Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. 25, no. 1, 3–19, 2022

1094-6950/25:3–19/$36.00
https://doi.org/10.1016/j.jocd.2021.10.001

Proceedings of the 2021 Santa Fe Bone Symposium: Advances in the Management of Osteoporosis and Metabolic Bone Diseases

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Abstract

The 2021 Virtual Santa Fe Bone Symposium was held August 5–8, with over 300 registered attendees from throughout the USA, and at least 18 other countries. This annual meeting focuses on applying advances in basic science and clinical research to the care of patients with osteoporosis and those with inherited and acquired disorders of bone metabolism. Participants represented a broad range of medical disciplines with an interest in skeletal diseases. These included physicians of many specialties and practice settings, fellows, advanced practice providers, fracture liaison service (FLS) coordinators, clinical researchers, and bone density technologists. There were lectures, case presentations, and panel discussions, all followed by interactive discussions. Breakout sessions included an FLS workshop, Bone Health TeleECHO workshop, special interest groups, meet-and-greet the faculty, and satellite symposia. The agenda covered topics of interest such as strategies for the use of osteoanabolic therapy, prevention of periprosthetic fractures, management of atypical femur fractures, what we know and don't know about vitamin D, advances in the use of dual-energy X-ray absorptiometry in the assessment of skeletal health, controversies and conundrums in osteoporosis care, skeletal health in transgender patients, management of patients with hypophosphatasia and hypophosphatemia, and treat-to-target approaches for managing patients with osteoporosis. The Proceedings of the 2021 Virtual Santa Fe Bone Symposium consists of highlights of each presentation with current strategies for optimizing the care of patients with skeletal disorders.

Key Words: Osteoporosis; transgender; periprosthetic fracture; atypical femur fracture; anabolic; hypophosphatasia; ECHO.

Introduction

The Santa Fe Bone Symposium is an annual multidisciplinary collaboration of healthcare professionals devoted to applying knowledge from recent research and guidelines to the care of patients with osteoporosis, metabolic bone diseases, and rare inherited disorders of the

Received 10/05/21. Accepted 10/05/21.
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skeleton. Participants include physicians of many different medical specialties and practice settings, advanced practice providers, dual-energy X-ray absorptiometry (DXA) technologists, scientists, and researchers. Due to safety concerns with the COVID-19 global pandemic, the symposium that was previously scheduled for 2020 was postponed to 2021, and conducted virtually instead of live in Santa Fe.

The 2021 Virtual Santa Fe Bone Symposium was held August 5–8, 2021. It was preceded, as in past years, by the Fellows' Forum in Osteoporosis and Metabolic Bone Diseases, which was held virtually July 23–24, 2021. These events were sponsored by Osteoporosis Foundation of New Mexico in collaboration with the Endocrine Fellows Foundation, the Rare Bone Disease Alliance, and Project ECHO (Extension for Community Healthcare Outcomes) at University of New Mexico Health Sciences Center. There were over 300 registered attendees, with 91% in the USA and 9% from at least 18 other countries. All sessions of the Santa Fe Bone Symposium were recorded and archived on the meeting website for later viewing. Symposium topics were selected according to evaluations of the previous symposium and new developments in the field of skeletal health. Faculty were internationally recognized for their knowledge of each topic selected. Topics for plenary sessions were clinical use osteoanabolic agents, prevention of periprosthetic fractures, management of atypical femur fractures, what we know and don't know about vitamin D, advances in the use of DXA in the assessment of skeletal health, controversies and conundrums in osteoporosis care, skeletal health in transgender patients, management of patients with hypophosphatasia and hypophosphatemia, treat-to-target approaches for managing patients with osteoporosis, and oral presentations of abstracts by fellows selected from the fellows' forum. Each pre-recorded presentation was followed by live interactive discussion, much the same as occurs at the face-to-face symposia in Santa Fe each year. There were also live interactive faculty panel discussions of patient cases and breakout sessions that included a fracture liaison service (FLS) workshop, Bone Health TeleECHO workshop, special interest groups, meet-and-greet the faculty, satellite symposia, and virtual exhibits.

Proceedings of past symposia are available in journals *(1–14)*, monographs in print and electronic formats *(15–19)*, online slide presentations *(20–22)*, and audiovisual webcasts. The Proceedings of the Virtual 2021 Santa Fe Bone Symposium that follow are composed of sections for the plenary topics with highlights written by faculty who gave each presentation.

Prevention and Treatment of Periprosthetic Fractures: Bone Health Optimization

Paul A. Anderson, MD

Periprosthetic fractures occur around implants and happen intraoperatively or, more commonly, postoperatively. In 60%–70% of cases they are associated with low bone mass and low-energy trauma, such as ground-level fall *(23)*. Most commonly, periprosthetic fractures are associated with total joint replacement, although they can also occur around internal fixation devices, and after spinal fusion. Important factors leading to increased fracture risk include degradation of bone quality around implants due to unloading from pain and postoperative restrictions, bone loss due local osteoclastic activation, and stress shielding *(24)*.

Total joint arthroplasty is being increasingly performed, with up to 1.4 million cases of total hip and knee performed annually *(25)*. In this older population, low bone mass is common, with 20%–30% having osteoporotic, and 50% osteopenic T-scores *(26)*. Further, patients are surviving longer with implants and thus increasing the risk of periprosthetic fracture. As a result, orthopedic surgeons are treating an increasing number of periprosthetic fractures, which has been termed by A Bottle et al as "the next fragility fracture epidemic" *(27)*. There is currently a treatment gap for arthroplasty patients, since few undergo skeletal health assessment and fewer still are treated for osteoporosis perioperatively.

Risk factors for the prosthetic fractures overlap with those of osteoporosis: increased age, female gender, family history of osteoporosis, thin cortical margins of the proximal femur, and malnutrition *(23,28)*. Additionally, greater than 75% of cases are associated with fragility mechanisms. Adaptive loss of bone along the femur occurs following both total hip arthroplasty (THA) and total knee arthroplasty (TKA). Prince reported that distal femur bone mineral density (BMD) decreases 18%–20% in the supracondylar region by 6 mo after TKA and does not recover *(24)*. Interestingly, multiple studies using antiresorptive medications show mitigation of this effect in both osteoporotic, and non-osteoporotic patients *(29)*.

The medical treatment of patients with periprosthetic fractures is generally inadequate. These fractures are not often considered as osteoporotic-related and thus patients are usually not evaluated and treated to reduce the risk of another fracture. At the University of Wisconsin, we manage these patients similar to a patient with an osteoporosis-related hip fracture using a FLS model of care.

Preoperative bone health optimization for elective orthopedic patients involves assessing bone health status, identifying and correcting metabolic deficits, and initiating pharmacological treatment to improve bone health, when appropriate *(30)*. The goals are to improve outcomes and reduce complications in a cost-effective manner. The rationale for bone health optimization is that osteoporosis is common in patients having elective orthopedic surgery, with a prevalence of 10%–30%, and a relative risk of 2.5–3.0 for skeletal complications *(29)*. Further, there is a risk of hardware failure from periprosthetic fracture, implant subsidence, and poor outcomes leading to increased revision surgery. A potential means to mitigate these results is bone health optimization. Bone health optimization is consistent with many of the

other optimization programs for orthopedic patients prior to elective surgery, such as glucose control, and discontinuation of smoking.

In a survey of orthopedic surgeons, Maier et al found that 77% of surgeons adjusted the surgical plan based on the presence of osteoporosis; however, only 5% of surgeons ever measured bone density *(31)*. There is need for a screening protocol to identify who needs BMD testing as outlined in recent Official Positions of the International Society for Clinical Densitometry (ISCD) *(32)*. At the University of Wisconsin, we recommend that patients age > 50 yr be preoperatively screened to determine if DXA is indicated. We utilize current ISCD indications for DXA, which includes women age ≥ 65 yr, men age ≥ 70 yr, history of fracture after age of 50 yr, and FRAX (without BMD) 10-yr probability of major osteoporotic fracture > 8.4%. Patients who meet any of these criteria undergo DXA; otherwise, patients proceed directly to surgery. We evaluated this protocol, finding that the sensitivity to identify patients with osteoporosis after DXA was 100%.

For the purposes of bone health optimization, we utilize the clinical diagnosis of osteoporosis which includes a T-score ≤ -2.5, history of hip or spine fracture, or a FRAX 10-yr probability of major osteoporotic fracture ≥ 20% and 10-yr probability of hip fracture ≥ 3% *(33)*. These patients are managed by our FLS, where a full bone health assessment is performed, including screening for secondary osteoporosis, assessment of fall risk, education, and communication with other practitioners. Appropriate smoking and alcohol cessation and nutritional support of calcium and vitamin D supplements are recommended.

Surgery may be delayed when it is appropriate and safe to do so. The need for delay and duration of delay is balanced by the patient's indications for surgery and the risk of bone-related complications from osteoporosis. Urgent conditions such as spinal stenosis with neurological deficits or inability to ambulate secondary to hip collapse are best optimized after surgical treatment. Other patients are risk-stratified, similar to recent guidelines of the American Association of Clinical Endocrinologists (AACE) *(34)*. Patients at low risk of fracture proceed directly to surgery without delay. High risk patients have medical management, usually for 3 mo before surgery. Patients with very high risk of fracture, such as those with a T-score < -3.5, history of multiple fractures, or hardware-related complications from prior surgery, may require 6–9 mo of preoperative treatment. Excellent outcomes from both antiresorptive and anabolic treatments have been reported. For example, in patients having spine fusions, multiple randomized controlled trials demonstrate equal or better outcomes in bisphosphonate-treated patients compared to placebo control *(30)*. In patients having total joint replacements, antiresorptive therapies have been shown to maintain bone mass after surgery with less subsidence, and lower revision surgery rates *(29)*. In multiple large database studies, the use of a bisphosphonate reduces the risk of revision arthroplasty by 50% *(29)*. Anabolic drugs, such as teriparatide, have been associated with better outcomes after spine fusion, and more rapidly improve BMD than antiresorptive drugs. We attempt to treat the pre-operative patient at high or very high risk with an anabolic drug prior to surgery. The medication is continued for the normal duration of treatment, as one would for any other patient with osteoporosis.

A concern among orthopedic surgeons is that antiresorptive medication will impair bone healing. However, investigations show that fracture healing at multiple anatomic sites is not adversely affected by antiresorptive therapy, with similar healing potential, and time-to-healing compared with placebo *(35)*. Surprisingly, anabolic drugs have not been shown to improve bone healing *(36)*.

Periprosthetic fractures are becoming more common and are usually related to low bone mass. Patients with these fractures should be treated medically for osteoporosis as with patients with any other fragility fracture of the femur. Orthopedic surgeons and bone health specialists must recognize that in elective surgery patients, bone health optimization likely leads to lower risk of complications, improved outcomes, and reduced revision surgeries. In patients with high or very high risk of fracture, anabolic treatment prior to surgery is recommended.

Update on Osteoanabolics: Are they Ready for Prime Time?

John P. Bilezikian, MD, PhD (hon)

The pharmacologic therapeutics of osteoporosis began ironically with the development of pharmaceuticals, such as the bisphosphonates, that maintain but do not improve skeletal microstructure. They are nevertheless efficacious, representing a landmark in the history of drug development for osteoporosis. Another irony is that the osteoanabolic drug first developed for osteoporosis is an active fragment of parathyroid hormone (PTH), a hormone that has been demonstrated to be bad for bones when present in excess *(37,38)*. While this is clearly true when PTH is present continuously and excessively, the best example being primary hyperparathyroidism, it became evident that when administered in low dosage and intermittently, the anabolic pathways utilized by PTH are enhanced while the catabolic pathways are mitigated *(39)*. Thus, under these conditions, PTH is good for bones. The efficacy and safety of teriparatide (PTH [1–34])was clearly demonstrated by Neer et al, who showed that both skeletal mass, and skeletal microstructure are enhanced while fracture risk is reduced *(40)*. The second osteoanabolic agent to become available for the treatment of postmenopausal osteoporosis is abaloparatide, an analog of PTH-related peptide (PTHrP). Abaloparatide contains the primary amino acid sequence of PTHrP through amino acid position 22 and then diverges in ways that appear to exploit an affinity for the Rg conformation of the PTH/PTHrP

receptor that favors an anabolic outcome (41). The major clinical trial of abaloparatide clearly demonstrated efficacy to reduce vertebral and non-vertebral fractures in postmenopausal women (42). It has recently been shown that abaloparatide is also efficacious in individuals with compromised renal function (43). The pharmacokinetic profile of abaloparatide and its effects of bone turnover appear to suggest that this osteoanabolic agent is more favorably inclined to enhance the anabolic window, a period of time when anabolic effects are maximal.

Most recently, romosozumab, the third member of this class of osteoanabolic agents, was shown to be efficacious in the treatment of postmenopausal osteoporosis (44). Different from teriparatide and abaloparatide, romosozumab does not increase bone resorption. It could thus, be considered to be a more exclusive osteoanabolic agent. Early work with animals, in fact, showed that this sclerostin inhibitor has the potential to be antiresorptive (45). Moreover, the kinetics of romosozumab suggest that the osteoanabolic properties are rather short lived, with bone formation markers rising quickly but only transiently. Bone resorption markers fall from the outset. It would appear, therefore, that this drug could be considered as a combination osteoanabolic, and antiresorptive agent.

Dual action, as is evident for romosozumab, may extend as well to denosumab, a classic antiresorptive agent. Denosumab administration is associated with an increase in levels of endogenous PTH (46). While this may be no more than a curiosity, the maintenance or increase in distal forearm BMD suggests that under these conditions, elevated PTH levels do not reduce distal forearm BMD, as is typically the case in primary hyperparathyroidism, but rather enhance BMD at that site. The mechanism by which this may occur is postulated to be due to shunting of PTH from its catabolic pathway, namely receptor activator of nuclear factor kappa-B ligand (RANKL), to the anti-sclerostin pathway mediated through anabolic Wnt signaling. In support of this concept, data from one aspect of the denosumab pivotal fracture trial has recently shown that forearm fractures are reduced by denosumab (47).

The concept of dual action drugs, as demonstrated for romosozumab and postulated to be evident for denosumab, extends as well to teriparatide, and abaloparatide. Both teriparatide and abaloparatide are associated in time with an increase in bone resorption. With teriparatide, the increase in bone resorption appears to occur earlier than with abaloparatide. Nevertheless, for both drugs, the increase in bone resorption occurs. One could view this increase in bone resorption as a mechanism by which the osteoanabolic actions of these 2 drugs are mitigated. In these 2 situations, therefore, the dual action is not facilitating the primary action of the drug but reducing it.

A question before us is whether the osteoanabolics are ready for prime time. Given their indications and recommendations by organizations such as the Endocrine Society (ES) and the AACE (34,48,49), the answer to that question is clearly yes. However, to make a decision to prescribe osteoanabolic therapy, one must take into account, in addition to the patient's high risk for fracture, a number of factors such as convenience, cost, payers, adverse event profile, physician judgement, knowledge of how these drugs reduce fracture risk, and goals of therapy.

What we Know, and Don't Know, About Vitamin D

Neil Binkley, MD

Despite massive amounts of vitamin D research and numerous publications (about 17 vitamin D-related manuscripts daily in the first 6 mo of 2021 indexed on PubMed [https://pubmed.ncbi.nlm.nih.gov/]), there is lack of consensus regarding definition of vitamin D inadequacy (50). This is of obvious importance to bone health practitioners, as vitamin D facilitates calcium transport, and participates in the regulation of calcium homeostasis (51). Moreover, vitamin D deficiency has been associated with (note, not causally linked to) a multitude of common human conditions including cancer, cardiovascular disease, and diabetes mellitus among a multitude of others (52). It is currently widely accepted that the best approach to defining an individual's vitamin D status is measurement of circulating total 25-hydroxyvitamin D [25(OH)D] (53). Unfortunately, there is disagreement regarding what 25(OH)D value defines optimal, and the dose of vitamin D needed to reach that target (50). Specifically, various expert organizations variously suggest that 25(OH)D concentrations above 12 ng/mL, 20 ng/mL or 30 ng/mL be utilized to define normal. Moreover, some within the vitamin D field recommend even higher values. Use of 25(OH)D cutpoints that differ by a few ng/mL might be viewed as inconsequential; however, the cutpoint selected with yield dramatically different prevalence values of hypovitaminosis D ranging from 7%–97% (Fig. 1) (54). It is immediately apparent that, based upon the 25(OH)D cutpoint selected, various proportions of our patients ranging from very few to essentially all will be identified as "low" in vitamin D. Given the plethora of research publications and systematic reviews, why does this situation persist?

The lack of consensus regarding how to clinically define vitamin D inadequacy is due to issues that include deficiencies in clinical trial designs, the use of 25(OH)D to define an individual's status, inconsistencies in 25(OH)D measurement by various assays, and the impact of inflammation on 25(OH)D (i.e., 25(OH)D is a negative acute phase reactant). Briefly, it is possible that other vitamin D metabolites, notably cholecalciferol, may contribute to the net vitamin D physiologic effect (55), but are not being considered clinically or in research studies. Additionally, it has long been recognized that different assays will report a different 25(OH)D result; this situation persists despite decades of effort to improve assay performance (56). Moreover, it is increasingly being appreciated that inflammatory conditions acutely reduce

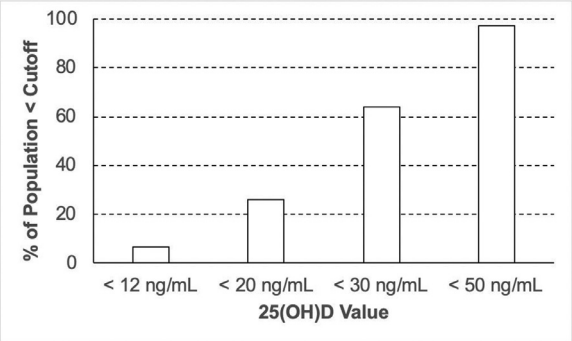

Fig. 1. Prevalence of vitamin D deficiency by cutpoint serum 25(OH)D value. The prevalence of vitamin D inadequacy is highly dependent upon the serum 25(OH)D concentration used to define optimal. If < 12 ng/mL is inadequate, then less than 7% of the United States National Health and Nutrition Examination Survey population is low, whereas if < 30 ng/mL is inadequate, then about 64% of the same population is low. Adapted from Schleicher et al (*54*).

measured 25(OH)D by as much as 20%–40% *(57)*. The mechanism(s) by which this occurs remains to be defined; however, it is plausible that this phenomenon contributes to the high prevalence of "low vitamin D" associated with a multitude of human conditions. Finally, many large randomized trials are flawed by inclusion of subjects that are not vitamin D deficient; greater vitamin D intake in the setting of sufficiency could not produce improved clinical outcomes and indeed could only cause toxicity *(58)*.

Given these uncertainties, what is a clinician to do? Despite ongoing controversy, measurement of circulating 25(OH)D seems likely to remain utilized to define our patient's vitamin D status for the foreseeable future; one then needs to consider what cutpoint value to utilize. In the absence of consensus, it has long been advocated that highly sun-exposed individuals, who are presumably producing a physiological amount of vitamin D in their skin, be utilized to define "normal" *(59)*. Doing so would lead one to a target level of serum 25(OH)D in the approximate range of 35–40 ng/mL *(60)*. Fortuitously, this is concordant with recommendations of bone-related organizations to maintain a level of at least 30 ng/mL; aiming for a level slightly higher than this target will allow for the known assay variation (i.e., a 25[OH]D of "30 ng/mL" may actually be slightly lower or slightly higher). Finally, given that some assays do not optimally detect 25(OH)D2, there is no known benefit in supplementing patients with ergocalciferol (vitamin D2), and virtually never a need to prescribe high dose (i.e., 50,000 IU) vitamin D2 *(61)*.

In conclusion, despite controversy, it is clear that vitamin D deficiency is common worldwide. Additionally, vitamin D is important for bone health, and potentially a multitude of other physiologic functions. Unfortunately, no consensus exists regarding what constitutes vitamin D deficiency; it seems unlikely that this situation will be resolved in the near future. Continuing to utilize circulating 25(OH)D to define an individual's vitamin D status is reasonable, but should be tempered by observations that this analyte is a negative acute phase reactant; thus, measurement in hospitalized patients will provide a value lower that the individual's baseline. In the current setting of uncertainly, it is reasonable to target a serum 25(OH)D of about 40 ng/mL, with the recognition that this will often require 1,000–2,000 IU of vitamin D3 daily. Use of high dose ergocalciferol is virtually never needed.

Update on Atypical Femur Fractures

Angela M. Cheung, MD, PhD

Atypical femur fracture (AFF), as defined by an international task force of the American Society for Bone and Mineral Research (ASBMR) *(62)*, is a femur fracture that is below the lesser trochanter and above the supracondylar flare, with at least 4 out of the following 5 major features: *(1)* little or no trauma, *(2)* transverse or mostly transverse. *(3)* non-comminuted or minimally comminuted, *(4)* complete fractures extend through both cortices and may have a medial spike, incomplete fractures (iAFF) involve only the lateral cortex, *(5)* localized periosteal or endosteal reaction of the lateral cortex. Minor features, which are common but not required, include generalized increase in cortical thickness, delayed healing, prodromal symptoms such as dull aching pain in groin or thigh, and bilateral fractures and symptoms. AFF appears to be a type of stress fracture due to repetitive loading, with impaired capacity for repair of microdamage, often due to antiresorptive therapy (i.e., bisphosphonates, denosumab) for osteoporosis *(63)*. AFF has also been reported in patients treated with romosozumab *(64)*, an osteoanabolic agent that has a dual effect on bone remodeling, increasing bone formation, and reducing bone resorption *(65)*. Although AFF may occur in patients never treated for osteoporosis, a study of 196,129 women with any bisphosphonate use in the Kaiser Permanente Southern California healthcare system reported 277 occurrences of AFF, with risk factors that included long duration (> 5 yr) of bisphosphonate treatment, Asian descent, and glucocorticoid use ≥ 1 yr *(66)*. The study found that the risk of AFF rapidly diminished after stopping bisphosphonates, with a 48% reduction in risk 3–15 months after discontinuation. The absolute risk of AFF was very low compared with the number of fractures that were prevented with treatment, especially for non-Asians. The reasons for greater risk of AFF in Asians are unclear, but may include better adherence to therapy, lower body weight, bowed femora, and genetic differences in drug metabolism and bone turnover. The balance of benefits and risks with bisphosphonate therapy appears to be less favorable in Asians than in other races.

Early detection of incomplete AFF (iAFF) or abnormalities in the spectrum of AFF may allow for interventions, such as a change in medication or surgical fixation, that prevent the occurrence of a completed AFF. The spectrum of imaging abnormalities of AFF includes focal periosteal and endosteal thickening of the lateral cortex, with or without beaking – a radiolucent defect perpendicular to the lateral cortex in the area of focal cortical thickening, reminiscent of a bird's beak. Since prodromal symptoms (e.g., pain and weakness in the thigh or groin of the involved femur) prior to AFF are common, clinicians should be alert to their presence, and evaluate these patients appropriately. When iAFF or AFF is suspected or confirmed, the opposite femur should be imaged, since bilaterality is common. The ISCD recommends the use of DXA to screen patients receiving a bisphosphonate or denosumab, especially those on long-term glucocorticoid therapy, by reviewing femur images for focal cortical abnormalities in the spectrum of AFF, and considering bilateral full-length femur imaging (FFI) with DXA for patients treated for ≥ 3 yr *(67)*. When reporting FFI, the presence or absence of focal cortical thickening should be noted. Focal thickening without a radiolucent line is not diagnostic of AFF, but is an indication for additional imaging, such as plain radiography. When a radiolucent line is present, a CT scan can determine the depth, and extent of the fracture. MRI may be useful to differentiate between an active lesion and a healed scar.

Strategies for managing patients with AFF were included in the 2014 ASBMR task force report on AFF *(62)* and more recently in a systematic review and recommendations from the European Calcified Tissue Society *(65)*. Given the paucity of high-quality medical evidence, these recommendations rely heavily on expert opinion. When a diagnosis of AFF is made, bisphosphonate/denosumab should be stopped, the risk of osteoporotic fracture should be assessed, the opposite femur should be imaged, and the patient should be monitored for healing and/or development of a new AFF. These patients should also be evaluated for secondary causes of osteoporosis and the presence of metabolic bone disorders, such as hypophosphatasia *(68)*, that could contribute to the risk of fragility fractures, and AFF patients discontinuing denosumab after receiving ≥ 2 doses can be at risk for rapid bone loss and high fracture risk, and should be monitored closely; those with high bone turnover after discontinuation from denosumab may benefit from a short course of a bisphosphonate or raloxifene. Complete AFFs are treated by surgical stabilization with an intramedullary (IM) nail, recognizing that fracture healing may be slow and there is a high risk of non-union *(69)*. Patients with iAFF are potential candidates for IM nailing depending on the extent and depth of the fracture line and patient preference. For AFF patients at high risk of fragility fractures, treatment with teriparatide or abaloparatide should be considered. These agents may be effective at treating the underlying osteoporosis, although the evidence is sparse for improving the healing of AFF *(70, 71)*. After the completion of teriparatide/abaloparatide, patients should be monitored for increased bone resorption; should bone resorption increases, consider treatment with a mild antiresorptive agent (e.g., estrogen, raloxifene, tibolone, calcitonin). For patients treated with bilateral IM nails, bisphosphonate/denosumab could be considered after completion of teriparatide/abaloparatide, although these potent antiresorptive therapies may increase the risk of atypical humeral, and other stress fractures.

Management of Hypophosphatasia and Hypophosphatemia in Adults and Children

Erik A. Imel, MD

Hypophosphatasia (HPP), caused by mutations in the *ALPL* gene encoding tissue nonspecific alkaline phosphatase, and X-linked hypophosphatemia (XLH), caused by mutations in the *PHEX* gene, are 2 rare lifelong bone diseases that share some similarities but many differences. Both may present in early childhood with evidence of rickets or in adulthood with symptoms of osteomalacia, bone pain, fractures and joint complications, but the clinical presentation and the severity of features at different ages can vary widely for each of these disorders. Table 1 compares important features of these 2 disorders. HPP patients are distinguished by low serum alkaline phosphatase levels, with serum calcium, and phosphorus levels typically in the upper normal range or elevated *(72,73)*. On the other hand, XLH is characterized by hypophosphatemia due to renal phosphate losses caused by elevated fibroblast growth factor 23 (FGF23), often accompanied by elevated serum alkaline phosphatase *(72,74)*. For diagnosing either of these disorders, it is important to apply appropriate reference ranges for age, as both serum phosphorus, and alkaline phosphatase are normally higher in children than in adults.

Alkaline phosphatase is critical for maintaining the appropriate ratio of phosphate to pyrophosphate in order to sustain formation of hydroxyapatite at the collagen matrix of bone. In its absence, pyrophosphate, a substrate for alkaline phosphatase, accumulates and osteomalacia and rachitic features develop. Pyridoxyl-5′-phosphate (PLP, the active form of vitamin B6) and phosphoethanolamine (PEA) are additional substrates that are usually elevated in patients with HPP. HPP ranges in severity from severe life-threatening perinatal-infantile forms with seizures and respiratory insufficiency to childhood rickets, to odontohypophosphatasia and adult osteomalacia with fractures and musculoskeletal pain *(73)*.

There are many challenges in treating HPP. Treatment with extra vitamin D and calcium do not treat the rickets and potentially increase risk for nephrocalcinosis. Antiresorptive agents have shown limited benefit, and there are reports of atypical femur fracture (AFF) in HPP patients both with, and without bisphosphonates. Teriparatide has

Table 1
Comparison of general characteristics of hypophosphatasia and X-linked hypophosphatemia. There are clinical similarities with these inherited disorders but very clear differences in the laboratory assessment and treatment.

Gene	Hypophosphatasia *ALPL*	X-linked Hypophosphatemia *PHEX*
Mode of inheritance	Autosomal recessive or dominant	X-linked dominant
Biochemistries (72)		
Total and bone alkaline phosphatase	Low	High or upper normal
Serum Calcium	High or normal	Normal
Serum Phosphorus	High or normal	Low
TmP/GFR	High or normal	Low
FGF23	Normal	High
PTH	Normal to low	High or normal
Clinical Features (73,74,134)		
Rickets	Present	Present
Osteomalacia	Present	Present
Growth impairment	Present (especially in severe forms)	Present
Bone pain	Present	Present
Fractures, pseudofractures	Present	Present
Respiratory failure	Perinatal - infantile forms	
Seizures	In severe forms (responsive to B6)	
Craniosynostosis	Reported	Reported
Dental phenotype	Early spontaneous tooth loss	Dental abscess, extractions
Nephrocalcinosis	Occurs due to HPP	Occurs due to medical treatment
Chondrocalcinosis	Present (usually adults)	
Enthesopathy		Present (usually adults)
Calcium pyrophosphate arthropathy	Present (usually adults)	
Osteoarthritis		Present (usually adults)
Impaired mobility	Present	Present
Medical Treatment (73,74)	Asfotase alfa	Calcitriol (active vitamin D) plus phosphate salts Burosumab

TmP/GFR, ratio of renal transport maximum of phosphate to glomerular filtration rate; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

been reported in use to help heal fractures, but its use is limited to short term.

Enzyme replacement with asfotase alfa provides a directed treatment for HPP and is approved for child onset forms of the disease. Asfotase alfa is measured in the circulation by clinical tests for alkaline phosphatase, which will be very elevated into the thousands, while measures of pyrophosphate and PLP decrease *(75)*. Treating severely affected infants with asfotase alfa improves the skeletal mineralization, respiratory function, and survival *(76)*. Treating older children also demonstrates improvements in rickets, physical function and mobility *(77)*. In adults with HPP, asfotase alfa tends to increase lumbar spine BMD, pain scores, mobility, and healing of fractures. Side effects include injection site reactions and lipohypertrophy. There are also potential risks for ectopic calcification.

XLH has been treated with conventional therapy for many years, typically consisting of calcitriol (or other active vitamin D analog) plus phosphate salts, which must be split into multiple doses per day *(74)*. Important complications include gastrointestinal symptoms (from phosphate) as well as risks of hyperparathyroidism, hypercalciuria, hypercalcemia, and nephrocalcinosis. It is important, however, not to treat with just phosphate, as it may worsen hyperparathyroidism. Frequent laboratory monitoring is necessary for safety, while the goal is not to specifically normalize serum phosphorus, which may increase risk for complications. Conventional therapy improves rickets, osteomalacia, and related symptoms in children and adults, although the skeletal response in children is variable; short stature persists and lower limb deformity surgeries are often necessary.

Burosumab, a fully human monoclonal antibody that binds FGF23, was approved to treat XLH in 2018, with dosing every 2 wk in children or every 4 wk in adults. Burosumab increases the ratio of renal transport maximum of phosphate to glomerular filtration rate (TmP/GFR), while conventional therapy does not. Serum phosphorus levels peak about 7 days after dosing. In clinical trials, dosing was titrated to normalize serum phosphorus. Endogenous calcitriol levels also increased acutely, peaking in the 3–7 days after injection, especially in the early months after starting burosumab. In a randomized placebo-controlled trial, adults with XLH and chronic pain were recruited, about half of whom also had active fractures or pseudofractures *(78)*. Burosumab increased serum phosphorus into the normal range. There was more healing of the fractures/pseudofractures in the burosumab-treated subjects, with 63% completely healed by 48 wk. There were also improvements in pain, stiffness, and mobility.

Sixty-one children, ages 1–12 yr, with XLH were recruited into the only randomized controlled trial of burosumab *vs* conventional therapy *(79)*. Inclusion criteria included persistent rickets on radiographs despite ongoing treatment with conventional therapy. Children were randomized to receive burosumab or to continue conventional therapy. Fasting serum phosphorus normalized after burosumab but remained low in those receiving conventional therapy. This study demonstrated that burosumab increases TmP/GFR while conventional therapy does not. The primary outcome was improvement in rickets as assessed by the Radiographic Global Impression of Change (RGI-C) score. This is a 7-point scale with -3 = severe worsening, 0 = no change, and +3 = near/complete healing. By week 64, 87% of burosumab treated children had achieved RGI-C scores between +2 and +3, indicating substantial healing, *vs* 19% of the conventional therapy group.

Side effects of burosumab include injection site reactions and restless legs syndrome. The risk of nephrocalcinosis did not appear to be different from conventional therapy in the short-term comparison periods (24–64 wk). It is also important to recognize that to date neither burosumab nor conventional therapy are demonstrated to have any benefit regarding enthesopathy or osteoarthritis, which are among the most debilitating features in adults with XLH, and take many years to develop or progress.

HPP and XLH are both rare diseases involving osteomalacia that can present with clinical features at any age. However, the pathophysiology and biochemical profile for these 2 diseases are vastly different and they should be easily distinguishable if the proper diagnostic testing is used.

The Astounding Versatility of DXA

Diane Krueger, BS, CBDT

DXA is widely accepted as the gold standard tool for clinical skeletal assessment at the lumbar spine, proximal femur, and radius. These measurements are the basis for osteoporosis diagnostic classification, fracture risk estimation (BMD values included in some algorithms), monitoring, and often a component of clinical practice guidelines. In addition to standard BMD measurement, DXA offers expanded features, some having current clinical utility and others of interest, but without well-established clinical value. Some of these features will be highlighted in this section.

Vertebral fracture assessment (VFA) is a feature that acquires a lateral thoracolumbar image, often at the time of BMD measurement. As vertebral fracture is frequently unappreciated and fracture status is a critical component when determining osteoporosis treatment approaches, this can offer vital information. Consequently, the ISCD and other organizations have developed indications for vertebral imaging, such as historical height loss > 1.5 inches, self-reported but undocumented prior vertebral fracture, and long-term glucocorticoid use in women age ≥ 70 yr, and men age ≥ 80 yr with lowest T-score < -1.0 *(80)*. However, some studies suggest routine acquisition in those over age 65 or 70 yr is a cost-effective approach to determine fracture status *(81,82)*. Furthermore, an International Osteoporosis Foundation (IOF) position paper urges routine use of DXA-VFA in patients evaluated by fracture liaison services *(83)*.

A more recent addition to clinical skeletal assessment is trabecular bone score (TBS), a tool that utilizes DXA to generate a surrogate of bone microarchitecture. The software evaluates greyscale variance from DXA lumbar spine images to determine bone texture. This measurement can be categorized into levels of trabecular structure (normal ≥ 1.31, partially degraded between 1.31 and 1.23, and degraded ≤ 1.23) *(84)* and offers insight on fracture risk independent of BMD. Consequently, it has been integrated into the fracture risk calculator FRAX to refine the 10-yr fracture probability estimations. TBS utilization may be most helpful in those with osteopenia or near a treatment threshold *(85)*.

In response to the increased recognition that AFF is related to long-term antiresorptive therapy, leading DXA manufacturers developed tools that can identify signs of unusual cortical thickening. This was prompted by the 2010 and 2014 ASBMR AFF Task Forces acknowledging the utility of DXA to aid in the early identification of a potential AFF. This feature acquires a femur image that includes not only the hip, but also the femur shaft to a point just proximal to the condyle flare. Cortical thickness is either manually or automatically measured to identify areas of increased thickening along the medial and lateral cortices.

Total body imaging has been a feature of DXA since its early inception and long been used to assess skeletal status in pediatric populations. More recently, its use has expanded to include other specialties such as geriatrics to diagnose sarcopenia and assess falls risk, bariatric providers to track fat *vs* lean loss with interventions, and sports performance professionals to monitor training or

rehabilitation interventions. These are evolving fields in relation to DXA, but all focus on its ability to measure lean mass. It is important to recognize that DXA does not actually measure muscle mass, but instead offers a surrogate that is essentially non-fat, and non-bone mass. Consequently, the majority of what is measured as "lean mass" is water; this is likely why DXA lean mass does not correlate well with functional change as people age. Specifically, non-muscle components of lean mass blunt the DXA's ability to measure muscle change. This is most notably evident at the head, which comprises 5%−10% of a body's total lean mass that will not increase or decrease with muscle mass changes *(86)*. Additionally, extracellular water (ECW) is preserved with advancing age while intracellular water (ICW) declines, resulting in an "expansion of ECW relative to ICW... which masked actual muscle cell atrophy with aging" when using DXA alone *(87)*. This limitation of DXA could be improved by excluding the head from total body analysis for surrogate muscle evaluation or combining with bioimpedance spectroscopy (BIS). This technology is similar to DXA in that multiple frequencies travel through various pathways at different speeds, this allows for independent measurement of ECW and ICW *(87)*. This has been documented in that standard appendicular lean mass (ALM) measurement combined with BIS correlates better with function than ALM alone *(88)*, and further use of a novel variable using DXA and BIS to measure lean mass of only the legs *(89)*. These data suggest DXA-measured ALM can, and should, be corrected for fluid distribution.

DXA has additional potential for applications in a range of clinical and research settings. It could perhaps be a tool to enhance cardiac health assessment by evaluation of aortic calcification and abdominal visceral fat. The extrapolation of the latter technology to the thigh might increase the utility of DXA in sarcopenia and falls. Evolution of work being conducted to measure regional bone mass near large joints might reduce post-surgical skeletal complications after elective joint surgery. For example, perhaps a comprehensive assessment of the hip could be offered to surgeons prior to elective hip arthroplasty that includes BMD, cortical thickness, Dorr classification, and TBS assessment, or post-surgery to evaluate loosening, stress shielding, or lucency around arthroplasty implants.

In summary, currently available DXA features such as VFA, TBS, and long femur imaging are likely being clinically under-utilized. In the short term, DXA evolution may include standardization of research orthopedic applications, thereby allowing routine clinical use. In this regard, DXA is an attractive technology given its excellent image quality, low radiation exposure, and ability to quantitatively measure around metal. Finally, we might expect expansion of opportunistic measurements that use existing DXA images similar to the approach employed by TBS companion software.

Osteoporosis: Should We Treat-to-Target or Target-for-Treatment?

Michael R. McClung, MD

Osteoporosis is a chronic disorder resulting in increased risk of fracture for which long-term if not lifelong management is required. The stages of osteoporosis management include identifying the appropriate patients to treat, selecting the best initial therapy for each patient and then monitoring response and adjusting therapy accordingly. The Treat-to-Target (TTT) concept has been employed the management of patents with rheumatoid arthritis with an objective clinical target (joint inflammation) and diabetes with a laboratory target (HgbA1c). Components of the TTT concept include (1) choosing a target and a method for measuring it, (2) selecting the best therapy to achieve the target, (3) assessing the target at a pre-specified time point, and (4) changing therapy if the target is not achieved, all of which includes shared decision-making *(90)*. Developing such a TTT or "goal-directed" strategy for the management of patients with osteoporosis has been proposed *(91)*. It was stated that "The goal is to improve the selection of initial drug therapy based on severity, improve follow-up of patients on treatment, and anticipate how to use new treatments that have a very potent effect on BMD and perhaps greater reductions in risk." Since that statement, new clinical information as well as the availability of 2 new osteoanabolic or bone-building drugs that induce large increases in BMD, improved skeletal architecture and strength, and substantial reduction in fracture risk, have provided momentum for the TTT concept.

Several potential osteoporosis treatment targets have been considered *(92)*. For various reasons, the absence of fracture (the primary treatment objective), estimated fracture risk, and quantitation of bone turnover rates are not clinically usable targets *(92)*. Ideally, improving bone strength to a desirable level would be useful target. While treatment-related changes in bone strength can be assessed clinically by applying a finite element analysis algorithm to quantitative computed tomography scans of the hip or spine, such changes in estimated bone strength have not yet been validated as surrogates of fracture risk reduction with therapy.

Several converging pieces of evidence suggest that the level of BMD achieved while on osteoporosis treatment (especially in the hip) is a robust reflection of the effects of treatment on fracture risk. Changes in hip BMD accounted for 87% [95% CI: 35% – >100%] of the reduction in non-vertebral fracture risk over 3 yr of denosumab therapy *(93)*. In a meta-regression of many large clinical fracture end-point trials with many types of drugs, changes in hip BMD with drug treatment accounted for 59% of the reduction in vertebral fracture risk, 63% of non-vertebral fracture risk, and 48% of hip fracture risk *(94)*. Hip T-score values achieved on therapy with denosumab, alendronate and romosozumab – drugs with very

Table 2
Percentage increases in total hip bone mineral density required to achieve a T-score target of -2.5, -2.0, or -1.5. These values were calculated using 12% as the standard deviation of young adult total hip BMD values.

Initial Total Hip T-score	Target Total Hip T-score		
	-2.5	-2.0	-1.5
-3.5	21%	31%	41%
-3.0	9%	19%	28%
-2.5	–	8.6%	17%
-2.0	–	–	8.6%

different mechanisms of action – strongly correlate with a patient's current risk of fracture *(95, 96)*. These data suggest that a hip T-score of at least -2.0 and perhaps -1.5 would be an appropriate and routinely available clinical target.

There are major limitations to the implementation of the TTT strategy. We have only limited ability to increase hip BMD with current osteoporosis therapies. The bone building effects of anabolic drugs wane after treatment for a few months (romosozumab) or a few years (teriparatide, abaloparatide), limiting the duration of their effectiveness. In Table 2, the percentage change in BMD required to move from an initial T-score to various target T-scores is summarized, while in Table 3, the percentage changes in total hip BMD with various treatments, and sequences are summarized. A total hip T-score increase from -2.5 to -2.0 can be accomplished with 10 yr of denosumab therapy or with romosozumab for 12 mo followed by denosumab for 24 mo. The largest increases in BMD accomplished with any sequence of therapies will not reliably increase total hip BMD by 1.0 T-score unit *(97)*, although the BMD response of individual patients may be more or less than the mean response reported for subjects in clinical trials. Perhaps greater gains could be achieved with repetitive courses of anabolic agents. Appreciating the magnitude of the change required to move from one T-score to another helps set expectations for patients and informs treatment decisions. Additionally, the TTT concept is not useful in some patients, such as a 65-yr-old woman with 2 recent vertebral fractures and hip T-score -1.5. Although her hip T-score is already at the target, her recent fractures place her at very high fracture risk, as defined in recent guidelines *(34,98)*.

A more familiar and currently used treatment strategy is choosing patients for osteoporosis therapy on the basis of their fracture risk, targeting high risk patients for treatment. We have excellent tools to identify patients at high or very high risk of fracture, including the knowledge that a recent fracture places an older adult at very high fracture risk for the next 1–2 yr. Treatment is targeted for patients at high risk, and more potent agents are chosen for the patents at very high fracture risk. This is justified by the larger increases in BMD and superior reduction in fracture risk with anabolic agents compared to oral bisphosphonates *(97)*. These concepts have already been incorporated into recently updated clinical guidelines *(34,48,49,98)*.

It is important to note that these 2 management strategies are complementary, not competitive options. Both approaches can be useful in guiding osteoporosis management. However, neither approach is ideal for or applicable to all treatment decisions. The Target-for-Treatment approach aids in identifying the appropriate patients to treat. Both approaches can be useful in guiding osteoporosis management. However, neither approach is ideal for or applicable to all treatment decisions. The TTT approach aids in identifying the appropriate patients to treat. Both strategies are useful in choosing both the initial therapy, while when, and how to use subsequent therapies can be guided by the hip BMD treatment target.

There is no single approach to a patient at high risk of fracture. In the clinic, we do not treat osteoporosis; rather, we treat patients with osteoporosis. Management must be individualized and should take into account the patient's perspectives and preferences. However, appreciating the concepts behind and the data supporting both the TTT and the Target-for-Treatment approaches may provide clarity and confidence for physicians and nurse practitioners when they encounter a patient with osteoporosis.

Table 3
Average percentage changes in total hip bone mineral density (BMD) achieved with osteoporosis therapy. Data compiled from multiple sources (97).

Treatment	Total Duration (Mo)	Total Hip BMD Change from Baseline
Alendronate	120	6.7%
Denosumab	120	9.2%
Teriparatide for 24 mo followed by denosumab for 24 mo	48	6.6%
Abaloparatide for 18 mo followed by alendronate for 24 mo	42–43	6.4%
Romosozumab for 12 mo followed by alendronate for 24 mo	36	7.0%
Romosozumab for 12 mo followed by denosumab for 24 mo	36	9.4%

Perhaps in this way, the woefully large and increasing gap between the number of patients who are appropriate candidates for therapy and those who actually receive and remain on therapy can be narrowed.

Controversies and Conundrums in Osteoporosis Care

Paul D. Miller, MD, HDSc (HON)

The first anabolic agent approved for the treatment of osteoporosis was teriparatide. The original product label contained a boxed warning regarding dose- and duration-dependent increased risk of osteosarcoma in male and female rats, with a recommendation that this medication not be prescribed for patients at high baseline risk of osteosarcoma. The purpose of a boxed warning is to call attention to serious or life-threatening risks of a drug; however, with regard to the risk of osteosarcoma in humans exposed to teriparatide, this was a theoretical possibility, not a known hazard. The product label also recommended that teriparatide not be used for more than 2 yr in a patient's lifetime. Since the original approval date in 2002, a 15-yr post-marketing surveillance study found no evidence for increased risk of osteosarcoma in patients treated with teriparatide, with risk no different than the background incidence rate of about 2.5 cases per million per year in US adults age ≥ 40 yr *(99)*. Informed by these data, the US Food, and Drug Administration (FDA) approved a revised product label for the original branded teriparatide (Forteo®, Lilly, Indianapolis, IN), released in November 2020, with removal of the boxed warning *(100)*. Another important change with the new product label was removal of the 2-yr lifetime limit for duration of treatment, replaced by a statement that treatment longer than 2 yr should be considered for a patient who "remains at or has returned to having a high risk for fracture" *(100)*. This statement begs the question, "Who are candidates for consideration of treatment longer than 2 yr?" A recently published commentary *(101)* offered suggestions for patients who might benefit from long-term therapy, largely based on anecdotal experience: those with (1) very high fracture risk unable to discontinue glucocorticoid therapy, (2) high fracture risk with serum P1NP that remains high after 2 yr of teriparatide, (3) high fracture risk with multiple vertebral fractures at baseline but none while on teriparatide, (4) adynamic renal bone disease, or (5) severe chronic obstructive pulmonary disease and vertebral fractures. These suggestions may apply to biosimilar teriparatide and abaloparatide as well, but at the time of this writing, the boxed warning about osteosarcoma risk with abaloparatide and the 2-yr lifetime limit have not been removed. Studies are needed to fully evaluate the efficacy and safety of long-term teriparatide and abaloparatide under these clinical circumstances and others.

The product label of another osteoanabolic agent, romosozumab, includes a boxed warning that this treatment may increase the risk of myocardial infarction, stroke, and cardiovascular death, and that it should not be used for patients who have had a myocardial infarction or stroke within the preceding year *(102)*. The duration of use in the label is limited to 12 mo, but this is not a lifetime limit, allowing for the possibility of 1 or more subsequent 12-mo courses of therapy if clinically appropriate. The boxed warning about the potential of increased cardiovascular risk was based on conflicting evidence, with the largest clinical trial of romosozumab vs placebo in postmenopausal women with osteoporosis showing no signal for increased risk with romosozumab *(44)*, while another study of romosozumab vs alendronate in postmenopausal women with osteoporosis and a fragility fracture found an imbalance of adjudicated serious adverse cardiovascular events (2.5% with romosozumab, 1.9% with alendronate) at 12 mo *(103)*. Given that there is no biologically plausible rationale for increased risk with romosozumab and differences in the studies with regard to the comparator, age of subjects, and baseline cardiovascular risk, it is uncertain whether the observed imbalance of events is because romosozumab increases the risk, alendronate reduces the risk, or due to chance. A recent perspective reviewing the data suggests that the imbalance is most likely due to chance *(104)*. Nevertheless, it is prudent for clinicians to discuss this potential but uncertain risk with patients, and consider the balance of expected benefits and possible risks, before prescribing this medication.

The issue of drug "holidays" after long-term bisphosphonate therapy has received attention as a strategy that enables patients to benefit from the long skeletal half-life and prolonged antiresorptive effects, while reducing the risk of rare possible adverse effects, such as atypical femur fractures and osteonecrosis of the jaw *(105)*. A bisphosphonate holiday is a concept that must be individualized for each patient, with uncertainty in determining who is a potential candidate for a holiday, how best to monitor patients on a holiday, and when to end the holiday. Drug holidays can be misused when treatment is not resumed when fracture risk is once again high, when therapy is inappropriately discontinued in a high-risk patient, and when treatment with a non-bisphosphonate, such as denosumab, is discontinued *(106)*. Discontinuation of denosumab is followed by a decline of BMD, a rise and overshoot of bone turnover makers above baseline, a return of vertebral fracture risk to baseline, and an increase in the risk of multiple vertebral fractures *(107)*. Since osteoporosis is a lifelong disease that warrants lifelong attention *(108)* and the efficacy of denosumab rapidly diminishes beyond 6 mo from the prior dose, denosumab should be continued as long as the benefits outweigh the risks; if it is discontinued, it must be followed by another therapeutic agent. There is uncertainty on how to treat after denosumab, although recommendations have been made based on the best medical evidence that is currently available *(109)*.

New and emerging strategies for managing patients with osteoporosis include fracture risk stratification *(34)* and treat-to-target to aid in the selection of initial therapy *(91)*, with a general theme of using the most aggressive treatment (e.g., an osteoanabolic agent) in patients with very high risk of fracture. As the cost of this type of treatment declines and convenience of administration improves, osteoanabolic therapy may someday be considered as initial therapy for many or most patients with osteoporosis.

Bone Health in Transgender Adults

Micol S. Rothman, MD

Transgender people are those whose gender identity is different from the sex they were thought to be at birth, cisgender refers to those whose gender identity corresponds with sex identification at birth. Recent data suggest that about 1.4 million people or 0.6% of the adult US population identify as transgender, with growing awareness of the health disparities that need to be addressed in this population *(110)*. Despite this attention, many transgender patients still report negative experiences with the healthcare system; providers, in turn, describe a lack of training in transgender health *(111)*. Since osteoporosis and fractures are common as people age, and sex steroids are a key determinant of bone health, many questions arise as to the effect of gender-affirming hormone therapy (GAHT) on the skeleton.

Case reports have shown that mutations in estrogen production and estrogen receptor defects have deleterious effect on the attainment of peak bone mass and interfere with closure of epiphyseal plates even in the face of normal to high testosterone levels *(112,113)*. Estrogen acts on osteoblasts, osteoclasts, and osteocytes to maintain bone formation and decrease resorption. Estrogen deficiency plays an important role in both the rapid decline in BMD seen in postmenopausal cisgender women as well as the more gradual loss seen with aging in cisgender men.

In transgender women, defined as adults assigned male at birth with a female gender identity, many studies show low BMD at baseline, even prior to the initiation of GAHT *(114)*. The etiology is unclear, but studies suggest that lower physical activity, vitamin D deficiency, and tobacco use could play a role. After initiation of GAHT with estrogen and anti-androgens, bone density increases, despite increases in fat mass and decline in muscle mass. A meta-analysis of 13 studies including 392 transgender women reported increases in spine BMD at 1 yr and 2 yr after GAHT although not in hip BMD *(115)*. A cohort of 711 transgender women from Amsterdam has now been studied for 10 yr, the longest study to date *(116)*. No subjects had used GAHT or undergone orchiectomy at baseline; nonetheless, at the start of the study, 21.9% had low BMD (defined as Z-score < -2.0 using reference male population). After 10 yr of GAHT, DXA was reassessed in 102 transgender women (14%) and there was a significant increase in lumbar spine (LS) Z-score but not BMD. An association between estradiol and LS BMD was seen. Transgender women with the highest tertile of estradiol levels (mean 443 pmol/L or 121 pg/ml) had an observed increase in LS BMD, while those in the lowest tertile (mean 118 pmol/L or 32 pg/ml) had a decrease in LS BMD. There was no association with luteinizing hormone (LH) or degree of testosterone suppression. Despite these benefits, a recent retrospective study including nearly 2000 transgender women found an elevated fracture risk in subjects over the age of 50 yr (4.4% experienced a fracture) when compared to age-matched cisgender men (2.4% experienced a fracture; OR = 1.90, 95% CI 1.32-2.74) and rates more comparable to cisgender women (4.2% experienced a fracture; OR = 1.05, 95% CI 0.75-1.49) *(117)*.

In contrast, baseline studies in transgender men, defined as adults assigned female at birth with a male gender identity, indicate their bone density is similar to the general population *(114)*. When testosterone is initiated despite the subsequent relative deficiency in estradiol, several studies, including a meta-analysis, have shown stable BMD *(115)*. Testosterone affects body composition by increasing muscle mass and decreasing fat mass, and also likely has direct action on the bone *(114)*. Longitudinal data on a group of 543 transgender men found 4.3% of subjects had low BMD for age at baseline (defined as Z-score < -2.0) *(116)*. In the 70 subjects who had DXA repeated at 10 yr, LS Z-score increased, largely driven by a change in those over 40 at the time of GAHT initiation. Overall, BMD was similar and there was no association with testosterone level, but larger gains were seen in transgender men with lower LH levels, indicating LH suppression may be an indicator of adequate sex steroid for bone health. Fortunately, no increased risk of fracture has been reported in transgender men across the lifespan, with recent data finding of 1.7% transgender men experiencing a fracture compared with 3.0% of age-matched cisgender men (OR = 0.57, 95% CI 0.35−0.94), and 2.2% of age-matched cisgender women (OR = 0.79, 95% CI 0.48−1.30) *(117)*. In summary, data in transgender men are reassuring; despite the relative reduction in estradiol levels with GAHT, skeletal health is preserved.

Transgender youth are often treated with gonadotropin-releasing hormone agonist therapy to delay the onset or halt puberty. These therapies are known to lead to bone loss in all users. Transgender youth do not seem to "catch up" to their peers, even with the initiation of GAHT *(118)*. A survey of students showed statistically significant differences with lower reported rates of sports participant and overall minutes of physical activity in transgender and gender non-conforming youth when compared to their cisgender peers *(119)*. Additionally, gender non-conforming students were more likely to be bullied for their weight or size and to be overweight. Exercise should be encouraged, as should adequacy of

calcium intake, vitamin D supplementation when needed, and avoidance of excess alcohol and tobacco.

Few osteoporosis screening recommendations exist for transgender people *(120)*. The ES guidelines suggest consideration for screening BMD at baseline prior to GAHT in transgender women. They encourage screening for transgender women at age 60 yr or for those who are not compliant with GAHT; however, they only suggest screening in transgender men who stop testosterone after gonadectomy, are not compliant with testosterone, or have risk factors for bone loss *(121)*[12]. The University of California San Francisco advocates for screening DXA in all transgender people over age 65 yr and between ages 50–64 yr for those with established risk factors for osteoporosis. A 2019 position statement from the ISCD suggests screening should be similar to the general population when considering risk factors for bone loss, and they suggest earlier screening in individuals with gonadectomy. The ISCD also recommends that DXA be reported using the Z-scores of the identified gender, not the sex assigned at birth, regardless of duration of GAHT *(122)*.

In summary, bone density changes seen in transgender people on feminizing or masculinizing GAHT largely relate to the known effects of sex steroids, namely estradiol, on the bone. However, BMD in a significant proportion of transgender women runs low even prior to initiation of GAHT. Lifestyle factors likely contribute to this. When estrogen is initiated in transgender women, there are positive changes in BMD as well as some measures of bone quality; however, fracture risk may still be higher than in cisgender men of similar ages. Studies to date show the baseline BMD in transgender men to be similar to the general population. When testosterone is initiated in transgender men, the changes in BMD are not as robust, but body composition changes, and direct effects of testosterone on the bone likely protect BMD despite relative reduction in estradiol. Low levels of estradiol likely still offer bone protection in transgender men as in cisgender men. Overall, more data are needed to understand the role of gonadectomy, duration and route of GAHT, and changes in bone quality that will impact fracture risk over the life span in transgender people.

Update on Bone Health TeleECHO

E. Michael Lewiecki, MD

Bone Health TeleECHO was established in 2015 at the University of New Mexico (UNM) Health Sciences Center in Albuquerque, NM in collaboration with the Osteoporosis Foundation of New Mexico. ECHO was first developed to address care gaps for patients with chronic hepatitis C in rural New Mexico communities *(123)*, later expanding to include many disease states and other conditions *(124)*. ECHO has been recognized by the US Department of Health and Human Services as the prototype for technology-enabled collaborative learning and capacity building models *(125)*. Progress with Bone Health TeleECHO and similar programs has been reported at previous Santa Fe Bone Symposia *(10–14)* and updated here.

The mission of Bone Health TeleECHO is to expand global capacity to deliver best practice skeletal healthcare *(126)*. It is a weekly, ongoing, collegial, case-based, highly interactive videoconference that includes many medical disciplines, with participants located throughout the USA and many other countries. Regular participation offers opportunities to improve clinical skills so patients can receive better skeletal healthcare, 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 *(127)*. Bone Health TeleECHO aims to move knowledge, not patients, and is a force multiplier *(128)* that enables each participant to apply the skills that have been learned, including strategies for individualizing treatment decisions in settings of uncertainty, to many patients *(129)*. Additionally, as more programs are developed in the right languages, and time zones for those who wish to participate, the force multiplier effect is further enhanced.

Over 1000 individuals have registered to participate in Bone Health TeleECHO since its launch in 2015, with weekly attendance improving from an average of 13 in 2015 to over 90 in 2021. Regular participation has been shown to improve self-confidence in managing patients with osteoporosis *(130,131)*. The growth of participation in the prototype Bone Health TeleECHO program has been paralleled by the development of more programs in the USA and others countries, with more expected to follow. There are now 12 bone ECHO programs worldwide, with 9 in the USA (6 focusing on osteoporosis, 3 for rare bone diseases) plus 3 in other countries, and more expected to follow. At this time, this includes Michigan Neurosurgical Institute Great Lakes ECHO LLC (Grand Blanc, Michigan); NOF FLS Bone Health TeleECHO (Washington, DC); Own the Bone Ortho Bone Health TeleECHO (Chicago, Illinois); University of Vermont Osteoporosis Management TeleECHO (Burlington, Vermont); and Strides for Strong Bones TeleECHO (Spokane, Washington). Programs devoted to rare bone diseases are Rare Bone Disease TeleECHO (Gaithersburg, Maryland) *(132)*, Osteogenesis Imperfecta TeleECHO (Gaithersburg, Maryland), and Hypophosphatasia TeleECHO (Boonton, New Jersey). Programs outside the USA are NUIG Bone Health TeleECHO (Galway, Ireland); Russia Bone Health TeleECHO (Moscow, Russia), and Australia/New Zealand Bone Health TeleECHO (Sydney, Australia). In addition, Ehlers Danlos Society has 2 programs for Ehlers Danlos Syndrome based in the USA and United Kingdom) for developed by the. Every ECHO program establishes its own agenda according to the needs of its participants while maintaining fidelity to the ECHO model of learning. ECHO programs have been well positioned to rapidly respond to challenges in managing patients with skeletal diseases that have arisen due to the global COVID-19 pandemic *(133)*.

Funding

Manuscript preparation and editing was supported by the Osteoporosis Foundation of New Mexico, Albuquerque, New Mexico, USA.

Disclosure

E. Michael Lewiecki is a consultant and speaker for Amgen, Radius, and Alexion. *Paul A. Anderson* is a consultant and speaker for Amgen and Radius, a consultant for Medtronic, and has stock ownership in Titan Spine. *John P. Bilezikian* is a consultant and speaker for Amgen and Radius. *Neil Binkley* is a consultant for Amgen. *Angela M. Cheung* has nothing to disclose. *Erik A. Imel* is a consultant for Ultragenyx and Inozyme. *Diane Krueger* has nothing to disclose. *Michael R. McClung* is consultant and speaker for Amgen, a consultant for Myovant, and a speaker for Alexion. *Paul D. Miller* has nothing to disclose. *Micol S. Rothman* is a consultant for Abbvie.

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