fracture risk even when adjusted for BMD and FRAX probability (111). Published data in men are inconsistent, though recent evidence supports a similar relationship in men (112). The 2015 PDC found strong evidence for use of HAL in fracture risk assessment in postmenopausal women, but that HAL (and other geometric parameters) was not useful for monitoring purposes (110). A method for incorporating HAL into the FRAX hip fracture probability measurement has been proposed (112).

QCT was originally used for measuring true vBMD in the lumbar spine (113). The 2015 PDC examined newer data related to proximal femur QCT, additional measures of skeletal strength assessment using FEA, and found that both techniques were useful for fracture prediction and for monitoring purposes (114,115). Strength assessment from FEA has been examined as a possible alternative to the BMD *T*-score for identifying a treatment threshold, although this is still preliminary (116). Proximal femur QCT can provide a “DXA-like” *T*-score through Food and Drug Administration (FDA)-approved commercial software (CTXA-Hip™, Mindways Software, Austin, TX) and the derived femoral neck *T*-score can be used in conjunction with FRAX for 10-yr fracture risk assessment (117). The potential for using CT scans acquired for non-bone-related clinical reasons (i.e., without a calibration scan) for “opportunistic screening” of osteoporosis is now feasible, but only if validated machine-specific cutoff values and scanner stability have been established. Asynchronous calibration in stable CT scanners allows for vBMD to be estimated from the clinical CT images in the absence of a simultaneous in-scan QCT calibration phantom. Together, these techniques may offer a method for enhanced detection of individuals with osteoporosis who are currently not being screened with DXA or appropriately treated.

Despite challenges from other advanced technologies, the potential for even more advances in DXA is good. The concept of 2-dimensional FEA (in contrast to FEA from QCT, which is 3-dimensional) is attracting attention with favorable initial results (118). Whether BMD alone or BMD combined with other treatment-response parameters (e.g., BTM) can be used to develop a treat-to-target strategy remains an area of clinical importance and research (119).

This Year in Osteoporosis: Are We Ahead or Behind Last Year? Comments on Selected Papers Published From July 2014 to June 2015

Michael McClung, MD

A review of papers about osteoporosis published between July 2014 and June 2015 was undertaken. About 25 of these were chosen for presentation at the Santa Fe Bone Symposium as being of special interest or importance. Highlighted here are the most relevant of those.

Wnt 16, an osteoblast-derived inhibitor of osteoclastogenesis, is an important and powerful modulator of cortical bone mass and structure. Wnt 16-deficient mice develop spontaneous fractures as a result of low cortical thickness and high cortical porosity, but trabecular bone volume is not altered (120). In humans, serum levels of Wnt 16 are correlated with cortical bone thickness and nonvertebral fracture risk. Given the unique effect on cortical bone, therapy with or to upregulate Wnt 16 may be an attractive strategy to reduce nonvertebral fracture risk.

An updated systematic review documented the effectiveness of pharmacological treatments for reducing fracture risk in patients with osteoporosis (121). Despite this strong evidence, criticism about treating osteoporosis appeared again (122). There is new evidence that the proportion of patients receiving treatment to reduce subsequent fracture risk after a hip fracture declined from 40% in 2002 to about 20% into 2011 (123). The proportion of women over age 65 referred for DXA testing remains very low but was improved when health systems allowed and encouraged self-referral (124).

FEA, calculated from DXA scan images, is a BMD-independent predictor of fracture risk (118). The ability of TBS to predict fracture was confirmed in postmenopausal women and in men (125,126).

Periodic reassessment of the need for continued bisphosphonate therapy is recommended. Age and BMD at the time therapy is discontinued remain predictors of fracture risk, justifying the use of BMD and FRAX estimates of risk in deciding whether treatment should be stopped (127). Monitoring changes in BMD and BTMs after stopping treatment was not helpful in identifying patients who experienced a fracture (128).

Atypical femoral fractures are associated with long-term bisphosphonate therapy and have been reported in patients treated with denosumab; they are also known to occur in patients receiving no osteoporosis therapy (129). Two studies documented that femoral geometry predicted the occurrence and site of the femoral shaft stress fractures (130,131). This raises the possibility that more data identifying risk factors for atypical femur fractures might allow physicians to customize drug therapy and use medications that are least likely to be associated with this rare complication. On the other side of the risk : benefit equation, bisphosphonate therapy was associated with a 50% decrease in skeletal metastases in women with local or regional breast cancer (132). A separate study suggested that the risk of invasive endometrial carcinoma was reduced by 20% in ever users of bisphosphonates (133).

Inhibition of sclerostin is an attractive strategy to increase bone formation to treat osteoporosis. Treatment with blosozumab resulted in marked but transient increases in markers of bone formation and a decrease in markers of bone resorption (35). Increases in lumbar spine and total hip BMD by 17.7% and 6.7%, respectively, were noted after treatment for 12 mo. In the 12 mo after stopping treatment, BMD values decreased but remained well above baseline values (134).

In a phase 2 study, daily subcutaneous dosing with 80 µg of abaloparatide increased BMD more than with 20 µg of teriparatide daily (23). The phase 3 trial results, recently presented

at a scientific congress, demonstrated that abaloparatide and teriparatide similarly reduced the incidence of vertebral and nonvertebral fractures after 18 mo of treatment.

Combining denosumab and teriparatide increases BMD more effectively than either drug alone. Continuing denosumab after 2 yr of combination therapy or switching from teriparatide to denosumab after 2 yr resulted in further gains in total hip and spine BMD over the subsequent 2 yr (135). In patients who switched from denosumab to teriparatide, a modest additional gain in spine BMD was noted. However, no further gain in hip BMD occurred, and a substantial decrease in midradius BMD (cortical bone) was observed. For patients in whom marked and rapid bone gain are desired, treatment with teriparatide or with a combination of teriparatide and denosumab for 2 yr followed by denosumab (25,26,135) or another antiresorptive agent (136,137) may be advantageous.

How Concepts of Bisphosphonate Drug Holidays May Be Linked to the Decline in Utilization of Osteoporosis Therapies

Paul D. Miller, MD

Osteoporosis is an underdiagnosed and undertreated disease (138). The annual costs in the United States of caring for osteoporotic-related fractures exceed the annual costs for myocardial infarction, breast cancer, or stroke (139). Equally disturbing are the data showing that the percentage of patients receiving an FDA-approved therapy for osteoporosis, even after sustaining a hip fracture, has declined in the United States from 41% in 2001 to 21% in 2011 (123). Finally, the greatest causes of the loss of independence in men and in women 70 yr of age and older are falls at home and fractures (140–142).

A number of factors contribute to the decline in the diagnosis and treatment of osteoporosis, including a decrease in the number of patients being tested by DXA (143), concerns about the long-term safety of bisphosphonates, for example, their rare associations with osteonecrosis of the jaw and/or atypical subtrochanteric femur fractures (ASFFs) (129,144), and underappreciation by physicians themselves of the seriousness of osteoporotic fractures, including asymptomatic vertebral fractures (145–148). The international movement to develop Fracture Liaison Services, spearheaded in the United States by the National Bone Health Alliance and internationally by the International Osteoporosis Foundation, is a multidisciplinary effort to reduce the incidence of the second osteoporotic fracture (149,150) by developing pathways for identifying and managing hospitalized patients with an osteoporotic fracture.

The attention given to the association of bisphosphonate use and the rare ASFFs has been a factor in the poor acceptance of therapies for osteoporosis by patients. Greater attention should be directed at the excellent data showing the far greater reduction in the incidence of typical hip fractures with bisphosphonate therapy, rather than to the very rare incidence for developing a bisphosphonate-associated atypical fracture—a benefit : risk ratio that exceeds 100:1 (151). Osteoporotic-related ASFFs represent approximately 10% of the total number of osteoporotic-related femur fractures that occur annually in the postmenopausal population (152,153). The term ASFF was coined by several investigators to describe a specific type of

sub-trochanteric femur fracture (152,154) and was articulated in the American Society for Bone and Mineral Research working group reports on ASFF (129,155). It is important to highlight that both American Society for Bone and Mineral Research task force papers documented that ASFF may develop independent of bisphosphonate exposure.

There have been an increasing number of ASFF reported in epidemiological studies since the approval of bisphosphonates for postmenopausal osteoporosis in 1995. It is also possible that the apparent increase in ASFF occurring in subjects on bisphosphonates has nothing at all to do with bisphosphonate exposure, as the very populations that are at risk for developing these forms of femur fractures are the very same subjects with low bone mass with a higher baseline risk for ASFF and who also may be selected to receive bisphosphonates because of their low bone mass (e.g., the data are confounded by indication).

There are plausible reasons why causality has not been confirmed in attributing the occurrence of ASFF to bisphosphonate exposure, including the absence of a known mechanism of action whereby bisphosphonates might induce ASFF. Bisphosphonates reduce bone remodeling but by doing so improve bone strength. This biology underpins the process whereby antiresorptive agents reduce fractures.

The US FDA held an advisory board meeting on September 9, 2011, to consider a change in bisphosphonate labeling to define a restricted duration of use. This consideration for the restriction of the duration of bisphosphonate use was predicated on 3 assumptions:

1. The limited long-term efficacy data of bisphosphonate use (i.e., limited data on continual fracture benefit beyond 5 yr)
2. The unique pharmacology of bisphosphonates (i.e., not metabolized, retained in bone, and recycled) would allow temporary discontinuation of bisphosphonates while preserving some of their biological effects.
3. The assumption that there exists a link between bisphosphonates, their duration of use, and the risk of ASFF.

The first assumption is a correct but unfair criticism because long-term fracture data are limited by the small sample sizes in bisphosphonate extension studies, as well as for all other medications for treating osteoporosis, and the inability to maintain the original randomized registration clinical trial placebo population sample size for an extended period of time. The second assumption is, in part, biologically correct. Bisphosphonates do retain some pharmacological effects after discontinuation, although the data supporting the maintenance of fracture reduction are based on weak data (146,156). The third assumption, that there exists a significant interaction between the duration of bisphosphonate use and the development of ASFF (i.e., longer bisphosphonate duration of use, greater rate of ASFF), is flawed. The duration data are mostly epidemiological and retrospective, much of which may be confounded by indication. In addition, the pivotal citation used to validate that there may be an incident rate for the development of bisphosphonate-associated ASFF is not a true incident rate (147).

With this knowledge, the independent FDA advisory panel did not support restricting the duration of use, a position with which some FDA employees later disagreed, publishing their own opinions on bisphosphonate duration of use (148). Regardless, there was no FDA label change limiting the duration of use of bisphosphonates for osteoporosis. Additionally, the average practicing clinician, not knowing the process of an independent FDA advisory vote, as opposed to FDA employees' ability to independently set a standard of care based on their own points of view, adopts practice patterns and at times a standard of care that might be at polar positions between the FDA-independent experts and the FDA. I believe this "standard" of terminating bisphosphonate use after 3–5 yr is largely driven by the FDA commentary rather than based on sound scientific data.

In conclusion, there are no sound scientific reasons for stopping any therapy for osteoporosis in patients at high risk for fracture. The Fracture Intervention Trial Long-Term Extension with alendronate proved this point. In the Fracture Intervention Trial Long-Term Extension, elderly patients (69 yr and older), even those with osteopenia and no prevalent vertebral compression fractures, still had more clinical (painful) vertebral fractures on a "drug holiday," and neither the baseline *T*-score nor the presence or absence of a vertebral fracture could predict who might or might not develop fractures off alendronate. There are no sound scientific data proving that long-term bisphosphonates cause ASFF. Bisphosphonates should be continued in patients at high risk for fracture; if patients insist that a therapy be changed, then it should be changed to a different approved therapy for osteoporosis, but stopping treatment should not be done, just as stopping treatment for most chronic systemic diseases is not done.

Telementoring for Osteoporosis

E. Michael Lewiecki, MD

Bone Health Extension for Community Healthcare Outcomes (ECHO) is telementoring to improve the care of osteoporosis (157). Its aim is to educate healthcare professionals (e.g., physicians, nurse practitioners, and physician assistants), especially those in underserved rural areas, to provide advanced care for patients with osteoporosis and metabolic bone diseases. For patients, this may obviate the need to travel long distances to see specialists in urban areas, often involving long wait times for appointments, allowing for more convenient care close to home in a familiar practice setting. For primary care providers, their level of knowledge is expanded, professional isolation is diminished, and no cost continuing medical education is provided.

The ECHO concept of telementoring was developed at the University of New Mexico School of Medicine in Albuquerque, New Mexico, beginning with a pilot project using chronic hepatitis C virus (HCV) infection as the model disease. A total of 21 HCV ECHO sites with 407 HCV-infected patients were enrolled in an outcomes study, with the finding that the ECHO sites performed as well as an academic medical center; about 58% of patients in each group sustained virological response (158). Since that time, ECHO telementoring has been applied to other medical conditions and replicated throughout the United States and in other world regions. ECHO demonopolizes medical care by creating knowledge networks, enabling delivery of advanced medical services by primary care providers located closer to

the patients they serve. Consistent with the principles proven to be effective with the Project ECHO strategy, the first Bone Health ECHO clinic has recently been established in New Mexico, with learning partners distributed throughout New Mexico and in other states. ECHO clinics have no boundaries, and can be attended by anyone with Internet access or a telephone connection.

Operationally, an ECHO clinic typically requires a passionate “champion” to initiate the project, a committed group of experts willing to participate in ongoing interactive learning, videoconferencing equipment, information technologists, support staff, and learning partners. Funding for ECHO clinics and outcomes research has primarily been from public and private grants, often with support from educational institutions. Other potential sources of ECHO funding include governmental agencies and insurance companies paying for healthcare services. These organizations have aligned interests in evaluating and supporting innovative methods for improving the cost-effectiveness of healthcare delivery. Potential cost savings with implementation of Bone Health ECHO include reduced or eliminated long-distance travel to specialty clinics for patients (currently paid by Medicaid in New Mexico) and prevention of costly complications of osteoporosis (e.g., hip fractures) while providing higher quality of care and reducing medical errors. With an estimated direct healthcare cost of about \$40,000 for a hip fracture (159) and a total lifetime cost of about \$81,300 per hip fracture (160), preventing just a few hip fractures will more than offset an approximate total annual cost of Bone Health ECHO of about \$250,000 (including start-up expenses, equipment, and fully compensated faculty and support staff).

Telementoring is not telemedicine, which typically makes use of audiovisual technology to provide one-on-one care for a patient located far from a specialist. Instead, telementoring with ECHO uses this technology to link a team of medical experts with many healthcare professionals, each of whom will potentially acquire skills necessary to provide advanced levels of osteoporosis care for their patients and possibly for patients of other providers in the community.

The Bone Health ECHO multidisciplinary teaching team interacts with learning partners through a weekly 1-h videoconference. Case-based discussions comprise the bulk of each session, with short (10 min) didactic presentations covering topics of interest. Patient confidentiality is maintained, with all ECHO clinics compliant with the US Health Insurance Portability and Accountability Act. The learning partners retain all responsibility for treatment decisions. Case discussions focus on teaching points that benefit all participants.

Measurement of outcomes with Bone Health ECHO will be through surveys of learning partners to evaluate achievement of stated learning objectives, self-efficacy questionnaires, and analysis of healthcare claims databases for diagnostic and procedural codes such as osteoporosis prescriptions, bone density tests, and fractures at baseline and after the ECHO intervention. Modeling can be performed to estimate expected changes in fracture rates when more patients are treated with antifracture medications. The Bone Health ECHO Collaborative has been established to share the New Mexico Bone Health ECHO experience with universities in other states. The intent is to replicate the achievements and avoid any missteps with New Mexico Bone Health, to use a common curriculum, and to pool outcomes

data. If proven successful, the innovative telementoring strategies of Bone Health ECHO will be a useful adjunct for addressing current unmet needs in the care of osteoporosis.

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