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Review Article

Proceedings of the 2023 Santa Fe Bone Symposium: Progress and Controversies in the Management of Patients with Skeletal Diseases

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Abstract

The Santa Fe Bone Symposium (SFBS) held its 23rd annual event on August 5-6, 2023, in Santa Fe, New Mexico, USA. Attendees participated in-person and remotely, representing many states and countries. The program included plenary presentations, panel discussions, satellite symposia, a Project ECHO workshop, and a session on healthcare policy and reimbursement for fracture liaison programs. A broad range of topics were addressed, including transitions of osteoporosis treatments over a lifetime; controversies in vitamin D; update on Official Positions of the International Society for Clinical Densitometry; spine surgery and bone health; clinical applications of bone turnover markers; basic bone biology for clinicians; premenopausal-, pregnancy-, and lactation-associated osteoporosis; cancer treatment induced bone loss in patients with breast cancer and prostate cancer; genetic testing for skeletal diseases; and an update on nutrition and bone health. There were also sessions on rare bone diseases, including managing patients with hypophosphatasia; treatment of X-linked hypophosphatemia; and assessment and treatment of patients with hypoparathyroidism. There were oral presentations of abstracts by endocrinology fellows selected from those who participated in the Santa Fe Fellows Workshop on Metabolic Bone Diseases, held the 2 days prior to the SFBS. These proceedings of the 2023 SFBS present the clinical highlights and insights generated from many formal and informal discussions in Santa Fe.

Keywords: Osteoporosis; ECHO; Vitamin D; ISCD; Nutrition.

Introduction

The Santa Fe Bone Symposium (SFBS) is an annual forum sponsored by the Osteoporosis Foundation of New Mexico (OFNM) for healthcare professionals interested in the care of patients with skeletal diseases. Clinical applications of the most current medical evidence are discussed in an informal collegial setting. Participants of the 2023

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"hybrid" SFBS convened in the historic city of Santa Fe, NM, USA, with 460 total attendees - 266 in-person and 194 participating remotely, representing 44 USA states and 16 countries. Physicians of many medical specialties and practice settings were represented, as well as advanced practice providers (e.g., nurse practitioners, physician assistants), basic science and clinical researchers, and dual-energy X-ray absorptiometry (DXA) technologists. Postgraduate physicians in-training attended at no cost, with registration fees awarded by OFNM. The 2-day SFBS was preceded by the Santa Fe Fellows Workshop on Metabolic Bone Diseases, a 2-day meeting for endocrinology fellows developed through collaboration of the Endocrine Fellows Foundation and OFNM. Endocrinology fellows were invited to present abstracts related to metabolic bone diseases, with the 4 best abstracts being selected for presentation at the SFBS.

Creation of enduring medical educational material is an important component of the SFBS. All sessions were recorded and archived on the OFNM website (https://www.ofnm.org/), with no charge for viewing and a modest cost for obtaining continuing medical education (CME) credits. Proceedings of previous SFBS have been published in peer-reviewed medical journals, *(1–16)* monographs in print and electronic formats, *(17–21)* audiovisual webcasts, and audio recordings. The proceedings of the 2023 SFBS presented here were written by the faculty to convey highlights that may be useful for optimizing the care of patients with skeletal diseases.

Transitions and holidays in osteoporosis therapy

Michael R. McClung, MD

Osteoporosis is a chronic disorder that requires life-long management. Multiple drugs with a spectrum of mechanisms of action are available to improve bone strength and reduce fracture risk in patients with osteoporosis. With the possible exception of denosumab, the effectiveness of all osteoporosis therapies plateaus or even wanes with long-term treatment. Duration-dependent risks of rare complications occur with long-term bisphosphonate therapy. Upon discontinuation of osteoporosis drugs, the skeletal benefit is lost, very quickly with most drugs and more slowly when bisphosphonates are discontinued. For these reasons, there is no single treatment approach to patients with osteoporosis. Optimal management must be individualized and will involve the sequential use of different classes of osteoporosis drugs over an interval of many years. There are nuances involved in the transitions between different types of treatments that influence the choices and timing of various sequences. Three frequently encountered transitions involve decisions about bisphosphonate therapy after 3-5 years and the possibility of a bisphosphonate holiday, managing the discontinuation of estrogen and denosumab, and the transitions between osteoanabolic agents and anti-remodeling (antiresorptive) drugs.

Long-term bisphosphonate therapy and bisphosphonate holidays. Bisphosphonates are the most commonly used drugs for treating osteoporosis and are recommended as initial therapy for most patients in many guidelines *(22)*. Bisphosphonates reduce bone remodeling (resorption and formation) by interfering with the intracellular function of osteoclasts *(23)*. Bone mineral density (BMD) increases modestly over the first 3-5 years of therapy, primarily due to the filling in of the remodeling spaces that are present when therapy is begun. Significant reductions in vertebral fracture risk of 50 % to 70 % are observed within the first 12 months of therapy. More modest reduction in hip and non-vertebral fracture risk are observed during the first 3 years of therapy. Beyond 5 years, no additional increase in hip BMD is observed. Fracture risk reduction persists but does not progressively decrease beyond 3 years. However, the risk of atypical femur fracture (AFF), while very low during the first few years of therapy, increases progressively from 16.1/100,000 persons/year at 5 years to 113/100,000 persons/year after 8-10 years of bisphosphonate therapy *(24)*. Importantly, the loss of fracture protection is minimal during the first two years following discontinuation of a bisphosphonate, and the risk of AFF appears to decrease substantially during those two years *(24,25)*. These findings provide the justification for temporary interruption of bisphosphonate therapy after 3-5 years in patients who are no longer at high risk *(26)*. In practical terms, this "bisphosphonate holiday" could be considered in patients who no longer meet criteria for therapy after 3-5 years of therapy. These patients should be monitored with clinical assessment and BMD testing at intervals of no longer than two years. When the patient again meets criteria for treatment because of declining BMD, having a fracture or developing new or worsening risk factors, treatment with a drug should be restarted, although not necessarily a bisphosphonate.

For patients remaining at high risk of fracture (i.e., who still meet criteria for therapy), an American Society for Bone and Mineral Research (ASBMR) task force recommended continuing the bisphosphonate or switching to another drug *(26)*. The lack of incremental benefit beyond 5 years therapy coupled with the increased risk of AFF beyond 5 years suggest that bisphosphonates should not be used for more than 5 years at a time. Switching to either denosumab or to any of the osteoanabolic drugs results in additional improvement in BMD while possibly reducing the risk of AFF *(27)*. An average increase in total hip BMD of 1-2 % is observed over 12 months when patients transition from alendronate to denosumab. Switching from alendronate to romosozumab results in an increase in hip BMD of about 3 %. Minimal change is observed during the first 12 months of teriparatide in patients who previously received alendronate, but small gains are seen during the second year of teriparatide therapy.

Summary points:

- There is no justification for use of a bisphosphonate for more than 5 years at a time.

- For patients with osteoporosis at moderate fracture risk, bisphosphonate therapy for 3-5 years may result in their no longer meeting criteria for treatment.
  - Temporary interruption of therapy with monitoring every 2 years may be considered.
  - Re-start a therapy when they again meet criteria for treatment.
- For patients remaining at high risk after 3-5 years of bisphosphonates, continuing bisphosphonate therapy provides no incremental benefit, and a switch to either denosumab or to an osteoanabolic agent would be warranted.
- The concept of "drug holiday" does not pertain to non-bisphosphonate osteoporosis therapies.

Managing the discontinuation of denosumab. Denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor-kappa B ligand (RANKL), is a potent inhibitor of bone remodeling. With therapy over 10 years, BMD increased progressively. Vertebral fracture risk was reduced by 61 % during the first year. Non-vertebral fracture risk was reduced by 20 % over 3 years, and further reduction in non-vertebral fracture risk was observed with longer term therapy. Of the 7800 patients initially enrolled in the denosumab pivotal trial, more than 2500 patients completed follow-up having received denosumab therapy for 7-10 years *(28)*. No duration-dependent adverse events were observed during that study. Thirteen patients had oral adverse events that met criteria for osteonecrosis of the jaw (ONJ) as assessed by an adjudication committee. Almost all of these lesions healed despite ongoing denosumab therapy. Two of seven femoral shaft fractures met criteria for being atypical. With so few events, the association between risks of ONJ or AFF and duration of therapy could not be evaluated.

When denosumab treatment is discontinued, there is a rapid rebound (increase) in bone resorption during the first 3-6 months to levels that exceed pre-treatment levels before returning to pre-treatment levels one to two years after denosumab discontinuation. Rapid loss of both BMD and vertebral fracture protection occurs during the first year off therapy, similar to what is observed after estrogen therapy is discontinued in younger postmenopausal women. Stopping denosumab has resulted in some patients presenting with multiple vertebral fractures. Patients receiving estrogen or especially denosumab should be informed that transition to a bisphosphonate is required to protect them from the rapid loss of BMD and fracture protection if treatment is stopped. Raloxifene only partially prevents bone loss after stopping estrogen and is not effective following denosumab discontinuation. Alendronate prevents bone loss after estrogen and after short term (< 2.5 years) denosumab therapy and should be taken until the potential for remodeling rebound has passed (about two years) *(29)*. Alendronate does not fully prevent resorption rebound or bone loss in some patients who discontinue longer-term denosumab treatment. Zoledronate, often requiring multiple doses within the first year after denosumab discontinuation, is the recommended drug to use when long-term denosumab therapy is stopped.

Based on European studies, the European Calcified Tissue Society (ECTS) has provided these recommendations for managing patients discontinuing denosumab after more than 2 years of therapy *(30)*:

- Administer one dose of zoledronate 6 months after the last denosumab dose.
- Measure serum C-telopeptide of type 1 collagen (CTX) measurements at 3 and 6 months.
- Administer another dose of zoledronate if CTX values exceed the premenopausal reference range at either time point.
- If CTX is not available, administer a second dose of zoledronate 6 and 12 months after the first dose.

Summary points:

- There is no limit to the duration of denosumab therapy.
- If therapy is discontinued, transition to a bisphosphonate, with appropriate monitoring, is appropriate.
- Preventing rebound remodeling and its consequences can be accomplished easily after short-term denosumab therapy.
- Managing discontinuation after long-term therapy simply takes planning and monitoring.
- Concern about denosumab discontinuation should not preclude the use of denosumab.

Transitions between osteoanabolic agents and anti-remodeling drugs. Osteoporosis drugs fall into two major categories: anti-remodeling drugs (estrogen agonists, bisphosphonates, denosumab) that inhibit both bone resorption and formation and osteoanabolic agents (teriparatide, abaloparatide, romosozumab) that stimulate new bone formation. The sequence of administration of these two classes of drugs and transitions between the two classes are important. Several facts support the use of an osteoanabolic drug as the initial therapy for osteoporosis *(29)*.

- Only osteoanabolic agents restore the disordered microarchitecture that characterizes osteoporosis.
- Osteoanabolic agents result in larger and faster increases in BMD than do anti-remodeling drugs.
- The BMD response to osteoanabolic drugs is smaller when given after an anti-remodeling drug than as initial therapy.
- Strong evidence exists for fracture risk reduction with osteoanabolic therapy as the initial drug.
- The effects on fracture risk of giving an osteoanabolic agent after an anti-remodeling drug are not known.
- The osteoanabolic agents teriparatide and romosozumab have been shown to be superior to oral bisphosphonates in improving BMD and reducing fracture risk.

The bone-forming effect of osteoanabolic drugs wanes with continuous therapy, so romosozumab is given in courses of 12 months, while the parathyroid hormone (PTH) receptor agonists are usually given for 18-24 months. The benefits of osteoanabolic therapies are lost if these drugs are stopped without follow-up with anti-remodeling therapy, whereas following the osteoanabolic drug with either a bisphosphonate or denosumab maintains or improves BMD. The BMD increase observed with denosumab after romosozumab or teriparatide appears to be somewhat larger than the response to alendronate. More importantly, the fracture protection afforded by a course of osteoanabolic therapy persists for at least two years after transition to the anti-remodeling drug *(29)*.

Most guidelines recommend that osteoanabolic agents be the initial therapy in patients at very high or imminent fracture risk *(22,31)*. The reason for restricting osteoanabolic agents only to the few patients at very high risk is unclear. It is intuitive that improving the structural derangement of osteoporosis by starting therapy with an osteoanabolic agent and then maintaining that better structure with a bisphosphonate or denosumab would be better than simply preserving the poor bone microarchitecture of osteoporosis with an anti-remodeling drug. As summarized above, that intuition has been proven correct. I personally believe that, if cost was not an issue, beginning therapy with an osteoanabolic agent, to be followed by an anti-remodeling drug, should be considered in every patient with osteoporosis.

Controversies in vitamin D

John P. Bilezikian, MD, PhD (hon)

Vitamin D is a threshold nutrient. A threshold nutrient is one in which increasing amounts will lead to more beneficial outcome(s) up to a point, beyond which further amounts will not have further beneficial effects. This concept, which was eloquently articulated for vitamin D many years ago by Dr. Robert Heaney, *(32)* considers variabilities such as the outcome measured and the health status of the individual. For example, a normal, free-living subject would appear to be adequately nourished with regard to skeletal health, when the 25-hydroxyvitamin D (25-OH D) concentration is at least 20 ng/mL *(33)*. Using this threshold, Bouillon and others pointed out that most of the world's population is either inadequate in vitamin D (25-OH D $<$ 20 ng/mL) or frankly deficient ($<$ 12 ng/mL) *(34–36)*. In patients with a metabolic bone disease, however, the threshold might be higher. For example, in primary hyperparathyroidism, the inflection point above which higher levels of 25-OH D do not lead to further control of parathyroid hormone is not 20 ng/mL but $>$ 25 ng/mL *(37)*. It should also be noted that in certain diseases, such as hypoparathyroidism or chronic kidney disease, a more accurate barometer of adequacy is not 25-OH D, but 1,25-dihydroxyvitamin D. This is because in those diseases, there is inefficient conversion of 25-OH D to the active metabolite *(38)*.

Several highly publicized, large placebo-controlled clinical trials have tested the efficacy of vitamin D not only with regard to osteoporosis but also with regard to other systems that have been implicated as part of the polyfunctional aspects of vitamin D. These studies are known as VITAL, VIDAL, and D2d *(39–41)*. Various endpoints included cardiovascular disease, fractures and falls, cancer, or diabetes. In the primary analyses, none of these studies showed that vitamin D supplementation had any effect on the endpoints. They were considered to be negative trials. The recent publication by LeBoff et al. showed that vitamin D supplementation had no effect on the incidence of total fractures, non-vertebral fractures, and hip fractures *(42)*. In the Discussion section of that paper, however, LeBoff and her colleagues cautioned that the results could not be extrapolated to populations who were vitamin D deficient. They recommended sufficient calcium and vitamin D supplementation to subjects with low bone mass and osteoporosis. The accompanying editorial, *(43)* however, emphatically concluded that, based on that and other studies, providers should stop screening for vitamin D deficiency, stop recommending vitamin D supplements, and stop taking vitamin D supplements to prevent major diseases or to extend life.

These negative conclusions regarding vitamin D seem to have lost sight of the Heaney dictum of vitamin D as a threshold nutrient. In all those studies, the baseline level of vitamin D was clearly greater than 20 ng/mL. If that concentration is taken as the threshold value, one would not expect these trials to have had any effect even though average levels of 25-OH D rose to significantly higher values in all studies. Moreover, in several substudies that had adequate power, vitamin D was shown to have had beneficial effects, with particular reference to the onset of diabetes mellitus in those with prediabetes *(41,44)* and on cancer *(45)*. Historically, several studies have shown that vitamin D and calcium (but not vitamin D alone) reduce fractures *(46–49)*. Conclusions related to effects of vitamin D on fall risk are uncertain due to heterogenous populations that have been studied, different doses employed, non-uniform assessment of the falls, and poor quality meta-analyses *(50–52)*.

Another controversial area is whether vitamin D reduces risk and severity of infections. Basic studies have clearly supported a role for vitamin D in innate and acquired immunity *(53)*. The use of sanatoriums, where patients with tuberculosis were typically exposed to sunlight in the pre-antibiotic era, is an intriguing historical footnote. A well-publicized meta-analysis by Martineau et al. *(54)* appeared to establish a link between vitamin D and infection. However, further studies have reported mixed results *(55–57)*.

The voluminous literature linking vitamin D to risk and severity of COVID-19 infection is also controversial *(58)*. Studies that have purported to show an effect of vitamin D on risk, severity, and mortality continue to be

intriguing but by no means definitive (59). A confounder of many of these studies relate to the measurement of 25-OH D in the context of an acute illness. The majority of circulating 25-OH D is bound to vitamin D binding protein (DBP), an acute phase reactant (60). As levels of DBP fall rapidly in the context of any acute illness, levels of 25-OH D will fall as a result since the assay is measuring primarily the component of 25-OH D that is bound to DBP. It is therefore possible that low levels reported among patients with COVID-19, or for that matter, any acute illness may not relate to true vitamin D deficiency. Only by measuring free levels of 25-OH D can this point be established.

Conclusions. Vitamin D is a threshold nutrient that is vital for human health. Studies designed to establish an effect of vitamin D on certain specific aspects of human health, need to utilize a design that identifies a population that is likely to benefit from the nutrient, namely those whose baseline levels of 25-OH D are below the threshold. Only in this way can we be certain of specific aspects of vitamin D on the skeleton as well as reported polyfunctional properties.

Clinical applications of bone turnover markers in the management of postmenopausal osteoporosis

Jacques P. Brown, MD

Acknowledgments. This presentation was developed using a recent review (61). I would like to acknowledge the contributions of the co-authors of this review: Andrew Don-Wauchope, Pierre Douville, Caroline Albert and Samuel D. Vasikaran.

Bone turnover markers (BTMs) have emerged as promising tools in the management of osteoporosis, as they provide dynamic information regarding skeletal status that is independent from, and often complementary to, BMD measurements (61).

Bone modeling and remodeling. The adult bone is continually remodeled through a process of removal of damaged tissue (resorption) with coordinated replacement of new bone (formation). The strict coordination of the two processes is referred to as "coupling." Among individuals not receiving osteoporosis treatment, resorption and formation rates are tightly linked and highly correlated (r = 0.6-0.8) (62). Both processes remain coupled with antiresorptive therapy (reduced) and osteoanabolic therapy with teriparatide and abaloparatide (increased). Modeling differs from remodeling, in that new bone is formed at sites that have not undergone prior resorption, resulting in a change in the shape of the bone during skeletal maturation and growth. Modeling has also been shown to occur in response to loading during adulthood. Teriparatide produces a combination of modeling (first 3 months) followed by remodeling-based bone formation. Romosozumab, another osteoanabolic agent, has a unique mechanism of action, stimulating bone formation by modeling-based bone formation while decreasing bone resorption.

Overview of bone turnover markers. Resorption-specific BTMs are typically degradation products of bone collagen molecules (C-telopeptide [CTX] and N-telopeptide of type 1 collagen [NTX]), which are released into the circulation and excreted in urine; or enzymatic activities reflecting osteoclastic resorption, tartrate-resistant acid phosphatase (TRACP). Formation-specific BTMs embrace different osteoblastic activities: type 1 collagen synthesis (procollagen type I N-propeptide [PINP]), osteoblast enzymes (bone-specific alkaline phosphatase [BSAP]), or bone matrix proteins (osteocalcin). PINP and CTX have been identified as the most promising markers of bone formation and resorption respectively in osteoporosis and designated the reference markers for osteoporosis by the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (63).

Biological variability. In premenopausal and postmenopausal women, and in men, genetic factors are a major determinant explaining the large interindividual variance of the levels of BTMs, with a heritability of 0.74 for BSAP, 0.62 to 0.8 for osteocalcin, 0.58 to 0.65 for CTX and 0.51 to 0.72 for PINP (61). Female reference intervals are established from healthy women aged 35 to 45 not taking oral contraceptives; CTX: 0.1-0.62 ng/mL or μg/L (100-620 pg/mL); PINP: 20-70 ng/mL or μg/L. Some sources of variability can be controlled by the physician, or if not controlled, can be considered in the interpretation of results (64). Blood sampling for CTX measurement should be performed early in the morning between 7:30 and 10:00 AM after an overnight fast in order to mitigate the effects of food and diurnal variation; ethylenediaminetetraacetic acid (EDTA) plasma is the preferred sample type. PINP is a trimeric molecule (two type 1 procollagen-α1 chains and one procollagen-α2 chain) specifically referred to as the intact PINP molecule to differentiate it from monomeric degradation products of the PINP molecule (total PINP) which are accumulating in patients with chronic kidney disease stage 3b, 4 and 5. Since PINP in blood shows minor diurnal variation or food effects, blood sampling can be performed any time of the day. Details of the pre-analytical and analytical variabilities of BTMs are reviewed elsewhere (61).

Clinical use for osteoporosis management

Diagnosis. BTM measurements do not have a role in the diagnosis of osteoporosis. However, a very high BTM (more than 1.5 times above the upper reference limit) should raise the suspicion of the presence of a secondary cause for osteoporosis (e.g., hyperparathyroidism with increased resorption and formation, multiple myeloma with increased resorption and decreased formation).

Prediction of bone loss in untreated postmenopausal women. Whilst population studies show an inverse relationship between BTMs and BMD, this relationship is not

precise at an individual level. BTMs are not useful for accurately predicting bone loss in individual postmenopausal women (61).

Prediction of fractures in untreated postmenopausal women. Increased BTMs have been shown in some prospective studies of postmenopausal women to be associated with increased fracture risk in univariate analyses, and these studies have also shown that BTMs predict fracture independently of and complementary to BMD at a population level (65). However, studies of BTMs are not available that examine the interaction of BTMs with other risk factors in fracture risk algorithms. BTMs are not included in the commonly used fracture risk assessment tool, FRAX (66).

Selection of pharmacological therapy. Whilst some studies have shown an association between baseline BTMs (CTX, PINP) or changes from baseline in BTMs (CTX, PINP) and the increase in BMD following antiresorptive therapy, anti-fracture efficacy of osteoporosis therapies is largely independent of baseline BTMs (61). Hence, BTMs are not used for guiding treatment selection in osteoporosis.

Monitoring of response to therapy. Following initiation of antiresorptive therapy, the decrease in CTX generally plateaus by one month (parenteral therapy) to three months (oral therapy) and PINP by three months (parenteral therapy) to six months (oral therapy) (61). Biochemical response to antiresorptive therapy can be assessed using either a decrease in BTMs beyond the least significant change (LSC; CTX: 31 %, PINP: 20 %) or a reduction to within a reference interval (RI): absolute value below the premenopausal geometric mean (CTX: 0.32 ng/ml [320 pg/mL]; PINP: 38 ng/mL) (67). Over 70 % of women achieved these target responses after 3 months of oral bisphosphonates in the TRIO study with positive correlations with adherence and BMD gains at 48 weeks (68). After 3 months of teriparatide, an increase in serum PINP of 10 ng/ml (LSC of 21 %) or an absolute PINP value above the upper reference limit, notionally $\geq$ 70 ng/ml together with the significant increase, is indicating effective treatment (69). Algorithms for using PINP to monitor treatments of patients with abaloparatide and romosozumab are not yet available.

Managing "drug holidays." BTMs do not predict future fractures following cessation of BP therapy. However, BTMs might guide decisions for the need and timing of re-starting therapy, often denoted by a BTM increase greater than the premenopausal geometric mean (CTX: 0.32 ng/ml [320 pg/mL]; PINP: 38 ng/ml) (61).

Managing cessation of denosumab therapy. Cessation of denosumab therapy is associated with a rebound increase in BTMs about 8-9 months after the last dose. ECTS has published guidelines recommending the measurement of BTMs after 3 and 6 months of bisphosphonate therapy following discontinuation of long-term denosumab therapy to confirm suppression of BTMs below the premenopausal geometric mean (30).

Risk assessment for atypical femoral fracture and osteonecrosis of the jaw. BTMs are not useful in predicting AFF or ONJ (61).

Summary and Conclusion. PINP and CTX have been identified as the most promising BTMs. Significant biological variability was reported in the past, but these issues have been greatly improved with automated assays and attention to pre-analytical and analytical factors that are known to influence bone turnover marker levels. BTMs are not useful in the diagnosis of osteoporosis, the individual prediction of bone loss, fracture, or rare complications, or in the selection of pharmacological treatment. Despite remaining issues with reference intervals and assays harmonization, BTMs have been useful in elucidating the pharmacodynamics and effectiveness of osteoporosis medications in clinical trials and are increasingly used in routine clinical management of osteoporosis, especially for monitoring therapy.

Osteoporosis associated with pregnancy and lactation

Christopher S. Kovacs, MD

Reproduction requires women to provide substantial calcium to their babies in amounts that exceed what they normally absorb each day for their own needs (70). About 300-350 mg calcium is transferred daily to the average fetus during the late third trimester, while 210 mg calcium is provided to milk each day during the first six months of lactation (70,71). Therefore, if maternal calcium intake and absorption are insufficient, reproduction may significantly compromise maternal skeletal strength.

During pregnancy, intestinal calcium absorption doubles, driven in part by a 2 to 5-fold increase in calcitriol, such that little or no skeletal resorption normally occurs (70). In contrast, during lactation the maternal skeleton is resorbed, independent of maternal calcium intake, to provide most of the calcium content of milk (Fig. 1) (72). This resorption is programmed by parathyroid hormone-related protein (PTHrP) released from the breasts during suckling, low circulating levels of estradiol, and possibly other factors (70). PTHrP and low estradiol synergize to stimulate resorption of bone and mineral content by osteoclasts and osteocytes. Over six months of near-exclusive lactation, areal BMD declines by 5-10 % in the lumbar spine and by about half that amount in the hip and radius (70).

Despite these normal losses of skeletal mineral during lactation (and to a much lesser extent during pregnancy), more than five dozen epidemiological studies have found that parity and lactation are not risk factors for osteoporosis, and may even protect against it.(70) This is because after weaning the baby, skeletal losses of mineral content are normally restored within 6-12 months through sustained anabolic activity by osteoblasts and osteocytes.

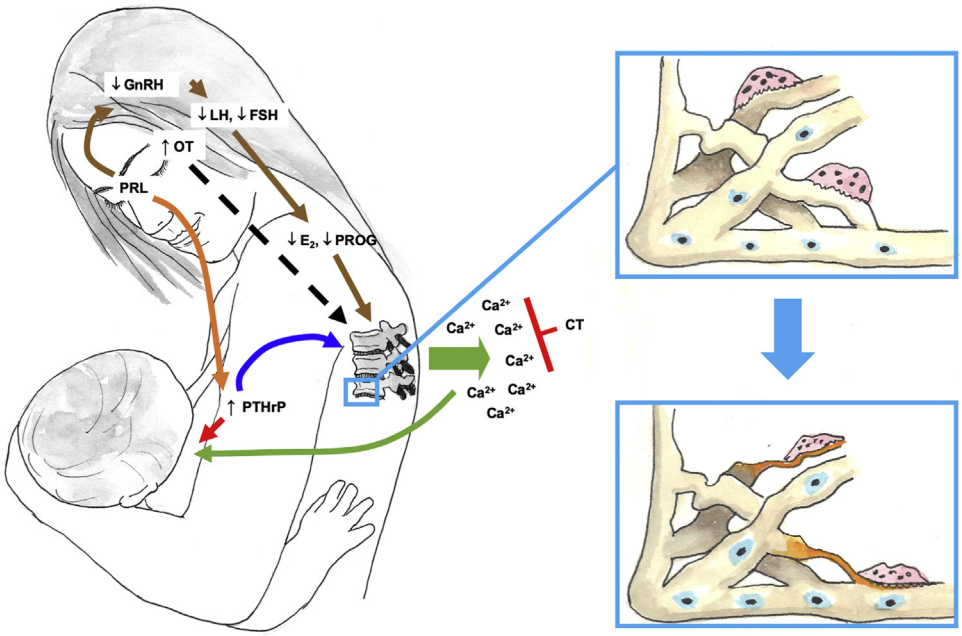

Fig. 1. Hormonal regulation of calcium mobilization during lactation. The upper right image shows osteoclastic bone resorption of maternal trabecular bone, resulting in degradation of trabecular microarchitecture seen in the lower right image. Original drawing by Christopher S. Kovacs, MD.

The factors that regulate this recovery remain to be identified *(70)*.

Although human reproduction is neutral or protective against developing osteoporosis in the long term, during the short-term women occasionally present with fragility fractures while pregnant or breastfeeding, and often as primigravidas *(73–75)*. Approximately 70-90 % of such fractures occur while breastfeeding, with the rest presenting in late pregnancy or early puerperium *(73,76,77)*. Classically these have been recognized in the literature (likely subject to reporting bias) as a cascade of 2-10 vertebral compression fractures in a single woman, although some studies suggest that appendicular fractures, especially those of the ankle and lower tibia, may be more common than realized *(73,76,78)*. How often vertebral compression fractures occur is uncertain; they may not be recognized because back pain is a common complaint during pregnancy and postpartum.

In women who experience such fractures, low lumbar spine areal BMD (aBMD) is typically found by DXA *(73)*. There is usually no pre-pregnancy DXA scan because there was no reason for it in otherwise healthy reproductive age women. Consequently, it remains uncertain whether BMD was normal before pregnancy, and how much bone loss developed during pregnancy or lactation.

Individual case reports and series, and on-line surveys, have revealed common precipitating factors for osteoporosis associated with pregnancy and lactation. During pregnancy, if dietary calcium absorption is insufficient, then the maternal skeleton must be resorbed to meet the fetal needs. Consequently, nutritional factors that reduce net calcium absorption are common and include low dietary calcium intake, high phytate intake (which blocks calcium absorption), lactose intolerance, dairy avoidance, vitamin D deficiency, gastrointestinal disorders (e.g., celiac disease, Crohn's disease), and renal disorders (calcium or phosphate wasting). Other categories include hormonal (excess PTHrP secretion from breasts or placenta, primary hyperparathyroidism, etc.), mechanical (petite skeleton, exaggerated lordotic posture of late pregnancy, increased weight), pharmacological (e.g., glucocorticoids, heparin, proton pump inhibitors), and underlying genetic or acquired skeletal disorders.

Lactation imposes an obligatory loss of bone that by itself may precipitate fragility in some women, especially if skeletal fragility preceded pregnancy, or if significant skeletal losses also occurred during pregnancy. Consequently, all factors associated with fragility during pregnancy are relevant for women who present with fractures while breastfeeding. Milk output is the principal determinant of the magnitude of skeletal resorption needed during lactation, which is why increased number or volume of feeds per day, nursing twins, and prolonged breastfeeding, have been associated with greater bone loss.*(70)* Additional factors include excessive release of PTHrP from the breasts, and the mechanical problem of frequent carrying and bending maneuvers with the baby and associated paraphernalia (e.g., car seat, stroller).

In some case reports, genetic screening of women presenting with fragility fractures while pregnant or breastfeeding has revealed causative mutations in COL1A1/A2,

WNT, or LRP5 genes (73,79). Reproduction can therefore unmask fragility that was not previously recognized.

For most women with fractures, spontaneous improvement in bone mass and presumed strength can be expected to occur post-weaning (70,73) Among women who had vertebral compression fractures, BMD spontaneously increased 10-20 % after weaning (as much as 40 % in one case), consistent with reversible bone loss that preceded the fracture (73,80). Cessation or avoidance of breastfeeding is encouraged to prevent further skeletal losses and allow the natural post-weaning recovery to be initiated.

Anecdotal and uncontrolled use of bisphosphonates, teriparatide, denosumab, romosozumab, strontium ranelate, and calcitonin have been reported with 10-30 % increases in BMD achieved, but whether this exceeds what would have occurred naturally after weaning remains unknown (73,81). One large case series reported no difference in the magnitude of increase in BMD after use of bisphosphonates, teriparatide, or combination therapy, but found twice as many fractures subsequently occurred in those who had been treated compared to those who were not treated (77). It is unclear whether this was an adverse effect of treatment or represents confounding by indication (e.g., if more severely affected women received pharmacotherapy). Use of antiresorptive medications could conceivably blunt post-weaning recovery, given that combination therapy blunted the effect of osteoanabolic treatment in women with osteoporosis (27). In postmenopausal women, any gains in BMD achieved with osteoanabolic treatment are lost in 12-18 months unless antiresorptive treatment is initiated, but limited data from women with osteoporosis associated with pregnancy and lactation suggest that the effects of osteoanabolic treatment may persist without need for antiresorptive medication (81). However, the reported follow-up was only one year.

Given these uncertainties and other concerns about off-label use of osteoporosis medications in reproductive age women, pharmacological treatment might be best reserved for the most severe cases, such as women with multiple painful crush fractures. Another approach is to consider pharmacotherapy only after assessing the magnitude of spontaneous recovery of BMD at 12 months post-weaning.

Most women can be reassured that fractures should not recur during subsequent pregnancies, especially because many cases have been nutritional in origin. However, recurrences have been documented in 20-25 % of cases, especially when genetic causes of skeletal fragility were identified or where nutritional deficiencies were not corrected (73,81).

Bone loss associated with treatment of breast cancer and prostate cancer

Azeez Farooki, MD

Bone loss is a consequence of cancer therapies with breast and prostate cancer, given that hormone deprivation is therapeutic goal in both malignancies. Bone loss at one year is accelerated compared to normal aging and thus checking bone density at that time point is justified if it is likely to influence clinical decisions. There are multiple uses of potent antiresorptives (bisphosphonates and denosumab) in patients with malignancy. In non-metastatic settings (the topic here), these agents are used to prevent aromatase inhibitor (AI) and androgen deprivation therapy (ADT) induced bone loss. In the setting of advanced cancer in the bone, these agents are approved to decrease skeletal morbidity (skeletal related events), reduce pain, and treat hypercalcemia of malignancy.

AIs have supplanted tamoxifen as standard of care adjuvant therapy in postmenopausal breast cancer. While tamoxifen in postmenopausal women exerts a weak antiresorptive effect on bone, AIs induce bone loss which is greatest in the first 2-3 years of use (82). AIs also increase fracture risk compared with tamoxifen and placebo. Clinical fracture was the primary endpoint of the ABCSG-18 study which showed that in an Austrian population, AIs increase fracture risk, even in subjects with normal BMD and relatively younger age (< 50 years) (83). Thus, to reflect this BMD-independent increase in fracture risk, the rheumatoid arthritis option in FRAX may be selected in AI treated patients. When AIs are stopped, there is a small improvement in BMD and a decrease in fracture risk (84). Bisphosphonates and denosumab are both good options to prevent bone loss and reduce fracture risk due to aromatase inhibitors.

Ovarian suppression is the use of leuprolide plus an aromatase inhibitor (or tamoxifen) in premenopausal breast cancer patients; the induction of menopause in this population can cause 17 % bone loss over 3 years, keeping in mind that BMD may be regained when ovarian suppression is halted and if menstrual cycles resume (85).

Stephen Paget made the analogy in 1889 that cancer cells are seeds that need a congenial “soil”, or bone, to grow. The bone matrix contains growth factors and thus can be thought of as fertile soil; the postmenopausal state, where osteoclastic resorption is elevated, could in theory feed dormant breast cancer cells and lead to the activation of metastatic bone disease. This theory was born out in 2015, when a large meta-analysis of randomized adjuvant bisphosphonate trials showed an improvement in disease free and overall survival in postmenopausal (but *not* premenopausal) breast cancer subjects that was driven by lower risk of bone recurrence. This absolute benefit from bisphosphonates was similar to adjuvant chemotherapy and led to a consensus statement advocating use of bisphosphonates in this population (86). Only two studies of adjuvant denosumab exist: 1) the ABCSG-18 study which showed similar results to the bisphosphonate adjuvant data (36) and 2) the D-CARE trial which showed no benefit.

In contrast to antiresorptives, teriparatide and abaloparatide cause a sequential increase in bone formation

followed by an increase in bone resorption. Increased seeding of breast cancer cells to bone has been shown in mice given recombinant PTH (rPTH) (87). Given the benefits of antiresorptives in malignancy, the theoretical risks of PTH analogues suggest caution in patients with a recent history of bone tropic malignancy. A pilot study at Memorial Sloan Kettering is investigating the use of romosozumab in active multiple myeloma.

In prostate cancer, in addition to ADT, androgen receptor inhibitors (ARIs), and abiraterone may lead to compromised bone health. Achievement of castrate levels of testosterone leads to loss of muscle mass and bone loss (in large part due to decreased estradiol levels), respectively. Gonadotropin releasing hormone (GnRH) agonist use for more than 1 year likely causes a persistent increase in fracture risk over many years, whereas use for less than 1 year results in a transient increase in fracture risk that returns to control levels when ADT is stopped (88). An underappreciated fact is that most clinical fractures in men with prostate cancer do not directly result from bone metastases and instead are fragility fractures. If fracture risk is elevated based on FRAX and/or clinical concern, bisphosphonate or denosumab therapy should be prescribed for at least the entire duration that a patient's testosterone level is < 200 ng/dl.

ARIs increase fracture and fall risk based on a meta-analysis of eleven trials (89). The mechanism of increased falls is not clear but apalutamide and enzalutamide cross the blood brain barrier while darolutamide does not.

The CYP17 inhibitor abiraterone produces testosterone levels 1 log lower than those achieved with traditional ADT. Shunting in the steroid synthesis pathway causes hypokalemia and hypertension.

Prednisone 5mg twice daily is standard concomitant therapy to control mineralocorticoid excess and thus likely is detrimental to bone health. Although a lower steroid is not as effective at controlling hypertension or hypokalemia, most oncologists will agree to reduce the steroid dose (with the optimal dose likely being 2.5 mg twice daily).

Prostate cancer patients with a large burden of osteoblastic metastases may have secondary hyperparathyroidism, implying consumption of calcium by bone metastases, and therefore a "stressed" calcium metabolism with significant risk for hypocalcemia after parenteral bisphosphonate or denosumab (90). PTH levels should be controlled with calcium and vitamin D; magnesium, phosphorus and renal function should also be scrutinized. Neuroendocrine prostate cancer represents a minority of cases; rarely, these tumors may secrete adrenal corticotropic hormone (ACTH) or fibroblast growth factor 23 (FGF23), causing Cushing's syndrome or tumor induced osteomalacia, respectively, and thereby potentially cause bone fragility.

Although guidelines only support use of zoledronic acid at oncologic doses to reduce symptomatic skeletal events (SSEs) due to bone metastases in castration resistant prostate cancer, the drug can certainly be used at osteoporosis doses during at any point in the prostate cancer disease continuum to reduce the risk of osteoporotic fracture.

Nutrition and skeletal health: updates and controversies

Deborah E. Sellmeyer MD

Nutrition is critical to optimizing skeletal strength throughout the lifespan. While most, if not all, nutrients contribute to bone health, there are limited data on the effects of supplements on bone density and fracture risk. Thus, controversy remains on the role of nutrition in general and the value of supplements in particular.

Calcium supplementation with or without vitamin D has been shown to reduce fracture risk in three meta-analyses, most recently in 2016 (91). Vitamin D controversies are addressed in a separate section. With regard to calcium, controversy has been raised as to whether calcium supplements may increase the risk of vascular calcification and adverse vascular outcomes; however, extensive literature reviews, consensus meetings, and meta-analyses have shown no increase in vascular calcifications, vascular events, or mortality for healthy individuals consuming calcium at recommended levels, including those using supplements (92,93). Since individuals with chronic kidney disease (CKD) are in neutral calcium balance with total calcium intakes of 1000 mg/day, lower than usual target intakes are appropriate for this group. Clinicians should also be alert to conditions where calcium absorption is impaired; higher calcium intakes may be needed for some individuals, such as those with inflammatory bowel disease or bariatric surgery.

The metabolism of sulfur-containing amino acids in dietary proteins produces a dietary acid load. Potentially offsetting acid intake, dietary base is consumed in the form of alkaline potassium compounds found in potassium rich fruit and vegetables. Higher intakes of dietary acid precursors relative to base precursors leads to a net dietary acid load which must be buffered. In the face of a dietary acid load, base from bone in the form of carbonates and phosphates is mobilized to neutralize dietary acid, potentially contributing to skeletal fragility with aging. Alkaline potassium compounds such as potassium citrate have been shown to improve calcium balance, (94) increase bone density, and improve bone architecture (95) although not all studies have shown improvements in bone density and data on fracture effects are lacking.

Isoflavones, plant compounds with weak estrogenic effects, have had mixed results on skeletal outcomes in the literature, in part due to methodological factors in clinical trial design, including variability in study interventions and study populations. However, two recent meta-analyses have shown increases in BMD with genistein and ipriflavone, a synthetic daidzein derivative (96,97).

Sodium chloride may have an adverse effect on the skeleton by increasing urine calcium excretion. Hypercalciuria and increased bone resorption induced by a high sodium diet can be offset by consumption of alkaline potassium compounds *(98)*.

Vitamin K is involved in bone formation by carboxylating the bone-forming protein osteocalcin. Data on the effects of vitamin K on bone density and fracture risk are mixed, with recent meta-analyses showing no clear evidence of benefit for K1, K2, or MK4 *(99–101)*. In some trials of vitamin K supplements, bone density did not increase, but fractures were non-significantly numerically lower in the vitamin K groups, leading to speculation that vitamin K may beneficially impact other aspects of bone strength known as bone quality. Larger studies with fracture outcomes are needed to test this hypothesis.

The proprietary compound strontium ranelate has been shown to reduce the risk of vertebral and nonvertebral fractures and has been available in Europe. However, due to post-marketing findings of an increased risk of thromboembolism and nonfatal myocardial infarction, use of strontium ranelate was progressively restricted and its current availability is very limited. Strontium compounds available in health food stores and via the internet are strontium citrate or strontium carbonate; benefits, risks, and side effects are unknown. Strontium replaces calcium in the hydroxyapatite crystal and artifactually elevates bone density readings. As risks are unknown and bone density testing is impacted, forms of strontium other than ranelate should be avoided.

Magnesium is important for proper structural formation of hydroxyapatite crystals in bone and adequate secretion of parathyroid hormone. Nutritional surveys have shown that magnesium intakes in the US are typically below recommended levels, however data are lacking on whether magnesium supplements provide skeletal benefits.

Other than calcium and vitamin D, data are very limited on the effects of nutritional supplements and bone health. Some aspects of nutrition such as acid/base balance and certain isoflavones have growing bodies of evidence supporting their ability to improve skeletal outcomes, but larger studies with fractures as an adequately powered outcome are needed to advance recommendations for use of these supplements.

New ISCD Official Positions for fracture risk assessment and reporting

William D. Leslie

The International Society for Clinical Densitometry (ISCD) is a professional association dedicated to advancing high quality musculoskeletal health assessment. At regular intervals the ISCD holds Position Development Conferences (PDCs) to provide guidance on controversial clinical questions and, through a well-defined process, develops these into Official Positions. As of 2019, there were approximately 300 adult-, 60 pediatric-, and 30 FRAX-related Official Positions. In 2022, three independent Task Forces were convened to study member-solicited topics that were not adequately addressed by the existing positions. The ISCD held a PDC in Chicago in March 2023 to review the compiled evidence and formulate new recommendations, which will be published and integrated into the existing Official Positions.

Trabecular bone score (TBS) was highlighted as an important area for attention due its increasing use in the US and other countries. Although TBS was addressed in previous PDCs, questions remain related to the performance and reporting of TBS; these were addressed by the Task Force. There was consistent evidence, including a recent large analysis of 73,108 individuals aged 40 years and older, that BMD and TBS are complementary in their ability to predict fractures independent of FRAX risk factors *(102)* (Fig. 2). The reporting of TBS-adjusted fracture risk was recommended over a categorical approach (e.g., tertiles) as the preferred way for integrating TBS into the clinical practice, since this takes maximal advantage of TBS as a continuous risk factor (similar to BMD), incorporates the different gradients of risk (steeper for BMD than TBS), includes TBS-age interactions (since TBS has a larger impact in younger than older individuals), and should provide seamless integration into clinical practice guidelines that include FRAX. The use of TBS-adjusted FRAX can change clinical management in 9.0 % to 17.9 % of individuals who are close to accepted pharmacologic intervention thresholds (within 5 % of the major osteoporotic fracture or within 1 % of the hip fracture treatment cutoffs) *(103)*. There is evidence supporting the use of TBS regardless of sex, race/ethnicity and osteoporosis treatment (prior or current) *(104–106)*. However, TBS was not found to be predictive of fractures in adults age 20 and 39 years *(107)*.

Technical factors related to TBS were highlighted. Since the TBS software adjusts for the effect of abdominal tissue thickness on image texture using body mass index (BMI) as a proxy for abdominal tissue thickness, it is essential that accurate height and weight are entered into the DXA scanner to avoid incorrectly calculated TBS measurements. This was demonstrated in a simulation from Binkley et al *(108)* where relatively modest changes in entered weight could change TBS by greater than the least significant change (LSC) (Fig. 3). BMD derived from DXA as g/cm^2 is unaffected by entering a different weight, height or sex, whereas changing these parameters directly affects TBS which must compensate for predicted effects of BMI. An updated version of the TBS algorithm that considers DXA-measured tissue thickness is still in development and will hopefully eliminate this dependency. Sensitivity of TBS to technical factors related to change in weight and body composition currently limits its utility for serial monitoring, especially bisphosphonate therapy for which change in TBS is quite

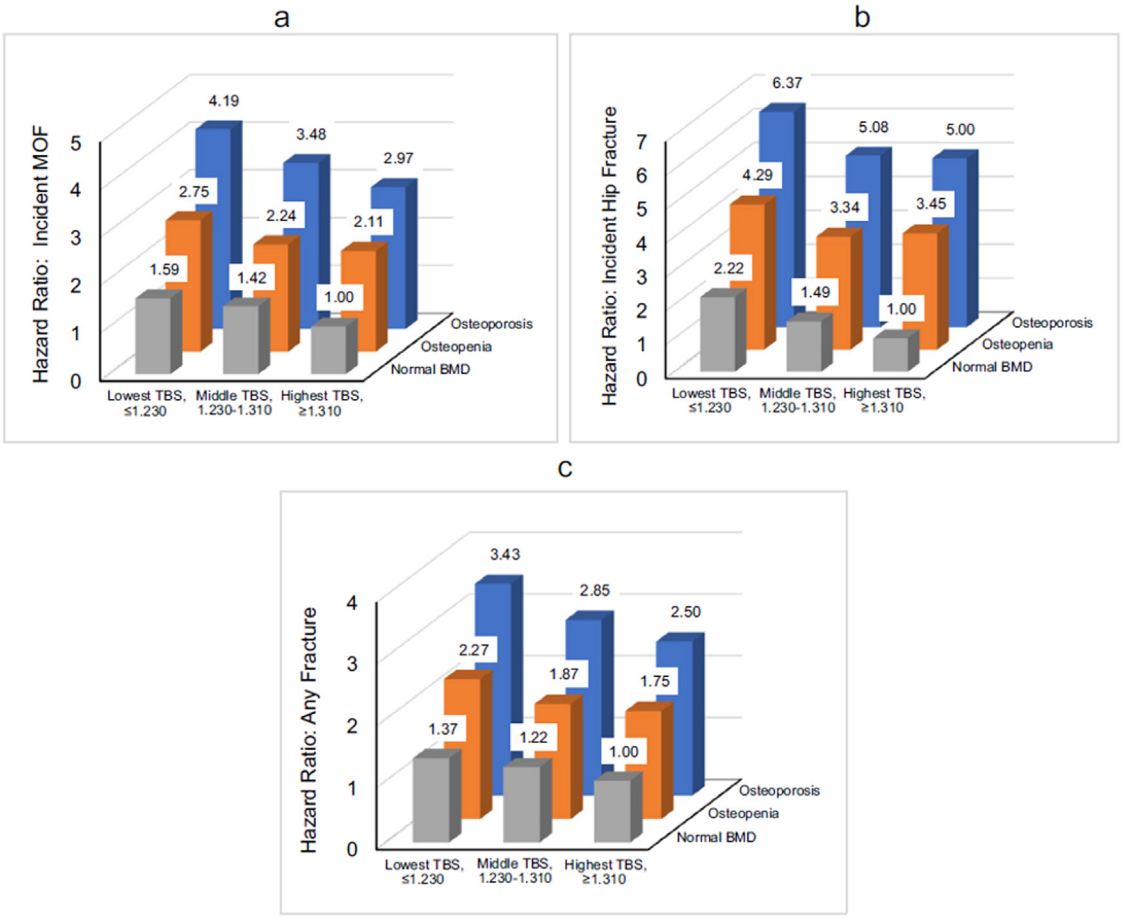

Fig. 2. Adjusted hazard ratios for fracture by bone mineral density (BMD) and trabecular bone score (TBS) category. Decreasing BMD (normal, osteopenia, osteoporosis) and TBS categories (lowest ≤ 1.230, middle 1.230–1.310, highest ≥ 1.310) were independently associated with stepwise increased risk for incident major osteoporotic fracture (a), hip fracture (b), and any fracture (c). Adjusted for type of scanner, age, sex, body mass index, previous fracture, parental hip fracture, glucocorticoid exposure in the prior year, smoking status, high alcohol intake, rheumatoid arthritis, and secondary osteoporosis**.** Reproduced with permission from Goel et al**.** *(102)*.

modest and usually not observed at the individual level *(109)*. Although exclusion of vertebral levels affected by structural artifact is recommended for BMD reporting, TBS is relatively unaffected by the most common source of structural artifact, intervertebral disc degeneration and/or facet arthropathy *(110)*. As with BMD, there are level-specific differences in TBS between the individual vertebral body measurements that increase from cranial to caudal. Since TBS is calculated as a simple average of TBS from the available individual vertebrae, this systematically decreases TBS when lower lumbar vertebral levels are excluded and increases TBS when upper lumbar vertebral levels are excluded. Treatment recommendations can change in over 10 % of individuals with baseline risk close to the FRAX-defined intervention threshold, potentially leading to overtreatment when lower lumbar vertebral levels are excluded and undertreatment when upper lumbar vertebral levels are excluded *(111)*.

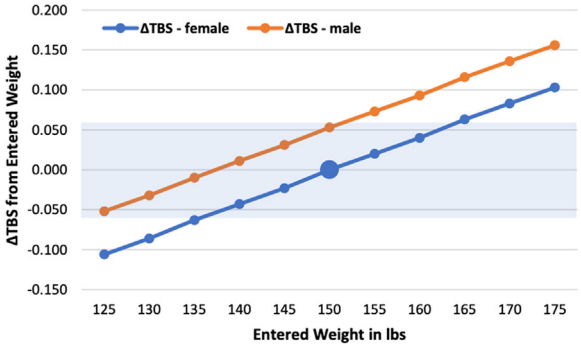

Fig. 3. Effect of changing entered weight and sex on calculated trabecular bone score (TBS). Large blue circle shows the reference value (TBS = 1.326 for a female weighing 150 pounds). Shaded area indicates the 95 % least significant change (LSC) limits. Adapted from Binkley et al. *(108)*.

Notably, the currently available TBS-adjustment to FRAX is based upon TBS derived from L1-L4 (112). This argues for the use of L1-L4 as the standard for TBS reporting until there are modifications to the TBS software that can accommodate measurements obtained from other combinations of lumbar vertebral levels. Finally, although evidence is limited, it was suggested that TBS not be used in situations where the lumbar spine is affected by extreme structural artifact, instrumentation, severe scoliosis, or metastatic disease. More recently, an independent statement on the clinical use of TBS has appeared from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and the International Osteoporosis Foundation (IOF) (113). Although many recommendations were similar, the latter was more positive on a role for TBS in monitoring treatment with long-term denosumab and anabolic agents.

Additional Task Forces provided guidance on DXA reporting and serial monitoring, respectively. There was alignment of terminology related to current language related to race/ethnicity (114). More detailed guidance on DXA full femur imaging (FFI) was provided, highlighting the importance of focal lateral cortical thickening and transverse lucencies as high likelihood features requiring urgent consultation and further imaging, whereas diffuse cortical thickening alone is nonspecific. DXA intervals for serial monitoring have also evolved from "one size fits all" to a more individualized approach. Testing intervals should be based upon clearly defined objectives and when results are likely to influence patient management, considering the individual's baseline BMD, pharmacological treatment, and presence of clinical risk factors and/or medications associated with more rapid BMD loss.

Perioperative bone health assessment for spine fusion

Mark L. Prasarn, MD

With the growing population of the elderly, there are many patients with osteoporosis needing surgical interventions for spinal disorders and other orthopaedic problems. These patients desire a high level of physical function and independence in their geriatric years. There have been great advances in anesthesia, surgical techniques, and instrumentation that now make patients surgical candidates who historically would not be. Nonetheless, complications due to poor bone quality can result poor surgical outcomes. Providers and institutions have now begun to use protocols for perioperative care to optimize outcomes. Exercise, smoking cessation, nutrition enhancement, and diabetes management have become a regular part of surgical preparation for many institutions. Some now include bone health assessment in protocols for orthopaedic and spinal procedures.

Spine fusion is a commonly performed procedure when operating on the spine. Over the past several decades, there has been an upward trend in the use of this procedure, with an estimated increase of more than 80 % by 2060 (115). Spinal fusion (also known as arthrodesis) is a surgical procedure where internal stability of the spine is achieved by facilitation of bone interconnections of two or more vertebrae. This is typically accomplished by decorticating bone edges, laying down a bone graft, and providing mechanical stability with spinal instrumentation. Fusion is facilitated by having a favorable biomechanical environment (e.g., stability of instrumentation and alignment of the spine) through a concerted effort of osteogenesis, osteoconduction, and osteoinduction. Low bone density and poor bone quality are major factors that result in failures of fusion (pseudarthrosis).

Patients with osteoporosis having spine fusions are at high risk for complications that include pseudarthrosis, hardware failure, and proximal junctional kyphosis. Unfortunately, it is currently common that patients with osteoporosis are not identified before surgery, and those who are identified are often not treated. For these reasons, spine surgeons are now beginning to use protocols to optimize bone health prior to surgery. Anabolic osteoporosis medications before and after surgery are often considered, with the aim of preventing hardware failure and enhancing ossification of the fusion mass. The efficacy and safety of anabolic therapy has been extensively studied with teriparatide and a few studies with abaloparatide, with some future studies evaluating romosozumab.

Common protocols involve referring women over age 60 years and men over age 70 years to an osteoporosis specialist for bone health assessment before spine fusion. When appropriate, BMD is measured and laboratory studies ordered. Non-pharmacological approaches should be discussed. Anabolic therapy, beginning about 90 days prior to surgery, may be considered, especially for those with very low BMD, prior fractures, smokers, long-term glucocorticoid therapy, and large skeletal deformities. Most protocols recommend continuing anabolic therapy for at least 12 weeks following surgery, and for patients at very high risk of therapy a full 1- to 2-year course of therapy may be appropriate.

The body of evidence supporting the use of anabolic agents in the perioperative period is growing. There is much evidence from animal studies that teriparatide and abaloparatide can help improve spine fusion rates, increase time to fusion, provide better fusion mass, and decrease the risk of hardware failure (116,117). Inoue et al. gave daily or weekly doses of teriparatide to patients with postmenopausal osteoporosis and found insertional torque for pedicle screws was higher in both groups versus control. This showed that bone strength and quality can be improved with teriparatide and possibly a decrease of hardware failures (118). In another study looking at a similar cohort of women, Ohtori et al. found a lower rate of

pedicle screw loosening at long-term follow-up with teriparatide compared with controls and a risedronate group (119) In a later study by the same group, 45 women with postmenopausal osteoporosis were given short or long-duration daily teriparatide, or a bisphosphonate after a posterolateral lumbar fusion with local autograft. Bone union rate and average duration for bone union were 92 % in the long-duration treatment group, 80 % in the short-duration treatment group, and 70 % in the bisphosphonate treatment group, respectively (120). Ebata et al. performed a multicenter prospective study looking at transforaminal lumbar interbody fusion (TLIF) and posterior lumbar interbody fusion (PLIF) in 75 patients all over the age of 50 years with osteoporosis. The dosing regimen was once weekly. At 4 months postoperatively, they were able to show better fusion in the cage center in the teriparatide group. The patients also demonstrated decreased bone resorption based on markers in this group (121). Finally, there is now evidence that teriparatide administration can decrease the incidence of proximal junctional kyphosis and failure in adult deformity surgery (122).

The role of anabolic therapy for patients having spine surgery has not been clearly defined. We do not know the ideal dosing regimen or optimal duration of therapy. Most commonly the medications are started several months (minimum 2 months) before surgery and continued for at least 3 months after surgery. There is need for future research to better define the role of these medications, cost effectiveness, and safety.

Genetic Testing in Skeletal Diseases

Brendan Lee, MD, PhD

Genotype-Phenotype Correlation. Genetic testing in skeletal diseases is a major element in the implementation of genomics in skeletal medicine. The impact of genetic testing has been driven by rapid advances in genomic technologies in terms of increasing resolution and decreasing cost of goods. Specifically, the advances in next generation sequencing (NGS) have rapidly increased the number of genotype-phenotype correlations. As of August 2023, there are over 4800 genes in which mutations have been correlated with defined clinical phenotypes (www.omim.org). Moreover, there have been 7400 distinct clinical phenotypes that have been correlated to mutations in these genes underscoring the increase in phenotypic expansion (i.e., different mutations in the same gene can cause distinct and potentially quite disparate clinical phenotypes). From a discovery perspective, this phenotypic expansion under-score the human consequences of specific structure-function correlations in proteins and the pathways in which they function. From a skeletal medicine perspective, over 3000 of these 7400 human phenotypes involve some skeletal complications (www.omim.org). Hence, genetic testing in skeletal diseases is important not just for diagnosis, but also for understanding the broad impact of human mutation on human health.

Human Variation in Disease. Deoxyribonucleic acid (DNA) variation can occur as sequence variation (single nucleotide variation (SNV) or single nucleotide insertion or deletions (Indel). Alternatively, copy number variation (CNV) of varying sizes can also occur. When chromosomal in size, they are characterized as aneuploidy (e.g., trisomy 21). From a diagnostic perspective, variants that are de novo (vs. those inherited from parents) are rarer (i.e., 1-2 coding SNVs per genome), and generally have larger clinical effect. Irrespective of whether de novo or inherited, the assignment of causality to DNA variants must integrate basic principles of human genetics including incomplete penetrance (i.e., the lack of a phenotype in an individual known to carry a pathogenic mutation) and variable expressivity (i.e., different severity of the phenotype in different individuals carrying the same mutation) with clinical phenotype.

Phenotypic Expansion. The most important driver of phenotypic expansion in the revolution in genetic testing has been the rapid reduction of costs of nucleic acid sequencing, faster than that predicted by Moore's Law (i.e., a doubling of the number of transistors on a microchip every 2 years). Over the past 30 years, human genetics has evolved from focusing on identifying rare variants in candidate genes with strong effects causing Mendelian phenotypes (e.g., osteogenesis imperfecta); to the discovery of common variants with weak effects contributing to common phenotypes (e.g., osteoporosis) in genome-wide association studies (GWAS); to now rare variants again, with strong effects often in combination to cause common phenotypes via genome-wide sequencing (123). This reflects the continuous spectrum of rare disease phenotypes (e.g., osteogenesis imperfecta) to early onset of common phenotypes (e.g., brittle bone diseases and osteoporosis). This overlap of Mendelian and complex phenotype is not surprising given that estimates of heritability of variation in bone mineral density and bone architecture are as high as 80 %, and that GWAS have identified over 500 loci associated with low BMD and/or fracture incidence (124,125).

Molecular Diagnostic Modalities. The advances in technologies have also driven the revolution in targeted vs. genome-wide approaches (126). Targeted approaches include methods such as Fluorescent In Situ Hybridization (FISH) for detecting CNVs, Sanger Sequencing of candidate genes, and most recently, Next Generation Sequencing (NGS) Panels for SNVs and also small CNVs. Genome-wide, detecting chromosomal aneuploidies with traditional karyotype has evolved to microarray-based approaches (i.e., chromosome microarray or CMA) to detect CNVs less than 1kb, to short-read whole exome sequencing (WES) and whole genome sequencing (WGS), and to now emerging, long-read WGS. Ultimately, all of these approaches have various sensitivities and specificities. In general, technical sensitivity (and

precision) is quite high with current technologies, but the range of diagnostic specificity can be quite broad and is impacted by many variables (discussed below). Irrespective, WGS is rapidly emerging as the best technical approach as it has the potential to cover the broadest range of human variation with increasingly lower cost with high sensitivity and precision.

Factors Impacting Diagnostic Yield. For unselected clinical phenotypes, the diagnostic yield of the various DNA testing approaches ranges from 15-20 % for chromosomal microarray analysis (CMA), to 30-50 % for WES, to an up to additive diagnostic yield of 10-15 % for WGS *(127–129)*. Admittedly, these estimates have been generated mostly from pediatric populations and the yields in adult disease are often lower. Irrespective, one important impact on yield is reanalysis because of the rapidly growing knowledge base of gene-disease association (described above) *(130)*. Because of this and other factors (i.e., the sensitivity of specific technologies for different human variants; the accuracy of reference genomes being used for interpretation; the availability of clinical phenotype for correlation; the limitations of variant frequencies for populations of differing ancestry [with current databases biased for European descent]; and the growth of rare [and eventually unique] genotype-phenotype correlations), the interpretation of genetic testing changes with time. Another consequence of the increasing power of genetic testing technologies, there is increasing recognition and diagnosis of multiple molecular gene defects in individual patients (i.e., oligogenic causes of blended clinical phenotypes). In recent studies, this has been reported to be detectable in up to 5 % of cases *(131)*.

Diagnostic interpretation. The clinical laboratory interpretation of human genomic variation is performed by professionals certified either by the American Board of Pathology (via the Molecular Pathology certification) or by the American Board of Medical Genetics and Genomics (via the Laboratory Genetics and Genomics certification). The professional guidelines for DNA testing interpretation are provided by the American College of Medical Genetics and Genomics *(132)*. Multiple lines of evidence (clinical case, population, experimental, and bioinformatics-predictive) contribute to the confidence level assigned to the likelihood a variant is associated with a clinical phenotype. This ranges from being pathogenic, likely pathogenic, a variant of uncertain significance, likely benign, or benign. Ultimately, making sense of genomic variation is a process to distinguish causal vs. correlative relationship. The ACMG professional guidelines for pathogenicity are a measure of confidence and not variant severity. For example, many severe "stop mutations" in the human genome leading to haploinsufficiency of the protein is well tolerated and not associated with definable phenotypes. Variant interpretation is ultimately relative to the clinical phenotype provided and the interpretation changes over time with reclassification of the variant not being uncommon as technologies change (long read vs. short read DNA sequencing) and as our knowledge base increases. Hence, a variant diagnostically classified as a "variant of uncertain significance" (VUS) may be in fact pathogenic and be considered as such by the provider when integrating the clinical correlation. An important consequence of genome wide approaches like WGS is the discovery and reporting of secondary findings that may be clinically actionable, but unrelated to the indicated clinical reason for testing. The reporting of such "medically actionable" variants is guided by the ACMG and providers should be aware whether patients have opted in for return of such information *(133)*.

On the horizon. The rapid pace of technological advances will continually change genetic testing practice and approaches in genomic medicine. The rapid drop in DNA sequencing cost will lead to a $100 genome making this the most cost effective and sensitive first-tier method of testing. Long-read technologies will empower reporting of a class of structural variations not previously identified *(134)*. Soon, whole transcriptome analysis or Ribonucleic acid (RNA) sequencing will be clinically available for complementing the prioritization of candidates identified in WGS and for RNA-first approaches of analysis *(135)*. The implementation of high-quality human genome references will further identify variation such as in repeat regions previously to be uninterpretable *(136)*. Finally, difficult to detect mechanisms of disease such as low-level mosaicism, epigenetic disorders associated with altered DNA methylation and histone modification, and higher order dysregulation of DNA interaction will become accessible for clinical DNA testing. Together, these new approaches will begin to fill in the "missing heritability" of genetic diagnosis in skeletal diseases.

Basic bone biology for clinicians

Teresita Bellido, PhD

Bone growth and maintenance throughout life is accomplished by bone cells. Therefore, the study of bone cell biology, the role of bone cells in the processes of bone modeling and remodeling, and the signaling and molecular mechanisms underlying their physiological function is indispensable to shed light on the mechanisms that trigger bone diseases and to design optimal treatment regimens tailored to specific bone maladies. These goals are accomplished by basic and translational research using in vitro, ex vivo, and preclinical animal in vivo approaches.

Bone cells. The three main bone cells are osteoclasts, osteoblasts, and osteocytes. Osteoclasts and osteoblasts are present on bone surfaces only transiently, in low number (1-2 % and 5-6 %, respectively) and in variable locations. Osteocytes, on the other hand, are the most abundant bone cells (> 90-95 %), are long-living, and are present in the entire bone volume.

Osteoclasts are derived from precursors of the hematopoietic lineage; their proliferation and differentiation are

regulated by cytokines (e.g., macrophage colony-stimulating factor [M-CSF] and RANKL) provided by cells of the bone marrow stromal and osteoblastic lineage. Differentiation and fusion of osteoclast precursors (mononucleated monocyte/macrophage-like cells) result in multinucleated mature osteoblasts. After finishing their bone resorption function, osteoclasts undergo apoptosis. Some osteoclasts appear undergo fission to form daughter cells called osteomorphs, which re-fuse to rapidly generate active osteoclasts in response to increases in the RANKL/osteoprotegerin (RANKL/OPG) ratio.

Osteoblasts and osteocytes belong to the mesenchymal lineage, the same lineage that gives rise to adipocytes and muscle cells. Several pathways regulate osteoblast precursor commitment, pre-osteoblast proliferation and differentiation into matrix-producing osteoblasts, including the Wnt and Notch pathways and signaling activated by bone morphogenetic proteins. After accomplishing their bone forming function, most osteoblasts undergo apoptosis, some turn into lining cells that cover quiescent bone surfaces, and some become entombed within the mineralized bone matrix and differentiate into osteocytes.

Osteocytes are the terminal cell type of the osteoblastic lineage. They express most of the same genes and proteins expressed by osteoblasts, although in some cases at different levels, and also exhibit a unique gene expression profile. Two features of the osteocytic transcriptome signature are the expression of genes/proteins that confer the characteristic dendritic cell shape (E11, fimbrin) and regulate phosphate and mineral homeostasis (FGF23, MEPE, DMP1, Phex). In addition, osteocytes express molecules that regulate bone formation and resorption. Only osteocytes in bone express the gene *SOST* and secrete its product, the protein sclerostin, a potent inhibitor of bone formation. And, both osteocytes and osteoblasts express the other Wnt inhibitor Dkk1. Osteocytes also express pro- and anti-osteoclastogenic molecules, including OPG and RANKL *(137)*.

It is now recognized that osteoclasts and osteoblasts are the cells that execute modeling/remodeling, whereas osteocytes drive modeling/remodeling by orchestrating osteoblast and osteoclast function in response to both mechanical and hormonal cues.

Bone modeling and remodeling. Bone modeling is the process responsible for changing the bone shape and takes place during longitudinal bone growth and during skeletal adaptation to mechanical needs. Bone modeling occurs on periosteal, endocortical and trabecular bone surfaces, and leads to increased bone mass. Bone remodeling is responsible for the renewal of bone throughout life, occurs also on all bone surfaces (periosteal, endocortical and trabecular) as well as within the intracortical bone areas. Bone remodeling maintains the structural function of bone by repairing fatigue-induced microdamage and maintains the metabolic function of bone by replacing over-mineralized bone, preserving osteocyte viability, and releasing minerals and growth factors.

During modeling, osteoblasts and osteoclasts work on separate surfaces adding or removing bone leading to changes in bone shape. In contrast, during remodeling, the bone cells work coordinately in sequence on the same surfaces, assembled within bone multicellular units (BMUs). Within the BMU, osteoclasts remove damaged/old bone and osteoblasts come behind to deposit new bone matrix that subsequently mineralizes. The ratio between the activities of osteoclasts and osteoblasts determines the focal remodeling balance within each BMU. Normal focal bone balance occurs when osteoclast activity is equal to osteoblast activity within each BMU; that is, the same amount of bone is resorbed than formed, and thus bone mass is maintained. In pathological conditions, osteoclast activity is increased over osteoblast activity resulting in focal remodeling imbalance, and bone loss. The imbalance might result from augmented osteoclast number/function or to decreased osteoblast number/function. Estrogen or androgen deficiency is an example of "osteoclast-mediated" bone loss and aging an example of "osteoblast-mediated" bone loss.

PTH and bone cells. Major effects of hormones on bone homeostasis are mediated by direct hormonal actions on bone cells. The profound skeletal effects of PTH are mediated through receptors (PTH1R) expressed on cells of the stromal osteoblastic lineage. PTH accelerates the rate of bone remodeling and induces bone anabolism. When PTH is elevated continuously in a chronic manner as during hyperparathyroidism, PTH increases the bone remodeling rate and can induce bone loss. In contrast, when PTH is elevated transiently in an intermittent manner as with daily injections induced bone anabolism. The mechanisms underlying these effects of PTH are complex. PTH stimulates bone resorption by regulating the expression of pro- and anti-osteoclastogenic cytokines in cells of the osteoblastic lineage. PTH stimulates bone formation by regulating osteoblast generation and life span. PTH promotes survival of mature osteoblasts prolonging their matrix synthesizing function. Further, PTH inhibits in osteocytes the expression of the inhibitor of bone formation sclerostin, potentiating the stimulatory effect of Wnt signaling on osteoblast differentiation. PTH might also re-activate quiescent lining cells to become matrix synthesizing osteoblasts *(138,139)*.

Bone cells, and in particular osteocytes, are mediators of the endocrine function of bone that regulates mineral homeostasis. PTH and FGF23 are two major regulators of inorganic phosphate (Pi) homeostasis. High circulating levels of Pi induce PTH secretion by the parathyroid glands and FGF23 production by bone cells (primarily osteocytes). In turn, PTH and FGF23 inhibit Pi re-absorption in the kidney. PTH also increases FGF23 production in bone, leading to further inhibition in Pi reabsorption. Further, FGF23 inhibits 1,25-dihydroxyvitamin D production in the kidney, which in turn reduces 1,25-dihydroxyvitamin D-mediated intestinal Pi absorption. Combined all these actions lead to normalization of plasma Pi levels.

PTH also controls calcium homeostasis. Low calcium in the blood increases PTH secretion by the parathyroid glands. Action of PTH in kidney and bone cells lead to normalization of circulating calcium levels. In the kidney, PTH increases calcium reabsorption in the proximal tubule and also stimulates the synthesis of the 1,25-dihydroxyvitamin D in the kidney, which in turn stimulates the synthesis of calcium binding proteins and increases calcium absorption in the intestine. In bone, PTH stimulates the release of calcium from mineralized bone by increasing bone resorption mediated by osteoclasts. This effect on osteoclasts is indirect, however, since only cells of the mesenchymal lineage (osteoblasts and osteocytes) express receptors for PTH. Therefore, through FGF23 production and PTH action, osteocytes mediate the endocrine function of bone of regulating phosphate and calcium homeostasis *(139)*.

Diabetes-induced bone disease and treatments. The mechanisms underlying the bone disease induced by diabetes are complex and not fully understood. Antiresorptive agents, the current standard of care, do not restore the weakened bone architecture. Recent preclinical studies in mice revealed the diabetic bone signature at the tissue, cell, and transcriptome levels and demonstrated that three US Food and Drug Administration (FDA)-approved bone-anabolic agents correct it. Diabetes decreased BMD and bone formation, damaged microarchitecture, increased porosity of cortical bone, and compromised bone strength. Teriparatide, abaloparatide, and romosozumab/anti-sclerostin antibody (Scl-Ab) all restored BMD and corrected the deteriorated bone architecture. Mechanistically, teriparatide and abaloparatide induced similar responses at the tissue and gene signature levels, increasing both formation and resorption with positive balance towards bone gain. In contrast, Scl-Ab increased formation but decreased resorption. All agents restored bone architecture, corrected cortical porosity, and improved mechanical properties of diabetic bone; and abaloparatide and Scl-Ab increased toughness, a fracture resistance index. Remarkably, all agents increased bone strength over the healthy controls even in the presence of severe hyperglycemia. These findings demonstrate the therapeutic value of bone anabolic agents to treat diabetes-induced bone disease and suggest the need for revisiting the approaches for the treatment of bone fragility in diabetes *(140,141)*.

Conclusions. Bone modeling and remodeling are accomplished by the bone cells, osteoclasts and osteoblasts, working on different or the same bone surfaces, respectively. Osteoclasts are the bone resorbing cells. They derive from progenitors of the hematopoietic lineage and are regulated by osteoblastic/osteocytic cells. Osteoblasts are the bone forming cells. They derive from progenitors of the mesenchymal lineage and work in concert with osteoclasts to maintain bone shape and strength. Osteocytes are differentiated osteoblasts that remain entombed in the bone matrix. Osteocytes orchestrate the function of osteoblasts and osteoclasts in response to both mechanical and hormonal cues. They produce and secrete factors (sclerostin, RANKL and OPG) that affect other bone cells by paracrine mechanisms; and they produce and secrete hormones (FGF23) that affect other tissues by endocrine mechanisms. Diseases and treatments act on bone cells by changing their generation, activity, or the rate of their death.

Update of Bone Health ECHO programs worldwide

E. Michael Lewiecki, MD

Project ECHO is technology-enabled collaborative learning with consistently positive effects found in areas that have been measured *(142)*. Bone Health ECHO programs are ongoing, collegial, case-based, highly interactive videoconferences linking healthcare professionals with an interest advancing their knowledge in the care of patients with skeletal diseases. The mission of Bone Health ECHO is to expand global capacity to deliver best practice skeletal healthcare *(143)*. These virtual communities of practice provide opportunities to improve clinical skills so that patients can receive better care, closer to home, with greater convenience, and lower cost than referral to a specialty center that may be located far from the patient who needs the care *(144)*. Progress with Bone Health ECHO programs has been reported at previous SFBS *(10–16)* and updated here.

The prototype Bone Health ECHO program was established in 2015 through collaboration of Project ECHO at University of New Mexico Health Sciences Center and OFNM. Weekly online interactive videoconferences typically consist of a short slide presentation on a topic of interest followed by discussion, and presentation and discussion of real but de-identified patient cases.

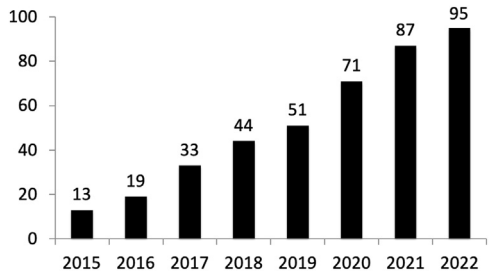

Fig. 4. Average weekly attendance for Bone Health ECHO. Over the first 8 years of the prototype Bone Health ECHO program, based at the University of New Mexico Health Sciences Center in Albuquerque, NM, USA, weekly attendance has progressively increased. Attendees are located throughout North America and South America, and sometimes European, Middle Eastern, and Asian countries. Original graph with data provided by Project ECHO, Albuquerque, NM, USA.

Average weekly attendance grown steadily from 13 in 2015 to over 95 in 2022 (Fig. 4), consistent with rising interest in this virtual community of practice. The slide presentations are recorded and archived on the Project ECHO website, with over 1,100 views since 2015. From 2015 through 2022, 8837 hours of no-cost continuing medical education credits have been provided to attendees. Participation with Bone Health ECHO has been shown to improve self-confidence in managing patients with osteoporosis, *(145,146)* with the likelihood that this results in better care for patients.

The success of the prototype Bone Health ECHO program has been followed by the development of additional programs, with the logistical support of Project ECHO, mentorship by directors of established ECHO programs, and sometimes with grant support from OFNM. A total of 9 bone-related ECHO programs have been started in the USA (6 focusing on osteoporosis, 3 for rare bone diseases), as well as 7 programs in other countries. These include Michigan Neurosurgical Institute Great Lakes ECHO LLC (Grand Blanc, Michigan); Bone Health & Osteoporosis Foundation (formerly National Osteoporosis Foundation) FLS Bone Health ECHO (Washington, DC); Own the Bone Orthopaedic Bone Health ECHO (Chicago, Illinois); University of Vermont Osteoporosis Management ECHO (Burlington, Vermont); and West Coast Bone Health ECHO: Strides for Strong Bones, Spokane (Spokane, Washington). Programs devoted to rare bone diseases are Rare Bone Disease ECHO and Osteogenesis Imperfecta TeleECHO (both with Osteogenesis Imperfecta Foundation, Gaithersburg, Maryland) *(147)*; and Hypophosphatasia TeleECHO (Soft Bones, Boonton, New Jersey). Programs outside the USA are National University of Ireland Galway Bone Health TeleECHO (Galway, Ireland); Bone Health TeleECHO Moscow (Moscow, Russia) *(148)*; ECHO Saint Petersburg Orthogeriatrics (St. Petersburg, Russia); Australia/New Zealand Bone Health ECHO (Sydney, Australia); Bone Health ECHO at AUB [American University of Beirut] and AUBMC [American University of Beirut Medical Center] (Beirut, Lebanon); Bone ECHO en español (Mexico City, Mexico): and Programa Educativo ENDO ECHO IDIM (Buenos Aires, Argentina). All programs are in English language, except for Russian language for the programs based in Russia and Spanish language for programs based in Mexico and Argentina. Each ECHO program functions independently, developing its own format and style, with different curricula, with scheduling of their choice, while adhering to the ECHO model of interactive case-based learning.

Challenges for developing and maintaining an ECHO program include obtaining funding and staff support, creating a curriculum with effective speakers, reluctance of some participants to present patient cases and engage in discussions, and generating and reporting outcomes data. These issues and more are discussed at regular online videoconferences ("collaboration" meetings) where the directors and staff of all ECHO programs are invited to share their experiences and learn from what has been working well, or not so well, with other ECHO programs.

An ECHO workshop was held at the 2023 SFBS to introduce the concept of case-based collaborative learning for attendees interested in joining an existing ECHO program or developing a new one. There was particular interest this year from endocrinology fellows for starting an ECHO program so that attendees of the 2023 Santa Fe Fellows Workshop on Metabolic Bone Diseases could remain connected and continue to expand their knowledge of metabolic bone diseases.

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