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Review Article

Proceedings of the 2022 Santa Fe Bone Symposium: Current Concepts in the Care of Patients with Osteoporosis and Metabolic Bone Diseases

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Abstract

The 22nd Annual Santa Fe Bone Symposium (SFBS) was a hybrid meeting held August 5-6, 2022, with in-person and virtual attendees. Altogether, over 400 individuals registered, a majority of whom attended in-person, representing many states in the USA plus 7 other countries. The SFBS included 10 plenary presentations, 2 faculty panel discussions, satellite symposia, Bone Health & Osteoporosis Foundation Fracture Liaison Service Boot Camp, and a Project ECHO workshop, with lively interactive discussions for all events. Topics of interest included fracture prevention at different stages of life; how to treat and when to change therapy; skeletal health in cancer patients; advanced imaging to assess bone strength; the state of healthcare in the USA; osteosarcopenia; vitamin D update; perioperative bone health care; new guidelines for managing primary hyperparathyroidism; new concepts on bone modeling and remodeling; and an overview on the care of rare bone diseases, including hypophosphatasia, X-linked hypophosphatemia, tumor induced osteomalacia, osteogenesis imperfecta, fibrodysplasia ossificans progressiva, and osteopetrosis. The SFBS was preceded by the Santa Fe Fellows Workshop on Osteoporosis and Metabolic Bone Diseases, a collaboration of the Endocrine Fellows Foundation and the Osteoporosis Foundation of New Mexico. From the Workshop, 4 participating fellows were selected to give oral presentations at the bone symposium. These proceedings represent the clinical highlights of 2022 SFBS presentations and the discussions that followed, all with the aim of optimizing skeletal health and minimizing the consequences of fragile bones.

Key Words: Osteoporosis; ECHO; Myeloma; Osteosarcopenia; Hyperparathyroidism; Hypophosphatasia.

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Introduction

The Santa Fe Bone Symposium (SFBS) was established in 2000 and has been held annually, until the onset of the COVID-19 global pandemic, in Santa Fe, New Mexico, USA. The 2020 SFBS was postponed to 2021,

when it was held virtually (1). The virtual aspect of the symposium provided an opportunity for greater participation than previous in-person events, with over 300 attendees from the US and 18 other countries in 2021. The planning of the 2022 SFBS took into consideration the desire by many to return to in-person gatherings, with the collegiality and personal interaction that is the hallmark of the SFBS; the need for attendee safety, considering local COVID-19 infection rates and regulatory restrictions; and the benefits of remote attendance, including less time away from home and office and lower total costs.

The 2022 SFBS was a "hybrid" meeting, with about 240 in-person attendees in Santa Fe and over 160 remote attendees, representing 44 US states and 8 other countries. Attendees included physicians of many medical specialties and practice settings, advanced practice providers (e.g., nurse practitioners, physician assistants), dual-energy X-ray absorptiometry (DXA) technologists, scientists, and researchers. There were 10 plenary presentations with 9 in-person speakers and 1 speaking remotely. The Santa Fe Fellows Workshop on Osteoporosis and Metabolic Bone Diseases, a collaboration of the Endocrine Fellows Foundation and the Osteoporosis Foundation of New Mexico, was held over the 2 days immediately prior to the SFBS. This was attended by 23 endocrinology fellows with lectures by 7 faculty. Abstracts were presented by the fellows, with 4 of them selected for oral presentations at the SFBS.

All sessions of the SFBS were recorded and archived on the meeting website for later viewing. Symposium topics, speakers, and format were chosen by the planning committee with consideration of evaluations from the 2021 SFBS and the emergence of new data, guidelines, and controversies over the past year.

Enduring medical education materials generated by previous symposia have included publications of proceedings in peer-reviewed medical journals (1-15), monographs in print and electronic formats (16-20), online archived video presentations (https://www.ofnm.org/), audiovisual webcasts, and audio recordings. These proceedings of the 2022 SFBS are written by the faculty to present the clinical highlights of each presentation.

Fracture Prevention at Different Stages of Life

Michael R. McClung, MD

Fractures are common across the lifespan with the highest rates being observed at puberty and in older adults. The pathogenesis of fractures varies among different ages groups. In children and adolescents, fractures are usually related to incomplete skeletal development, trauma (including child abuse), and congenital and acquired bone diseases. Among older adults, the important risk factors for fracture include a previous (especially recent) fracture, advanced age, low bone mineral density, frequent falls, and many diseases and medications. Unique, often transient, fracture syndromes occur at birth (osteoporosis of prematurity), the time of puberty (juvenile osteoporosis) and in the post-partum period (pregnancy- and lactation-associated osteoporosis (PLO).

Evidence for fracture prevention comes primarily from studies to obtain government registration for new osteoporosis drugs or fall prevention programs in elderly adults. Multiple drugs from different classes, including anti-remodeling (often called antiresorptive) drugs and osteoanabolic or bone-forming agents have been approved on the basis of fracture risk reduction in women with postmenopausal osteoporosis (PMO) in large randomized, placebo-controlled trials, lasting from about 19 to 48 months (21). Studies evaluating fracture prevention in other populations are quite limited.

Postmenopausal Women with Osteoporosis. In women with PMO, fracture risk reduction occurs within the first few months of therapy and is greater with drugs inducing larger gains in bone mineral density (BMD). The skeletal benefits of bisphosphonates and denosumab (anti-remodeling drugs) persist as long as treatment is given. With bisphosphonates, neither hip BMD nor fracture risk reduction improve beyond 5 years of treatment, while the rare risk of atypical femur fractures continues to increase (22). A temporary interruption of therapy (i.e., bisphosphonate holiday) may be considered in patients at low fracture risk after 3-5 years of bisphosphonate therapy (23). For patients remaining at high risk of fracture (i.e., still meeting criteria for treatment), switching to another therapy rather than continuing the bisphosphonate should be considered. During 10 years of denosumab therapy, no duration-dependent adverse events were observed (24). Non-vertebral fracture risk decreased beyond 3 years of therapy, consistent with the progressive increase in total hip BMD observed over 10 years of follow-up. There is no limit to the duration of denosumab therapy, but transition to a potent bisphosphonate is advised if denosumab is discontinued to prevent rapid loss of BMD and vertebral fractures (23).

Teriparatide and romosozumab, osteoanabolic agents, are more effective that bisphosphonate in improving BMD and preventing fractures in women with PMO at high fracture risk. Recent guidelines recommend that the initial choice of osteoporosis therapy be based on the patient's fracture risk: raloxifene or bisphosphonates for patients at moderate fracture risk, bisphosphonates or denosumab for patients at high fracture risk, and osteoanabolic agents for patients at very high or imminent risk of fracture (23). Switching to a bisphosphonate or denosumab after a course of osteoanabolic therapy maintains the BMD gain and the fracture protection benefit of the anabolic agent for at least 2 years (25).

Elderly Women with Postmenopausal Osteoporosis. In subgroup analyses of several pivotal PMO fracture trials, fracture risk reduction with treatment was similar in older (usually age $\geq$75 years) vs younger subgroups. In the Hip Intervention Program (HIP) study, reduction in hip

fracture with risedronate was not evident in the group of patients aged 80 years and older who were enrolled primarily with fall-related risk factors rather than osteoporosis (26). There is not an age above which osteoporosis therapy should not be considered. Multifactorial fall prevention programs including activities to improve strength and balance; good nutrition including adequate intakes of calcium, vitamin D and protein; correcting visual and neurologic impairments; and minimizing polypharmacy reduce the frequency of falls but have not been shown to reduce fracture risk. Correcting severe vitamin D deficiency in elderly adults reduced hip fracture risk (27).

Men with Osteoporosis. Most drugs for treating PMO are also approved for men with osteoporosis, based upon small studies demonstrating effects on BMD rather than fracture prevention. Vertebral fracture risk reduction has been shown with alendronate and teriparatide in men with osteoporosis.

Adults Without Osteoporosis. Vitamin D supplements of 2000 IU daily did not reduce fracture risk in healthy, vitamin D-replete, community-dwelling adults (28). Vertebral fracture risk is reduced with risedronate and teriparatide therapy in adults receiving glucocorticoids, while denosumab reduced vertebral fracture risk in men and women (mostly postmenopausal) receiving hormone ablative therapy non-metastatic prostate and breast cancer. The Women's Health Initiative (WHI) studies enrolled postmenopausal women ages 50-79 years (average 63 years) without regard to BMD status. In the BMD subgroup, mean T-scores were about -1.2 at the lumbar spine and -0.8 at the total hip. Estrogen therapy with or without progesterone significantly reduced fracture risk (29). BMD and protection from vertebral fracture were quickly lost when estrogen was discontinued (30).

Children, Adolescents and Young Adults. Bisphosphonates have been shown prevent fractures in children with osteogenesis imperfecta and adolescents with idiopathic juvenile osteoporosis. Teriparatide and bisphosphonate therapy reduce vertebral fracture risk in premenopausal women with PLO. While osteoporosis therapies increase BMD in premenopausal osteoporosis and idiopathic osteoporosis in men, none of the studies has demonstrated reduction in fracture risk.

Perimenopausal Women. The rapid bone (9-12%) and significant deterioration of bone structure that occurs across the menopausal transition can be prevented with estrogen or bisphosphonates. Fracture prevention with estrogen was observed in the Danish Osteoporosis Study (31). In the WHI, the relative reduction in fracture risk was the same in women age 50-59 years as in older subgroups.

Summary. Fracture protection in older adults should include both fall prevention and pharmacologic therapy to strengthen the skeleton. However, because these strategies are only partially successful, perhaps we should reconsider the merits of more aggressive therapy to prevent osteoporosis by use of estrogen to prevent bone loss at menopause in patients at risk for osteoporosis, to be followed by a bisphosphonate for 3-5 years if or when estrogen is discontinued.

How long to Treat, When to Change, and How to Change

Paul D. Miller, MD, HDSc (Honorary)

The 2000 National Institutes of Health (NIH) definition of osteoporosis includes both BMD as well as bone quality as contributors to bone strength (32). While DXA is a widely available and highly effective method to measure BMD, it is more difficult to measure bone quality in clinical practice. The development of trabecular bone score (TBS), a DXA based software package, is a major step forward to partially measure bone quality in clinical practice. TBS software can be added to most DXA platforms and incorporated into the FRAX^{TM} algorithm to enhance fracture risk prediction beyond that associated with BMD alone (33). It is important to understand the role that bone quality plays in determining bone strength, since many women and men who fracture have BMD that is normal or osteopenia according to the World Health Organization (WHO) classification (34). Identifying and treating these patients is important, since limiting treatment to patients with T-scores $\leq$ -2.5 would miss many patients who might benefit from therapy. Understanding fracture risk before and during treatment is useful for selecting initial treatment and later considering changing treatment.

How Long to Treat. Since the mechanism leading to osteoporosis is a life-long process, therapies to treat osteoporosis must be considered as long-term interventions (35). The fundamental pathophysiology leading to both postmenopausal and idiopathic male osteoporosis is an imbalance of bone remodeling, with bone resorption exceeding bone formation. All approved osteoporosis treatments exert their pharmacological effects by modulating bone turnover. Bisphosphonates were among the first US Food and Drug Administration (FDA) approved drugs to treat osteoporosis and continue to be the most widely prescribed agents to treat osteoporosis worldwide. Bisphosphonates reduce bone turnover, decrease the bone remodeling space, prolong the process of secondary mineralization, and increase BMD, resulting in improved bone quality and reduction of the risk of osteoporotic fractures (36). Bisphosphonates are not metabolized and have a long skeletal retention time due to local and systemic recycling during the remodeling process (37). In that regard, after 3-5 years of treatment with a bisphosphonate, low-risk patients may be considered for a bisphosphonate "holiday" (38), a temporary cessation to bisphosphonate treatment that may be accompanied by persistent benefit while reducing the risk of rare side effects such as atypical femur fracture (AFF). These patients can be monitored with serial testing of BMD and a bone turnover marker, such as serum C-telopeptide

(39). Holidays are not suitable for non-bisphosphonate osteoporosis treatments (e.g., estrogen, raloxifene, denosumab, teriparatide, abaloparatide, romosozumab), since the treatment effect rapidly diminishes after stopping. The FDA recommends continuation of bisphosphonate therapy in high-risk patients (38), without defining what that therapy should be. It is reassuring that continuous treatment with denosumab for as long as 10 years is associated with continuing efficacy and a favorable safety profile (24).

The boxed warning restricting teriparatide to 24-months of lifetime use has been removed. This provides opportunities to use this anabolic agent for longer than 2 years in some patients who continue to be at high risk or once again are at high risk after completing 2 years of treatment (40). At the time of this writing, the 2-year lifetime limit for the use of abaloparatide remains in place. Romosozumab is administered once monthly for 12 months, but there is no prohibition for another 12-month course of therapy sometime later.

When to Change. A change in treatment may be considered when there is an unacceptable adverse drug effect, poor compliance with therapy, suboptimal response to therapy, cessation of non-bisphosphonate treatment, change in fracture risk, or drug no long available or affordable. The occurrence of a fracture (including a radiographic vertebral fracture) in a treated patient is not necessarily treatment failure (41), but it does suggest that fracture risk is higher than previously recognized (42,43). In such a patient, anabolic therapy should be considered (23,44-46). Anabolic agents are superior to bisphosphonates in high risk patients (25) and should ideally be prescribed first in first patients, followed by antiresorptive therapy (47).

Combination therapy with teriparatide and denosumab provides a bigger increase in BMD than either drug alone (48). This suggests possible clinical applications of this combination in high-risk patients (e.g., adding teriparatide to denosumab), although it is not known whether the combination provides additional fracture risk protection, and this may expose the patient to additional risk of adverse medication effects and higher costs.

How to Change. For a patient on a bisphosphonate holiday because of low fracture risk, treatment should be resumed when fracture risk is once again high. The post-holiday drug could be a bisphosphonate or a non-bisphosphonate, depending on clinical circumstances. Patients at high fracture risk who are stopping a non-bisphosphonate should be transitioned to another therapeutic agent. This is especially important when long-term denosumab therapy is stopped, since it will likely be followed by loss of BMD, increase and overshoot of bone turnover markers, and increase of vertebral fracture risk (49). When denosumab must be stopped, it is generally followed by a bisphosphonate, provided there is no contraindication. A position statement of the European Calcified Tissue Society suggests a pragmatic approach of giving intravenous (IV) zoledronic acid 6 months after the last dose of denosumab and then monitoring with a bone turnover marker 3 months and 6 months later (50). If bone turnover is unacceptably high, consider giving a second dose of zoledronic acid.

It is essential for anabolic therapy to be followed by an antiresorptive agent to enhance and consolidate the treatment effect (25).

Osteosarcopenia, Fracture Prevention in Older Adults, and Vitamin D

Neil Binkley, MD

The osteoporosis "treatment gap," i.e., failure to identify and utilize approaches to reduce fracture risk in older adults, is a worldwide concern (51) However, too often this treatment gap is viewed as failure to provide a drug prescription, despite pharmacologic therapy only reducing risk of non-vertebral fractures by about 20-40%. This less- than-ideal treatment outcome emphasizes the need to consider both pharmacologic and non-pharmacologic approaches to reducing fracture risk. Said succinctly, this suboptimal outcome is due in large part to current osteoporosis drugs not reducing falls risk. Emphasizing falls makes consideration of muscle weakness an integral part of fracture prevention and logically leads to consideration of the concept of "osteosarcopenia," i.e., the joint present of low bone mass/strength with low muscle mass/strength (52). The relationship between bone and muscle has long been recognized and indeed, the pathogenetic factors underlying bone and muscle loss, e.g., sedentariness, dietary inadequacy, toxins, etc., are very similar (53). Moreover, the cellular crosstalk between bone and muscle is increasingly recognized (54). The breadth of factors contributing to this crosstalk makes it likely that a pharmacologic target(s) could be developed to simultaneously improve bone and muscle thereby reducing both falls and fractures.

Unfortunately, pharmacologic interventions to target muscle, i.e, sarcopenia (or muscle and bone simultaneously), have languished. In part, this is the result of prior reliance upon DXA-measured lean mass which, rather than being a measure of muscle mass, is largely a measure of water. The preservation of extracellular water with advancing age blunts the ability of DXA to detect true muscle loss (55). Methods to improve DXA measurement of lean mass, e.g., addition of bioimpedance spectroscopy, or other approaches to lean mass measurement, such as D3-creatine dilution or CT-based muscle attenuation (Hounsfield Units), are promising and may move the sarcopenia field forward. Indeed, multiple pharmacologic agents remain under consideration for sarcopenia treatment (56). Based upon history of the osteoporosis field, it seems plausible/likely that development of a pharmacologic agent concomitantly with availability of a widely available muscle mass/quality measurement will be

needed to bring sarcopenia to widespread clinical awareness.

Given current absence of drug treatment, what can the clinician do today? One short-term approach will be inclusion of falls as a fracture risk factor into the forthcoming FRAX update. Even while awaiting this advance, clinically we can emphasize non-pharmacologic approaches to fracture risk reduction including falls assessment, balance training, exercise/physical therapy and nutritional interventions. In this regard, a potential nutritional intervention that has garnered substantial recent interest is vitamin D supplementation.

Vitamin D deficiency can clearly have adverse skeletal consequences; whether it adversely affects muscle function or contributes to falls risk is not clear. The recently published VITamin D and OmegA-3 TriaL (VITAL) fracture substudy did not find a fracture risk reduction benefit from additional vitamin D supplementation *(28)*. However, this negative result was expected given that the study cohort was not selected to have low bone mass or high fracture risk; even more importantly, the study subjects were largely vitamin D replete, with a mean baseline 25(OH)D concentration of about 30 ng/mL. Given that nutrients have a threshold effect, i.e., once the status of a nutrient is adequate, provision of more will have no beneficial effect *(57)*, the finding of no fracture reduction upon providing additional vitamin D supplementation to vitamin D replete people is precisely what one should expect. Moreover, the subanalysis of the relatively small number of subjects with low 25(OH)D in VITAL was underpowered to identify a fracture reduction effect. Thus, this study should not alter the practices of clinicians interested in fracture risk reduction. Specifically, provision of daily vitamin D_3 supplementation to patients with osteoporosis and/or prior fracture to attain a circulating 25(OH)D level of about 30 ng/mL remains reasonable. An important additional nutritional intervention available today is optimization of protein intake, with guidance suggesting 1.0-1.2 grams of protein daily/kg of body weight daily for older adults *(58)*.

In summary, increased recognition of the concept of osteosarcopenia can be implemented clinically at this time by emphasizing non-pharmacologic approaches to fracture risk reduction, e.g., falls risk reduction strategies, physical therapy/exercise/balance training (notably Tai-Chi) and optimization of calcium, vitamin D, and protein status. It is likely that improved muscle measurement approaches and, hopefully, muscle and bone active pharmacologic agents, will become clinically available to further reduce fracture risk.

New Concepts on Bone Modeling and Remodeling with Osteoporosis Treatments

David W. Dempster, PhD, FRMS

In humans, bone remodeling begins *in utero* and continues throughout the entire life span. Bone remodeling serves several functions, including mineral homeostasis, maintenance of bone strength by repair of microdamage, and ongoing renewal of the osteocyte population. In each remodeling cycle, osteoclasts remove older bone and, through a tight coupling process, osteoblasts replace that old bone with new *(59)*. In this manner, resorption and formation are both temporally and spatially linked. By contrast, in bone modeling osteoclast and osteoblast teams work independently; resorption can occur at one site and formation at another. Bone modeling is the process by which bones are sculpted during growth and is the mechanism by which bones change shape and mass in response altered mechanical loads. Harold Frost and colleagues showed that, under normal loading conditions, a small amount of modeling persists in the adult human skeleton *(60)*. They distinguished between remodeling and modeling by examining the cement line that binds new bone to old. If that line is scalloped, indicating prior resorption, the new bone was formed by modeling, whereas if the cement line is smooth, the new bone was formed by modeling. Frost also recognized that bone formation occurring within traditional remodeling units could spill over onto smooth adjacent bone surfaces, termed here "overflow modeling-based formation". Our group became interested in modeling-based formation while studying the anabolic action of PTH *(1-34)*, also known as teriparatide. Using a quadruple tetracycline labeling schedule to assess bone formation longitudinally in single iliac crest bone biopsies, we showed that following treatment with daily teriparatide for one month, modeling-based formation accounted for 20-30% of the newly formed bone on trabecular and endocortical surfaces *(61)*. In the same year, similar observations were made with teriparatide treatment over 12-24 months *(62)*. Later, Cosman and colleagues demonstrated that early treatment with teriparatide-stimulated remodeling- and overflow modeling-based formation, with a strong trend to increase modeling-based formation in the human femoral neck *(63,64)*.

The Anabolic vs. Antiresorptive (AVA trial) compared the early effects of teriparatide with those of denosumab, also using a quadruple tetracycline labeling approach. At 3 months, teriparatide treatment resulted in a significant increase in remodeling-based, modeling-based, and overflow modeling-based formation on cancellous and endocortical surfaces with a 4-fold increase in modeling-based formation on the periosteal surface *(65)*, *(66)*. Similar findings have recently been reported for the parathyroid hormone related protein (PTHrp) *(1-34)* analog, abaloparatide, with a 17-fold increase in modeling-based formation on the periosteal surface *(67)*. With regard to the effects of denosumab in the AVA trial, as expected, remodeling-based formation was significantly reduced, but modeling-based formation was unchanged or slightly increased.

One of the most intriguing observations in recent years has been the ability of denosumab to cause progressive

increases in BMD at hip and spine over 10 years, despite ongoing and substantial inhibition of bone remodeling (24). The underlying mechanism for this phenomenon is unclear. Dempster et al (68) used quantitative microradiography to assess mineralization density in bone biopsies from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial and its extension. Compared to placebo, mineralization density was higher in denosumab-treated patients at three years, continued to increase up to 5 years and then plateaued at 10 years. Thus, prolonged secondary mineralization of the bone matrix may account for some of the ongoing gains with denosumab through 5 years, but not beyond that. The first clue that modeling-based formation may play a role in the progressive gain in BMD came from a preclinical model in which denosumab markedly inhibited remodeling in cancellous bone of the proximal femur but modeling on the periosteal and endocortical surfaces was unaffected. It was theorized that preservation of modeling-based formation in the face of marked inhibition of bone resorption would contribute to sustained gains in BMD. A recent pilot study confirmed that modeling-based formation occurs in the human femoral neck; compared to a historical group of control subjects, remodeling-based formation was lower and modeling-based formation was numerically higher in 4 patients who had received denosumab (69). This suggests that denosumab preserves modeling-based formation in the human femur neck, and possibly increases it.

The mechanism of action of the sclerostin antibody, romosozumab, is unique. Unlike teriparatide and abaloparatide, which stimulate both formation and resorption, romosozumab stimulated formation and, simultaneously, inhibits resorption (70). One would, therefore, have predicted that this agent would primarily work by early stimulation of modeling-based formation and this has been confirmed (71).

For many years it was thought that bone strengthening drugs worked by manipulating the bone remodeling; antiresorptive, or more correctly, antiremodeling drugs inhibited remodeling and anabolic agents increased remodeling (72). We now recognize that modeling also plays an important role in how anabolic agents work and this is possibly also true for potent antiremodeling agents (73).

Update on Primary Hyperparathyroidism from the International Workshop

John P. Bilezikian, MD, PhD (hon)

Since the proceedings of the Fourth International Workshop on the evaluation and management of primary hyperparathyroidism (PHPT) were published in 2014 (74), advances in many aspects of this disease led to the Fifth International Workshop. Over a two-year period, 2020-2022, about 100 international experts in the parathyroid diseases convened virtually, reviewing new information that has become available over the past decade. These new insights addressed the following aspects of PHPT: epidemiology, genetics, physiology, pathophysiology, clinical presentations, new imaging modalities, target and other organ systems, diagnosis, pregnancy, evaluation, management, and outcomes. The methodologies included Grading of Recommendations, Assessment, Development and Evaluations (GRADE) when the data fit those criteria for systematic review (75). Recognizing that some noteworthy information could not be incorporated into GRADE methodology, narrative reviews were also undertaken. The work was divided among 4 Task Forces: Epidemiology, Pathophysiology, and Genetics of PHPT (76); Classical and Non-classical Manifestations (77); Surgical Aspects (78); and Management (79); as well as a document following GRADE methodology for surgical and medical management of PHPT (80).

Compiling this wealth of information for the practicing endocrinologist, we also published a summary statement that provides graded and ungraded recommendations with regard to the aforementioned topics (81). The summary statement summarized our evidence-based review of the diagnosis of PHPT and its differential diagnosis. We recognized three phenotypes of PHPT: symptomatic, asymptomatic, and normocalcemic. Differentiating further among those with hypercalcemic and normocalcemic asymptomatic PHPT, we recognize that after evaluation, some individuals will have evidence for target organ involvement (e.g., skeleton and/or kidney) while others will not.

All patients should be evaluated with biochemical indices (calcium, PTH, 25(OH)D), skeletal imaging (3-site DXA and another vertebral imaging modality such as X-ray, vertebral fracture assessment or trabecular bone score), renal indices (creatinine clearance, 24-hour urinary calcium, stone risk profile when indicated, and imaging for renal calcifications). We do not recommend formal testing of non-classical manifestations (neurocognitive, quality of life, cardiovascular) because there are no data that argue for intervention based upon any abnormalities that may be detected in these off-target systems.

Parathyroidectomy should be recommended in anyone with symptomatic PHPT, defined as overt complications of the skeleton or kidneys. Surgery can also be performed in anyone with the diagnosis, even if they do not meet surgical criteria, and in whom there are no contraindications. Surgery in these individuals would be with the concurrence of the patient and the physician. The panel identified specific indices, any one of which, would lead to a recommendation for surgery: a. hypercalcemia > 1 mg/dL (> 0.25 mmol/L) above normal; b. T-score (≤ -2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius) or a fracture by VFA or vertebral X-ray; c. creatinine clearance < 60 cc/min; nephrocalcinosis or nephrolithiasis; hypercalciuria (> 250 mg/day in women; > 300 mg/day in men); d. Age < 50 years. These guidelines apply to those

with hypercalcemic PHPT, because we do not have enough data to recommend these guidelines in those with normocalcemic PHPT.

When surgery is to be performed, preoperative imaging is strongly recommended. Widely used parathyroid imaging modalities include ultrasound, technetium-99m-sestamibi subtraction scintigraphy, and contrast-enhanced four-dimensional computed tomography (4D-CT). Parathyroid surgery should be performed by an experienced parathyroid surgeon, defined as someone who performs at least 50 parathyroidectomies per year *(82)*. In those who meet criteria for parathyroid surgery but in whom surgery is not to be performed, pharmacological management can include cinacalcet to lower the serum calcium and/or alendronate or denosumab to increase bone mineral density.

In those who are not going to have parathyroid surgery, annual measurements of the serum calcium, PTH, and 25(OH)D are recommended. Yearly or every 2-year assessment by DXA is recommended with other spine imaging as clinically needed. Yearly assessment of renal function (creatinine clearance or estimated glomerular filtrations rate [eGFR]) with renal imaging as clinically indicated is also recommended. In those who develop any criterion for surgery during monitoring, they should be recommended for surgery, if there are no contraindications.

Nutritional guidelines include calcium intake according to national guidelines; serum 25(OH)D level should be maintained > 30 ng/mL (> 75 nmol/L).

Although many aspects of these guidelines are similar to previous ones, they are based upon an expanded database of evidence currently available. Despite the progress of the past several years, we recognize the need for more research to augment our current knowledge base. The published summary statement also provides a blueprint for future research in this disease *(8)*.

Perspective on the State of Healthcare in the United States

Elisabeth Rosenthal, MD

United States hospitals and doctors offers up the most advanced medical care in the world. But even patients with insurance suffer unduly or don't seek the care they need because it's too expensive. More than 100 million Americans – 41 percent of adults – have medical debt and an alarming one-in-five of those folk don't expect to be able to pay it off ever in their lifetime *(83)*. As they face the hardship of illness, the financial strain is enormous.

I wrote my book, "An American Sickness: How Healthcare Became Big Business and How You Can Take it Back," *(84)* to research and document how our healthcare system arrived in such a troublesome place, beset by runaway prices. Here's the essence of what I found: Our medical care had been highjacked by business. The care patients receive is often determined by considerations like profit, revenue generation or return on investment, rather than what is best or right for patient health.

Of course, doctors and hospitals have to be financially sustainable and (if they have a good "payer mix") ideally are self-sustaining. But when I became a doctor in 1986, good patient care was on the front burner, and business-of-medicine on the back. In the last two decade that positioning has, sadly, been reversed. Optimal, affordable patient care is fading into distance.

I'll give you just a few pieces of evidence of how this plays out today: Every few weeks I get a list of hospitals that are closing departments or units *(85)*. The units are predominantly services that I regard as some of the most essential to communities - obstetrics, rehabilitation, pediatrics, in-patient psychiatry. What they have in common is that are money-losers, yielding poor return on investment. I never see units shuttered for joint replacement or cardiac catheterization, or interventional radiology. That's because they are big profit centers. Or how about this: Private equity investors are now major owners of services like hospitals, cataract centers, and nursing home *(86)*. They have often taken ownership from non-profits. When I was in medical school, we used to be asked the question: "To whom is duty owed?" The answer was, of course, "the patient." Today many health professionals have no choice but to first serve their corporate officers, who – first and foremost – serve the investors.

In my book, I document how different sectors of health care system turned away from their sense of mission and towards an appreciation of making money: Hospitals taught and forced doctors on staff how to bill for more revenue value units; they renovated functional buildings into 5 stars hotels, while jacking up prices to unsupportable levels. Entrepreneurial doctors got in on the act, doing things like opening surgery centers, pain treatment clinics, and billing for in-office infusions. (Those who merely did the work, found their revenues suffer).

In many markets, consolidation of hospital systems (horizontal consolidation) as well as their purchase of surgery centers and doctor's practices (vertical consolidation) has allowed monopoly pricing, as well as enabled unsavory business practices.

Pharmaceutical companies and device makers took out dozens of patents on each invention and took to the courts to defend them – often for copycat drugs of others already on the market or for not very effective drugs. With years-long monopolies they raised prices. When the first lifesaving drug for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), zidovudine (AZT), came on the market in 1989 at a price of $8000 a year (about $667 a month), the price was slammed as "astoundingly high" and "inhuman." *(87)* Today, hundreds of medicines are over that price point. Virtually all the disease-modifying medicines for multiple sclerosis cost at much in a month as AZT cost in a year.

Likewise consider the prescription drug Duexis (Horizon Medicines LLC, Deerfield, IL, USA), which is nothing more than a combination of two common generic drugs, ibuprofen and famotidine. It retails for nearly $1000 a month *(88)*. Our collective notion of what is a reasonable price for all sorts of medical services and products has skyrocketed.

The Kaiser Health News/National Public Radio (KHN/NPR) "Bill of the Month" series *(89)* highlight some of the harms to patients: Patients who get estimates of a few thousand pre-procedure and are then billed for tens of thousands after care is rendered. Women who walk onto the maternity ward in active labor may be charged thousands extra for an obstetrical emergency department ("Ob-ED") visit – a charge levied when cervical dilation is checked.

Physicians who sell practices to a hospital system find themselves under pressure to refer patients within the system, despite its high prices; they find themselves complicit in charging additional fees for their patient visit – like hundreds in new facility fees, even for a telemedicine visit. Those who have tried to remain independent find thy have little negotiating power compared to big hospital networks and insurers and so often receive reimbursement that doesn't cover their costs. The financial incentives which now govern how our health care is delivered (and rationed) are terrible for both patients and on-the-ground providers.

As for what to do about it, I have ideas. But they are piecemeal and somewhat unsatisfying for a system that likely needs major overhaul. Overhaul to put care rather than finance back in the driver's seat. Here are a few things I recommend: When doctors order tests and scans, know which facilities in your area offer a reasonable price. The price for a vitamin D test in New York can vary between $14 and $700+ dollars. Likewise know the price of the drugs you prescribe. What physician would prescribe Duexis if they knew it would cost close to $1000? I tell patients to be cautious when the receive a pile of consent forms checking into a hospital or surgery center. One of them is likely a financial consent that says "I agree to pay for anything my insurance doesn't cover." Cross it out. That clause leaves patients sitting ducks for surprise bills. But we need government and regulatory intervention to make really medical care more accessible and affordable. And to save patient as well as providers from wasting hours of their time arguing about bills.

Here are a few step-wise interventions that could help, some of them easier than others:

a. Require binding estimates and simple medical bills in plain English so they can be scrutinized by patient for fairness and accuracy.
b. Let's have list prices on order sheets and prescribing software so that providers ordering a test or medicine knows its "retail" cost. Is it high or low?
c. Require that any ancillary or physician services delivered at an in-network hospital be paid at in-network rates.
d. The Federal Trade Commission needs be more active in scrutinizing and rejecting healthcare mergers that don't serve the public interest. (The Biden Administration says it will do so.)
e. Let the government negotiate prescription drug prices and judge cost-effectiveness to help inform that negotiation. (Congress is taking the first steps to make this happen in Medicare.)

In the long term the system may well require more radical overhaul. This might include national price setting for drugs, devices and services (as in Germany), a so-called "public option" (supported by President Biden on the campaign trail) or a full-scale national health system, which advocates refer to as "Medicare-for-all" (though I think it would be unlikely to resemble today's Medicare program).

Could it happen here? Maybe. That's a political question, though I do believe we're reaching a tipping point where the current health care delivery system has failed so many – patients and providers - as to be unsustainable. In a 2004 poll taken by the Canadian Broadcasting Company, Tommy Douglas, the father of Canada's national health care scheme, was voted the greatest Canadian of all time *(90)*. Just remember: Before Canada had its current system, the healthcare there was much like ours.

The Skeletal Impact of Cancer and Cancer Therapies

Matthew T. Drake, MD, PhD

Cancer and therapies used for the treatment of cancer are often overlooked by providers and patients alike with respect to their deleterious effects on bone health. Cancer more commonly occurs in aged individuals, where it is associated with an increased risk for generalized osteoporotic-type bone loss independent of the type of primary malignancy *(91)*. Bone loss in cancer results from numerous factors, including direct effects of the cancer cells themselves, as well as from the effects of the cancer therapies on bone cells, either directly as can occur with chemotherapeutics and glucocorticoids, or indirectly as occurs with hormonal therapies used for the treatment of hormone-responsive malignancies. Bone is also the most common site for cancer metastasis, with cancer cells that grow within the skeleton inducing both osteoclasts and osteoblasts to produce factors that further stimulate cancer cell growth *(92)*. In this context and given that continued improvements in cancer therapies have resulted in progressively longer survivals from diagnosis in patients with cancer, optimization of skeletal health must be acknowledged as increasingly important for optimal patient care.

Although it is well-recognized that breast cancer therapies are associated with both bone loss and a higher risk for fracture, many women with breast cancer fail to undergo BMD evaluation as clinically recommended, with factors including older age, minority race, rural locality, and lower socioeconomic status among those associated with a lower likelihood of receiving recommended care (93). Estrogen plays an essential role in bone homeostasis via its effects at the estrogen receptor, with approximately 75% of breast cancers showing estrogen receptor positivity. Early menopausal onset is common in premenopausal women treated with hormonal or chemotherapy for breast cancer and is associated with rapid bone loss. In premenopausal women, there is good evidence that treatment with zoledronic acid prevents adjuvant endocrine therapy-induced bone loss (94). Data on fracture prevention in premenopausal women is limited. In postmenopausal women receiving aromatase inhibitor therapy for breast cancer, zoledronic acid limits BMD losses and likely reduces fracture rates, although the effects on both BMD and fracture risk reduction in postmenopausal women has been shown to be greater with denosumab treatment (95).

Prostate cancer is dependent on testosterone at the time of diagnosis in most men. Analogous to endocrine therapies used for breast cancer, androgen deprivation therapy (ADT) is commonly used for the treatment of prostate cancer. As in women, skeletal health evaluations in men initiating ADT occur far less commonly than recommended by societal guidelines (96). Treatment with zoledronic acid has been shown to limit bone loss in men in response to androgen deprivation therapy (97). Likewise, the anti-resorptive denosumab has also been shown to increase BMD in men receiving ADT for prostate cancer and to reduce fracture risk (98).

Multiple hematologic malignancies are also associated with increased fracture risk. The best characterized of these is multiple myeloma, in which monoclonal plasma cells secrete cytokines to simultaneously increase osteoclast activity and suppress osteoblast activity. Collectively, this skeletal derangement results in both localized osteolytic lesions and generalized bone loss with associated osteoporotic-type fractures. Two-thirds of patients with multiple myeloma present with bone pain at the time of diagnosis, and fracture rates are increased approximately 16-fold in the year preceding diagnosis when compared to an age- and sex-matched normative cohort (99). Further, the use of supraphysiologic glucocorticoid dosing is a mainstay of nearly all chemotherapeutic regimens used for myeloma treatment, with resultant detrimental skeletal effects superimposed upon those resulting from the multiple myeloma itself. Both intravenous bisphosphonates (initially pamidronate and subsequently zoledronic acid) have been shown to limit bone disease in multiple myeloma (100). More recently, denosumab has been shown to be non-inferior to zoledronic acid for preventing skeletal related events in this patient population, which has led to rapid uptake of denosumab use in patients with multiple myeloma (101). Given the increasing life expectancy in patients with multiple myeloma, it is critical that both patients and providers understand that denosumab discontinuation may result in rapid bone loss and multiple vertebral compression fractures, as recognized in the most recent recommendations from the International Myeloma Working Group (102).

Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant condition that uniformly precedes multiple myeloma. The risk for developing MGUS increases with age, such that roughly 3.5 million persons in the United States are currently affected (103). Since the risk for progression from MGUS to multiple myeloma or a related plasma cell disorder is approximately 1% per year for most persons, the vast majority will never develop multiple myeloma. However, MGUS is associated with a substantially increased risk for fracture, and patients with MGUS have evidence of significant bone loss and deterioration of bone microstructure (104). The judicious treatment of patients with MGUS and low bone mass, for example with bisphosphonate therapy, is likely to maintain bone mass and reduce future fracture risk (105).

With the advent of improved therapies, more children are also surviving cancer into adulthood. It is notable that while approximately 40% of peak bone mass is typically obtained in adolescence, both nutritional and physical activity deficits are common in children with cancer, as are the use of treatments such as chemotherapy or glucocorticoids that may affect the skeleton or cranial radiation which may result in hormonal deficits (106). Skeletal treatment in children affected by cancer should include efforts to address modifiable risk factors including identifying nutritional deficits, providing increased physical activity as tolerated, and identifying early hormonal deficits (107).

Lastly, it is important to recognize that patients with cancer, particularly those who are elderly or significantly debilitated, are at substantially increased risk for falls and therefore fractures. Potential risk factors include dehydration (as can occur with infections), medications such as sedatives which can alter the sensorium or anti-hypertensives which can cause hypotension, muscle weakness due to either reduced physical activity or treatment with supraphysiologic glucocorticoid dosing, and the presence of home structural impediments (such as throw rugs or extension cords) that can cause patients to stumble. Prophylactic efforts to reduce each of these risks have the potential to limit fractures in these vulnerable patients.

Update on Rare Bone Diseases

Laura L. Tosi, MD

The world of rare diseases, and particularly rare bone diseases, is exploding. In the US, rare diseases are defined as disorders affecting fewer than 200,000 US residents or

disorders for which there is no reasonable expectation that drug development costs will be recoverable by US sales (108). The latter spurred the development of the Orphan Drug Act of 1983 to incentivize development of drugs to treat rare diseases (109). Rare bone diseases have, until recently, been a largely neglected area in healthcare. Their rarity and heterogeneity have unfortunately hindered their exploration at both clinical and scientific levels, even though almost 500 of the approximately 7,000 defined rare diseases are bone disorders. In the last decade, however, wider availability of genetic testing, development of new pharmaceutical treatment options, and patient advocacy have motivated efforts to study, diagnose, and treat these disorders.

The Nosology and Classification of Genetic Skeletal Disorders: 2019 Revision identifies 461 genetic skeletal disorders and divides them into 42 groups based on their molecular, biochemical, and radiographic features (110). The *Nosology* is now in its tenth edition and has grown considerably since first created in 1969. Moreover, the next edition is expected to be far larger, as the genetic variation and pleiotropy underlying the disorders is expected to take center stage. Already, 437 genes associated with 425 of these disorders (92%) have been identified, thus providing significant hope for future treatments.

Rare bone diseases have been described as including approximately 5% of all rare disorders, or less than five per 10,000 individuals. For rare bone disease this translates to about 200,000 individuals in the US; however, this number is likely to increase as genetic testing expands and more individuals with milder forms of these disorders are identified. Moreover, there is tremendous variability in the prevalence of different rare bone disorders. For example, it is estimated that there are 25,000 to 50,000 people with osteogenesis imperfecta (OI), about 15,000 with achondroplasia, and 10,000 - 15,000 with X-linked hypophosphatemia (XLH), but fewer than 1000 individuals worldwide with fibrodysplasia ossificans progressiva (FOP), and perhaps 30 cases of Janson's disease. This variability significantly impacts issues ranging from delay in diagnosis, access to knowledgeable physicians, and ability to attract research interest.

The Rare Bone Disease Alliance (RBDA), founded by the OI Foundation in 2015, has extended the successes of the Rare Bone Disease Patient Network (established in 2006) to advocate for expanding research on rare bone disorders. The expansion is the direct result of collaboration among patient organizations, researchers, and medical professionals. The RBDA now represents a coalition of 16 rare bone disease advocacy organizations. It focuses on educating medical professionals, expanding research, and assisting patients and communities affected by rare skeletal diseases. The RBDA uses each group's existing professional networks to share information. They believe strongly in collaboration and sharing by leaders of advocacy groups and academics from a wide spectrum of universities.

A fundamental goal of the RBDA is to "democratize" healthcare and to promote activities that will allow the prompt and correct diagnosis of individuals with rare bone disease. One of the RBDA's most successful programs is Rare Bone Disease TeleECHO (111). This is different than traditional post-graduate medical education with passive learning through lectures, medical journals, and more recently webinars. Instead, Rare Bone Disease TeleECHO (Extension for Community Healthcare Outcomes) is a highly interactive ongoing virtual community of practice that combines short didactic programs with case discussions that actively engage attendees in the learning process. Rare Bone Disease TeleECHO strives to support the success of community-based care teams and encourage the creation of an ever-growing population of clinicians with rare bone disease expertise. The yearly agenda is one-half disease-specific and one-half differential diagnosis-specific in an effort to include as many disorders as possible. Rare Bone Disease TeleECHO meets on the first Thursday of every month, with about 30% of attendees located in countries outside the US, so far reaching 34 different countries. Over 1000 individuals are registered on the email announcement list. Continuing medical education (CME) credits are provided without charge. For reasons of privacy, only the didactic portions of the presentations are recoded and made available on YouTube. This model of adult education has been so successful that the OI Foundation and Soft Bones have both launched their own TeleECHO programs focused on OI and hypophosphatasia, respectively.

Nationally, there has been slow recognition that adults with rare childhood-onset disorders, which includes the rare bone disease community, are an expanding population. Most children with skeletal dysplasias can expect a normal or near normal life expectancy. While many children with rare bone disorders receive care multidisciplinary comprehensive care clinics, there are very few such clinics prepared to provide care for adults with rare bone disorders. Moreover, thanks to the current availability of no-charge genetic testing for some skeletal dysplasias, more and more individuals are being diagnosed earlier than in the past. While there remain significant numbers of undiagnosed disorders, the long "diagnostic odyssey," often described by patients and families in the past, has been reduced for many individuals. In addition, the development of registries and natural history studies for many disorders has helped patients and clinicians acquire a better understanding of the full breadth of many rare bone diseases. A brief overview of just a few of the exciting advances in rare bone disease management is summarized below.

First, the OI Foundation is part of the Brittle Bone Disease Consortium (BBDC), which has been tracking the natural history of OI for the past 8 years as part of an NIH-funded natural history initiative. OI is a skeletal dysplasia characterized by bone fragility and skeletal deformities. The majority of cases are associated with

pathogenic variants in *COL1A1* and *COL1A2*, the genes encoding type I collagen. Clinically, OI is heterogeneous in features and variable in severity (112). Besides the skeletal findings, it can affect multiple systems, with consequences that include dental and craniofacial abnormalities, muscle weakness, hearing loss, respiratory and cardiovascular complications. The BBDC has the largest sample size available to inform clinical endpoints. This has allowed the discovery of clinical signals not previously appreciated, such as postpartum hemorrhage and the significant impact of pain and anxiety. Researchers have begun to look at broad connective tissue targets well beyond bone. While bisphosphonates, frequently combined with rodding of the long bones, remain the mainstay of treatment in OI, new strategies such as sclerostin inhibitory antibodies and transforming growth factor (TGF) beta inhibition, are being explored to address poor bone quality as well as low BMD that is associated with this disease.

Another disorder, XLH, is caused by mutations in the Phosphate Regulating Endopeptidase X-Linked (*PHEX*) gene which result in Fibroblast Growth Factor-23 (FGF23) excess and renal phosphate wasting. Children with XLH present with rickets, bone deformities and short stature. Recently available treatment with an anti-FGF23 monoclonal antibody (113) has led to remarkable improvement in pediatric bone deformities; however, these patients still face significant challenges in adulthood, including bone and joint pain, muscle weakness, osteomalacia-related fractures or pseudofractures, spinal stenosis, osteoarthritis, enthesopathy, hearing loss, adult tooth loss and renal failure. In addition, adult XLH patients are also prone to secondary and tertiary hyperparathyroidism, cardiovascular and metabolic disorders. Early reports of the impact of anti-FGF23 monoclonal antibody therapy on clinical outcomes in adults are just starting to be available.

While we don't yet have a drug for fibrous dysplasia there have been several important clinical advances (114), (115). First, a staging evaluation at age 5, typically with a bone scan, can identify all the areas of clinically significant fibrous dysplasia, allowing clinicians to focus their monitoring efforts. In addition, fibrous dysplasia is associated with a variety of endocrinopathies. Early diagnosis and aggressive management of endocrine disease can improve skeletal outcomes such as fracture, basilar invagination, scoliosis, vision and hearing loss.

Hypophosphatasia (HPP) is a rare inherited skeletal disorder caused by loss-of-function mutations in the tissue non-specific alkaline phosphatase (*TNSALP*) gene. Reduced activity of *TNSALP* leads to the accumulation of its substrates, mainly inorganic pyrophosphate and pyridoxal-5′-phosphate (vitamin B6), that lead to the musculoskeletal and systemic features of the disease. Presentation varies significantly, ranging from death in utero to asymptomatic adults. In infants and children, clinical features include skeletal, respiratory and neurologic complications, while recurrent, poorly healing fractures, muscle weakness and arthropathy are common in adults (116). Treatment with subcutaneously administered synthetic human alkaline phosphatase has been approved for treatment of patients, including adults (117). This treatment can be life-saving for infants and children with severe forms of HPP; however, for adults the indications for treatment and the benefits are less well established (118).

In summary, the rare bone disease "story" is changing daily. Advances in diagnosis and treatment are moving at an incredible rate. More and more patients now face a more healthy and productive future than previously imaginable.

Update on Non-DXA Imaging Approaches to Assess Bone Strength and Predict Fracture Risk

Mary L. Bouxsein, PhD

Despite the availability of efficacious and safe treatments that prevent fractures, many patients are not evaluated and/or not treated for osteoporosis. Identifying this "Crisis in the Treatment of Osteoporosis," Khosla et al (119) proposed that we need "better identification of high-risk patients" in order to reduce the burden of fragility fractures. Whereas measurement of spine and hip BMD by DXA has been the standard tool for osteoporosis assessment, the number of individuals undergoing a DXA exam has declined precipitously in the past decade (120). Furthermore, many fractures occur in individuals who do not have osteoporosis by BMD testing, perhaps because DXA fails to capture key determinants of bone strength, such as bone geometry, morphology, microarchitecture as well as the density of the trabecular and cortical bone compartments. Thus, it is possible that new imaging approaches may help to: 1) increase the number of individuals who undergo bone health assessment; and 2) improve the prediction of fracture risk. This is a critical review of several non-invasive imaging techniques, detailed below.

Radiofrequency Echographic Multi-Spectrometry (REMS) Ultrasound. REMS ultrasound is a relatively new approach that utilizes the ultrasound signals acquired during an echographic scan of the lumbar spine or femoral neck (121). The software analyzes the unfiltered ultrasound signals using a statistical approach to compare the signal spectra from an individual to previously measured spectral models for pathologic and normal conditions. The main outcomes of the REMS measurement include an estimated BMD and a "fragility score". Clinical studies have reported strong associations between REMS measurements and DXA-BMD measurements as well as strong concordance among diagnostic categories (e.g., normal, osteopenic and osteoporotic). For instance, in a multicenter European study of 4307 adults, aged 30-90 years, REMS measurements at the hip and spine were

strongly associated with femoral neck (r=0.88) and lumbar spine (r=0.90) BMD (122). Another study examined the ability of REMS to predict fracture risk, comparing 175 adults with incident fracture to 350 no-fracture controls. Lower femoral and lumbar spine REMS were associated with higher fracture risk (OR per SD decrease = 2.8 and 2.6, respectively), results that compared favorably with DXA-based femoral neck and lumbar spine BMD measurements (OR per 1 SD decrease = 2.7 and 1.7, respectively) (123). Short-term precision of REMS measurements is similar to or better than DXA-BMD, though it must be noted that these studies were performed with highly experienced operators. Whether technicians with lesser experience and training can achieve similar measurement precision remains to be determined. To date, there are no longitudinal studies using this technique, thus the utility of REMS to assess age- or treatment-related changes remains unknown.

High-resolution Peripheral Quantitative Computed Tomography. High-resolution peripheral computed tomography (HR-pQCT), a low-dose X-ray-based technique for assessment of volumetric bone density and microarchitecture in the appendicular skeleton, was introduced more than 10 years ago. Since that time, many studies have reported an association between architectural deterioration and increased fracture risk, often independent of DXA-BMD. The largest prospective study to date included 7254 older adults (mean age = 68 ± 9 years) from seven cohorts across Europe and North America (124). All subjects had femoral neck BMD and HR-pQCT outcomes and were followed for occurrence of fracture over 4.5 ± 2.6 years. In total, there were 756 incident fractures, of which 60% occurred in individuals with osteopenia by femoral neck BMD measurements. Deteriorated bone microarchitecture was associated with increased fracture risk independently of femoral neck BMD, with a 25 to 40% increase in the risk of fracture per standard deviation decrement in bone microarchitecture. Consistent with these results, a meta-analysis of 40 studies that enrolled over 13,000 subjects found that several HR-pQCT outcomes were associated with increased fracture risk, noting that "our study supports the use of HR-pQCT in clinical fracture risk prediction" (125). In addition to fracture risk assessment, HR-pQCT has been used to gain insight into the pathophysiology of several conditions and/or disorders associated with increased skeletal fragility, including diabetes, chronic kidney disease, glucocorticoid-induced osteoporosis, rheumatoid arthritis, osteogenesis imperfecta, acromegaly, hyper- and hypoparathyroidism, celiac disease, hypophosphatasia, and X-linked hypophosphatemia (126).

Bone Strength Measurements by Biomechanical Computed Tomography. Biomechanical computed tomography (BCT) uses a patient's computed tomography (CT) scan to measure both bone strength (via finite element analysis) and bone mineral density at the hip and spine (127). BCT is available in the US as a Medicare screening benefit for diagnostic testing for osteoporosis. BCT measurements of spine and hip BMD are equivalent to DXA-BMD (including T-scores) and thus can be used to evaluate fracture risk and make decisions about initiating treatment. Bone strength measurements from BCT are categorized as normal, low or fragile bone strength, and provide information about fracture risk that is independent of BMD. For instance, a prospective study compared ability of BCT to DXA-BMD for prediction of hip fracture risk in older men and women (mean age = 77 years, n=1306 with hip fracture, n= 1477 fracture-free controls). The authors reported the femoral bone strength measures provided equivalent (or slightly better) prediction of hip fracture than DXA-BMD, and furthermore, that compared to CT-BMD measurements alone, adding femoral strength assessments identified approximately 20% more individuals who would suffer a hip fracture (128). Given this excellent clinical performance, it is important to note that BCT is well suited for "opportunistic" use, as it can be performed on pelvic and abdominal CT scans that have been collected for reasons other than osteoporosis testing, as those scans usually include the lumbar spine and/or proximal femur. US Medicare data reveal that each year there are nearly 8 million adults who meet the established guidelines for osteoporosis screening who undergo an abdominal or pelvic CT scan suitable for BCT analyses — many more than the 1.5 million individuals who receive a DXA scan each year. Thus, opportunistic BCT may be an efficient approach to help address the marked underdiagnosis and undertreatment of osteoporosis.

Opportunistic CT Imaging and Machine Learning. The opportunistic use of CT images acquired for other medical purposes to assess osteoporosis has been studied for over a decade, advances in automated image analysis and machine learning have led to renewed interest in this approach (129). Recent studies have used automated image analyses to evaluate bone density in tens of thousands of CT scans, in some cases with simultaneous assessment of vertebral fracture from the images and/or extraction of clinical risk factors from the electronic medical record (130-132). For example, Pickhardt et al performed automated bone and muscle analysis of abdominal CT scans in 9223 adults, in whom 686 major osteoporotic fractures were recorded in the subsequent 8.8 years of follow-up (131). They found that low trabecular bone density in the L1 vertebral body and low muscle attenuation at the L3 spinal level were both associated with increased risk of major osteoporotic fracture. In another study, Dagan and colleagues (132) used automated methods to measure vertebral fracture, spine DXA T-score, vertebral trabecular bone density, and extract FRAX-relevant risk factors from the electronic medical record. They recorded over 5000 major osteoporotic fractures and 1900 hip fractures during ~ 5 years of follow-up, and showed that their CT-based method had similar sensitivity and specificity to FRAX (without

BMD). Clearly these newer approaches for osteoporosis screening based on 'opportunistic' use of CT images, with possible extraction of meta-data from the electronic medical record, have huge potential to improve the diagnosis of osteoporosis. However, there are several important issues that need to be addressed before these techniques can be applied in clinical practice. For example, the use of CT-based Hounsfield units to diagnose osteoporosis is subject to significant errors due to a lack of i) standardization across approaches, ii) consistent calibration and iii) established intervention thresholds (that may vary by skeletal site). Furthermore, to date there are limited prospective fracture studies, though more are likely to be published. At the moment, none of these techniques are approved by the FDA, nor are they reimbursed by Medicare, so the pathway to their use in clinical practice remains limited at the moment.

Perioperative Bone Health Care

Susan V. Bukata, MD

With our aging population, we face a silver tsunami of patients with both osteoporosis and low bone mass as well as osteoarthritis and spinal stenosis. Patients desire high levels of physical function and independence well into their geriatric years. Pain and functional deficits from osteoarthritis and spinal stenosis impair patients' quality of life, making them seek treatment for these diseases. Improvements in orthopaedic instrumentation now make surgical candidates of patients who historically would not have been offered procedures. A wider age range of patients with the health issues as well as chronic diseases are now being managed with orthopedic procedures. Patients also have expectations of long-term success spine and joint procedures. How this care is delivered has also evolved into a highly structured, protocol driven environment for perioperative care. Many procedures are now outpatient or short stay. Perioperative classes and surgery preparation is a cooperative experience between the patient and the surgical team. Smoking cessation, nutrition enhancement, and diabetes management are a regular part of surgical preparation leaving an opportunity for bone health intervention to occur as a part of these protocols.

Joints surgeons are worried about intraoperative fractures, implant subsidence, and long-term risk of periprosthetic fracture. As millions of patients with joint arthroplasties age, periprosthetic fractures are becoming more common but are unrecognized as a fragility fracture. Spine surgeons are worried about compression fractures adjacent to their large fusion constructs, pedicle screws pulling out of the bone due to the weak bone, and subsidence of their cage reconstruction constructs into the weaker vertebral bodies above and below these constructs. There are currently no established bone health management protocols for these patients. When a patient is sent for bone health assessment, often both the surgeon and the patient are looking for a rapid improvement of the quality and strength of osteoporotic bone. However, we need to change the dialog from attempting perioperative bone strength miracles to getting the patient on track for a lifetime of success and bone health. By making both the patient and the surgeons aware of the diagnoses of osteoporosis and a sense of the severity, the surgeon can make instrumentation and operative technique choices to accommodate the osteoporosis and the patient can better understand the needs for medication treatment for osteoporosis in order to enjoy the results of the surgery for a long time. Both patients and physicians need to recognize this as a long-term investment in the success of this surgery and the overall health of the patient's bones.

Two small studies in the total joint population showed a high prevalence of the problem with 2/3 of patients having either low bone mass (osteopenia) or osteoporosis from DXA measurements alone *(133)*. These studies did not take into account the additional factors that weaken bone quality and bone strength. Another study looked at FRAX scores in 124 patients who were referred for bone health assessment prior to spine or joint replacement surgery. Risk of major osteoporotic fracture or hip fracture was high in 82% of patients when BMD was included and in 70% of patients if BMD was not included in the calculation. Correlation without BMD was slightly better in women but still demonstrated the clinical utility of FRAX for perioperative bone health assessment *(134)*.

While there is no current established protocol for perioperative bone health assessment, Kadri et al *(134)* recommended a flowchart to current bone health assessments for patients at risk for osteoporosis with preoperative bone healthcare. Standard labs, including a comprehensive metabolic profile, serum intact PTH level, and 25(OH)D level are recommended, as well as DXA and FRAX scoring. Calcium and vitamin D intake should be optimized and osteoporosis medication started when indicated. In addition, fall prevention treatment and optimization of nutrition and medications are recommended. If patients have no or low osteoporosis risk, if surgical indication is urgent, or if it is the patient's preference, they should precede to surgery immediately and focus on bone health management postoperatively. If the patient and the procedure allow for some preoperative treatment, anabolic or antiresorptive therapy can be started while the patient waits 3 to 6 months for surgery. Three studies showed a decreased rate of acute periprosthetic joint infections in patients with normalized serum 25(OH)D levels (>30 ng/mL) compared to patients with low 25 (OH)D (<20 ng/mL) *(135)*. In addition, patients with infections have lower calcium and albumin levels, suggesting a role for nutritional optimization prior to surgery that extends beyond bone health *(136)*.

Choice of treatment for osteoporosis and low bone mass in the perioperative setting remains controversial, although individual patient needs can allow antiresorptives, such as bisphosphonates and denosumab, as well as anabolic medications, possible treatments. Small studies

of teriparatide in spine surgery patients have shown both small improvements in bone fusion rates as well as decreased pedicle screw loosening rates compared with bisphosphonates (137). In another study, patients started on teriparatide at least one month prior to spine surgery were found to have increased torque power required for the placement of pedicle screws suggestive of improvements in bone strength (138). The recommendation of a 3- to 6-month delay a prior to surgery after the start of the bone medication recognizes that there is a period of time before demonstrable changes in bone mass and bone structure can be seen in patients, it even with the best anabolic agents. It takes approximately 12 months on treatment to obtain 5% improvement in lumbar spine BMD and 3% improvements in hip BMD for both bisphosphonates and denosumab (139). While spine BMD increases greater than 5% can occur within the first six months with the anabolic agents (i.e., teriparatide, abaloparatide, and romosozumab), it can take 12 months to see 3% increases in hip BMD with teriparatide and abaloparatide (140). Romosozumab demonstrates gains greater than 3% in hip BMD within six months (141). Treatment with IV zoledronic acid can cause transient muscle aches, fever, and flu-like symptoms, particularly in bisphosphonate-naïve patients. This can be problematic in the perioperative period, as post-operative fever can be interpreted as signs of infection. Infusions given close to scheduled surgical dates can also be problematic if the patient becomes symptomatic, potentially leading to a delay in surgery. If zoledronic acid is to be used as treatment, infusion more than one month prior to surgery or at least six weeks after surgery is suggested. Management of acute phase reaction symptoms with either acetaminophen (1000 mg three times daily) or nonsteroidals started on the day of infusion and continued for one week is also recommended.

Identifying patients with osteoporosis or low bone mass early before elective joint and spine surgery allows time for perioperative treatment to improve bone strength prior to surgery. For patients newly identified with osteoporosis or low bone mass in urgent need of surgery, there may be insufficient time to improve bone health. However, addressing bone health concerns should be considered as long-term investment to reduce fracture risk as well as an effort to optimize surgical outcomes. Bone health assessment with appropriate interventions should be a standard component of perioperative treatment protocols for spine and joint surgery, especially for older adults. This creates opportunities for care teams that include nurses, physical therapists, primary care doctors, hospitalists, and surgeons, to address bone health issues and prevent problems before they happen.

Bone Health ECHO Progress Report

E. Michael Lewiecki, MD

Project ECHO is technology-enabled collaborative learning, with a US government report stating that consistently positive effects have been 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 in bone diseases, located in the USA and many other countries. This is a form of telehealth (143) that aims to expand global capacity to deliver best practice skeletal healthcare (144). 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 (145). Progress with Bone Health ECHO programs has been reported at previous SFBS (1), (11-15) 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 the Osteoporosis Foundation of New Mexico. Since that time, there have been weekly online meetings, usually consisting of a short slide presentation on a topic of interest followed by discussion, and presentation and discussion of real but de-identified patient cases. Weekly attendance has increased from an average of 13 in 2015 to over 90 in 2021. The slide presentations are recorded and archived on the Project ECHO website, with over 1,100 views since 2015. More than 7,000 hours of no-cost continuing medical education credits have been awarded to attendees. Regular participation with Bone Health ECHO has been shown to improve self-confidence in managing patients with osteoporosis (146,147).

The growth of the prototype Bone Health ECHO program has inspired the development of others in the US and beyond. There are now 9 programs in the USA (6 focusing on osteoporosis, 3 for rare bone diseases) plus 5 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) (111); 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); and Bone Health ECHO at AUB and AUBMC (Beirut, Lebanon). In addition, the Ehlers Danlos Society has 2 programs for Ehlers Danlos

Syndrome based in the USA and United Kingdom. Each of these ECHO programs has its own "flavor" to meet the needs of its participants and the skills of the organizers, while adhering to the ECHO model of learning.

An ECHO workshop was held at the SFBS to introduce the concept of case-based collaborative learning for attendees interested in attending an existing ECHO program or developing a new one. Project ECHO resources to facilitate new development were presented and opportunities for grant support explained.

Disclosure

E. Michael Lewiecki is an investigator, consultant, and speaker for Amgen; investigator for Radius; speaker for Alexion.

John P. Bilezikian is a consultant for Amgen, Radius, Amolyt, Ascendis, Takeda, and NovoNordisk; speaker for Amgen and Radius; data safety and monitoring board for Regeneron.

Neil Binkley is a consultant for Amgen; investigator for Radius.

Mary L. Bouxsein is a consultant for Keros Therapeutics.

Susan V. Bukata is a consultant for Amgen and Radius; board member for Orthopaedic Research Society.

David W. Dempster is a consultant and speaker for Amgen and Radius.

Mathew T. Drake has nothing to disclose.

Michael R. McClung is consultant and speaker for Amgen; speaker for Alexion.

Paul D. Miller has nothing to disclose.

Elisabeth Rosenthal has nothing to disclose.

Laura L. Tosi is an investigator for Ultragenyx.

References

1. Lewiecki EM, Anderson PA, Bilezikian JP, Binkley N, Cheung AM, Imel EA, et al. 2022 Proceedings of the 2021 Santa Fe Bone symposium: advances in the management of osteoporosis and metabolic bone diseases. J Clin Densitom 25(1):3–19.
2. Lewiecki EM. 2006 Proceedings of the Santa Fe Bone Symposium 2006. Womens Health 2(6):825–828.
3. Lewiecki EM, Bilezikian JP, Cooper C, Hochberg MC, Luckey MM, Maricic M, et al. 2008 Proceedings of the eighth annual Santa Fe bone symposium, August 3-4, 2007. J Clin Densitom 11(2):313–324.
4. Lewiecki EM, Baim S, Bilezikian JP, Eastell R, LeBoff MS, Miller PD. 2009 2008 Santa Fe Bone Symposium: update on osteoporosis. J Clin Densitom 12(2):135–157.
5. Lewiecki EM, Bilezikian JP, Laster AJ, Miller PD, Recker RR, Russell RG, et al. 2010 2009 Santa Fe bone symposium. J Clin Densitom 13(1):1–9.
6. Lewiecki EM, Bilezikian JP, Khosla S, Marcus R, McClung MR, Miller PD, et al. 2010 Osteoporosis update from the 2010 Santa Fe bone symposium. J Clin Densitom 14(1):1–21.
7. Lewiecki EM, Bilezikian JP, Jankowski LG, McCloskey EV, Miller PD, Morgan SL, et al. 2012 Proceedings of the 2011 Santa Fe bone symposium. J Clin Densitom 15(1):1–20.
8. Lewiecki EM, Adler RA, Bilezikian JP, Bouxsein ML, Marcus R, McClung MR, et al. 2013 Osteoporosis update from the 2012 Santa Fe bone symposium. J Clin Densitom 16(4):584–600.
9. Lewiecki EM, Bilezikian JP, Bonewald L, Compston JE, Heaney RP, Kiel DP, et al. 2014 Osteoporosis update: proceedings of the 2013 Santa Fe bone symposium. J Clin Densitom 17(3):330–343.
10. Lewiecki EM, Bilezikian JP, Binkley N, Hans D, Krueger D, Miller PD, et al. 2015 Update on osteoporosis from the 2014 Santa Fe Bone Symposium. Endocr Res 40(2):106–119.
11. Lewiecki EM, Baron R, Bilezikian JP, Gagel RE, Leonard MB, Leslie WD, et al. 2016 Proceedings of the 2015 Santa Fe bone symposium: clinical applications of scientific advances in osteoporosis and metabolic bone disease. J Clin Densitom 19(1):102–116.
12. Lewiecki EM, Bilezikian JP, Bukata SV, Camacho P, Clarke BL, McClung MR, et al. 2017 Proceedings of the 2016 Santa Fe bone symposium: new concepts in the management of osteoporosis and metabolic bone diseases. J Clin Densitom 20(7):134–152.
13. Lewiecki EM, Bilezikian JP, Carey JJ, Dell RM, Gordon CM, Harris ST, et al. 2018 Proceedings of the 2017 Santa Fe bone symposium: insights and emerging concepts in the management of osteoporosis. J Clin Densitom 21(1):3–21.
14. Lewiecki EM, Bilezikian JP, Giangregorio L, Greenspan SL, Khosla S, Kostenuik P, et al. 2019 Proceedings of the 2018 Santa Fe bone symposium: advances in the management of osteoporosis. J Clin Densitom 22(1):1–19.
15. Lewiecki EM, Bilezikian JP, Kagan R, Krakow D, McClung MR, Miller PD, et al. 2019 Proceedings of the 2019 Santa Fe bone symposium: new concepts in the care of osteoporosis and rare bone diseases. J Clin Densitom 23:1–20.
16. Lewiecki EM, Bilezikian JP, Miller PD, Recker RR, Russell RGG, Whyte MP. 2011 Highlights from the 2009 Santa Fe Bone Symposium. Osteoporosis Foundation of New Mexico; 2009 8/25/Available from: http://www.2009santafebonesymposium.com/downloads/2009-Santa-Fe-Bone-Newsletter.pdf.
17. Lewiecki EM, Bilezikian JP, Khosla S, Marcus R, McClung M, Miller PD, et al. 2011 Highlights from the 2010 Santa Fe Bone Symposium. Osteoporosis Foundation of New Mexico; 2010 8/25/Available from: http://santafebonesymposium.squarespace.com/storage/assets/2010_Santa_Fe_Bone.pdf.
18. Lewiecki EM, Bilezikian JP, McCloskey EV, Miller PD, Morgan SL, Orwoll ES, et al. 2011 Highlights of the 2011 Santa Fe Bone Symposium. Osteoporosis Foundation of New Mexico; 1/19/2012Available from: http://www.2011santafebonesymposium.com/2011-Santa-Fe-Bone-Newsletter.pdf.
19. Lewiecki EM, Bilezikian JP, Bonewald LF, Compston JE, Heaney RP, Kiel DP, et al. 2013 Santa Fe Bone Symposium Highlights2013 9/06/2015. Available from: http://2013santafebonesymposium.com.
20. Lewiecki EM, Bilezikian JP, Binkley N, Hans D, Krueger D, Marcus R, et al. 2014 Santa Fe Bone Symposium Highlights2014 9/6/2015. Available from: http://www.2014santafebonesymposium.com/.
21. Compston JE, McClung MR, Osteoporosis Leslie WD. 2019 Lancet 393(10169):364–376.

22. McClung M, Harris ST, Miller PD, Bauer DC, Davison KS, Dian L, et al. 2013 Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med 126 (1):13–20.
23. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. 2020 American association of clinical endocrinologists/american college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. Endocr Pract 26(Suppl. 1):1–46.
24. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 2017 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 5(7):513–523.
25. McClung MR, Rothman MS, Lewiecki EM, Hanley DA, Harris ST, Miller PD, et al. 2022 The role of osteoanabolic agents in the management of patients with osteoporosis. Postgrad Med 134(6):541–551.
26. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. 2001 Effect of risedronate on the risk of hip fracture in elderly women. NEnglJMed 344:333–340.
27. Chapuy MC, Arolt ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. 1992 Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 327:1637–1642.
28. LeBoff MS, Chou SH, Ratliff KA, Cook NR, Khurana B, Kim E, et al. 2022 Supplemental Vitamin D and incident fractures in midlife and older adults. N Engl J Med 387 (4):299–309.
29. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. 2003 Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 290 (13):1729–1738.
30. Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, et al. 2008 Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 299(9):1036–1045.
31. Mosekilde L, Beck-Nielsen H, Sorensen OH, Nielsen SP, Charles P, Vestergaard P, et al. 2000 Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women - results of the Danish Osteoporosis Prevention Study. Maturitas 36(3):181–193.
32. Klibanski A, Adams-Campbell L, Bassford T, Blair SN, Boden SD, Dickersin K, et al. 2001 Osteoporosis prevention, diagnosis, and therapy. JAMA 285(6):785–795.
33. Couraud G, Souffir C, Gaigneux E, Kolta S, Roux C, Briot K. 2017 Adjusting FRAX(R) on TBS for identification of subjects at high risk of fractures. Bone 101:214–218.
34. Mai HT, Tran TS, Ho-Le TP, Center JR, Eisman JA, Nguyen TV. 2019 Two-thirds of all fractures are not attributable to osteoporosis and advancing age: implications for fracture prevention. J Clin Endocrinol Metab 104(8):3514–3520.
35. Lewiecki EM, Binkley N, Bilezikian JP. 2019 Treated osteoporosis is still osteoporosis. J Bone Miner Res 34(4):605–606.
36. Pazianas M, van der Geest S, Miller P. 2014 Bisphosphonates and bone quality. Bonekey Rep 3:529.
37. Cremers S, Drake MT, Ebetino FH, Bilezikian JP, Russell RGG. 2019 Pharmacology of bisphosphonates. Br J Clin Pharmacol 85(6):1052–1062.
38. Whitaker M, Guo J, Kehoe T, Benson G. 2012 Bisphosphonates for osteoporosis - where do we go from here? N Engl J Med 366(22):2048–2051.
39. Chang LL, Eastell R, Miller PD. 2022 Continuation of bisphosphonate therapy for osteoporosis beyond 5 years. N Engl J Med 386(15):1467–1469.
40. Miller PD, Lewiecki EM, Krohn K, Schwartz E. 2021 Teriparatide: label changes and identifying patients for long-term use. Cleve Clin J Med 88(9):489–493.
41. Lewiecki EM, Watts NB. 2008 Assessing response to osteoporosis therapy. Osteoporos Int 19(10):1363–1368.
42. Balasubramanian A, Zhang J, Chen L, Wenkert D, Daigle SG, Grauer A, et al. 2019 Risk of subsequent fracture after prior fracture among older women. Osteoporos Int 30 (1):79–92.
43. Barron RL, Oster G, Grauer A, Crittenden DB, Weycker D. 2020 Determinants of imminent fracture risk in postmenopausal women with osteoporosis. Osteoporos Int 31 (11):2103–2111.
44. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. 2020 Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. J Clin Endocrinol Metab 105 (3).
45. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. 2019 Pharmacological management of osteoporosis in postmenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 104 (5):1595–1622.
46. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. 2022 The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int: Epub.
47. Cosman F, Nieves JW, Dempster DW. 2017 Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res 32(2):198–202.
48. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, et al. 2013 Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet 382(9886):50–56.
49. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. 2018 Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res 33(2):190–198.
50. Tsourdi E, Zillikens MC, Meier C, Body JJ, Gonzalez Rodriguez E, Anastasilakis AD, et al. 2020 Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. J Clin Endocrinol Metab: Epub.
51. McCloskey E, Rathi J, Heijmans S, Blagden M, Cortet B, Czerwinski E, et al. 2022 Prevalence of FRAX risk factors and the osteoporosis treatment gap among women >/= 70 years of age in routine primary care across 8 countries in Europe. Archives of osteoporosis 17(1):20.
52. Duque G. 2021 Editorial: osteosarcopenia: a geriatric giant of the XXI century. J Nutr Health Aging 25(6):716–719.
53. Kirk B, Miller S, Zanker J, Duque G. 2020 A clinical guide to the pathophysiology, diagnosis and treatment of osteosarcopenia. Maturitas 140:27–33.
54. Lara-Castillo N, Johnson ML. 2020 Bone-muscle mutual interactions. Curr Osteoporos Rep 18(4):408–421.
55. Yamada Y, Schoeller DA, Nakamura E, Morimoto T, Kimura M, Oda S. 2010 Extracellular water may mask actual muscle atrophy during aging. J Gerontol A Biol Sci Med Sci 65(5):510–516.

56. Cesari M, Bernabei R, Vellas B, Fielding RA, Rooks D, Azzolino D, et al. 2022 Challenges in the development of drugs for sarcopenia and frailty - report from the international conference on frailty and sarcopenia research (ICFSR) task force. J Frailty Aging 11(2):135–142.
57. Heaney RP. 2014 Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev 72 (1):48–54.
58. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. 2014 Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 33(6):929–936.
59. Dempster DW. 2017 Tethering Formation to Resorption: Reversal Revisited. J Bone Miner Res 32(7):1389–1390.
60. Hattner R, Epker BN, Frost HM. 1965 Suggested sequential mode of control of changes in cell behaviour in adult bone remodelling. Nature 206(983):489–490.
61. Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, et al. 2006 A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. J Bone Miner Res 21(3):366–373.
62. Ma YL, Zeng Q, Donley DW, Ste-Marie LG, Gallagher JC, Dalsky GP, et al. 2006 Teriparatide increases bone formation in modeling and remodeling osteons and enhances IGF-II immunoreactivity in postmenopausal women with osteoporosis. J Bone Miner Res 21(6):855–864.
63. Cosman F, Dempster DW, Nieves JW, Zhou H, Zion M, Roimisher C, et al. 2016 Effect of teriparatide on bone formation in the human femoral neck. J Clin Endocrinol Metab 101(4):1498–1505.
64. Rooney AM, Dempster DW, Nieves JW, Zhou H, Bostrom MPG, Cosman F. 2022 Effects of teriparatide and loading modality on modeling-based and remodeling-based bone formation in the human femoral neck. Bone 157:116342.
65. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, et al. 2018 Remodeling- and modeling-based bone formation with teriparatide versus denosumab: a longitudinal analysis from baseline to 3 months in the AVA study. J Bone Miner Res 33(2):298–306.
66. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, et al. 2016 Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA osteoporosis study. J Clin Endocrinol Metab 101(4):1353–1363.
67. Dempster DW, Zhou H, Rao SD, Recknor C, Miller PD, Leder BZ, et al. 2021 Early effects of abaloparatide on bone formation and resorption indices in postmenopausal women with osteoporosis. J Bone Miner Res 36(4):644–653.
68. Dempster DW, Brown JP, Fahrleitner-Pammer A, Kendler D, Rizzo S, Valter I, et al. 2018 Effects of long-term denosumab on bone histomorphometry and mineralization in women with postmenopausal osteoporosis. J Clin Endocrinol Metab 103(7):2498–2509.
69. Dempster DW, Chines A, Bostrom MP, Nieves JW, Zhou H, Chen L, et al. 2020 Modeling-Based Bone Formation in the Human Femoral Neck in Subjects Treated With Denosumab. J Bone Miner Res 35(7):1282–1288.
70. Chavassieux P, Chapurlat R, Portero-Muzy N, Roux JP, Garcia P, Brown JP, et al. 2019 Bone-Forming and Antiresorptive Effects of Romosozumab in Postmenopausal Women With Osteoporosis: Bone Histomorphometry and Microcomputed Tomography Analysis After 2 and 12 Months of Treatment. J Bone Miner Res 34(9):1597–1608.
71. Eriksen EF, Chapurlat R, Boyce RW, Shi Y, Brown JP, Horlait S, et al. 2022 Modeling-Based Bone Formation After 2 Months of Romosozumab Treatment: Results From the FRAME Clinical Trial. J Bone Miner Res 37(1):36–40.
72. Dempster DW. 1997 Exploiting and bypassing the bone remodeling cycle to optimize the treatment of osteoporosis. J Bone Miner Res 12(8):1152–1154.
73. Langdahl B, Ferrari S, Dempster DW. 2016 Bone modeling and remodeling: potential as therapeutic targets for the treatment of osteoporosis. Ther Adv Musculoskelet Dis 8 (6):225–235.
74. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. 2014 Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the fourth international workshop. J Clin Endocrinol Metab 99(10):3561–3569.
75. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. 2013 GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 66 (7):719–725.
76. Minisola S, Arnold A, Belaya Z, Brandi ML, Clarke B, Hannan FM, et al. 2022 Epidemiology, pathophysiology and genetics of primary hyperparathyroidism. J Bone Miner Res: Epub.
77. El-Hajj Fuleihan G, Chakhtoura M, Cipriani C, Eastell R, Karonova T, Liu J-M, et al. 2022 Classical and non-Classical Manifestations of Primary Hyperparathyroidism. J Bone Miner Res: Epub.
78. Perrier N, Lang BH, Bandeira Farias LC, Poch LL, Sywak M, Almquist M, et al. 2022 Surgical Aspects of Primary Hyperparathyroidism. J Bone Miner Res: Epub.
79. Bilezikian JP, Silverberg SJ, Bandeira F, Cetani F, Chandran M, Cusano NE, et al. 2022 Task Force #8: Management of Primary Hyperparathyroidism. J Bone Miner Res: Epub.
80. Yao L, Guyatt G, Ye Z, Bilezikian JP, Brandi ML, Clarke BL, et al. 2022 Methodology for the guidelines on evaluation and management of hypoparathyroidism and primary hyperparathyroidism. J Bone Miner Res: Epub.
81. Bilezikian JP, Khan AA, Silverberg SJ, El-Hajj Fuleihan G, Marcocci C, Minisola S, et al. 2022 Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. J Bone Miner Res: Epub.
82. Sosa JA, Powe NR, Levine MA, Udelsman R, Zeiger MA. 1998 Profile of a clinical practice: Thresholds for surgery and surgical outcomes for patients with primary hyperparathyroidism: a national survey of endocrine surgeons. J Clin Endocrinol Metab 83(8):2658–2665.
83. Levey NN. 100 Million People in America Are Saddled With Health Care Debt. June 16, 2022. Access Date: September 14, 2022. Available from: https://khn.org/news/article/diagnosis-debt-investigation-100-million-americans-hidden-medical-debt/.
84. Rosenthal E. 2017 An American sickness : how healthcare became big business and how you can take it back. New York: Penguin Press; 2017.
85. Becker's Healthcare. Becker's Hospital Review. Access Date: September 14, 2022. Available from: https://www.beckershospitalreview.com/care-coordination/17-hospitals-scaling-back-care.html?origin=BHRE&utm_source=BHRE&utm_medium=email&utm_content=newsletter&oly_enc_id=1361J3009034G8F.

86. Tribble SJ. Buy and Bust: Collapse of Private Equity-Backed Rural Hospitals Mired Employees in Medical BillsDate Accessed: September 14, 2022. Available from: https://khn.org/news/article/noble-health-private-equity-rural-hospitals-missouri-employees-medical-bills/.
87. Editorial Board. AZT's Inhuman Cost. 1989. Date Accessed: September 14, 2022. Available from: https://www.nytimes.com/1989/08/28/opinion/azt-s-inhuman-cost.html#:~:text=At%20%248%2C000%20a%20year%20for,do%20not%20pay%20for%20drugs.
88. GoodRx. Duexis. Date Accessed: September 14, 2022. Available from: https://www.goodrx.com/duexis.
89. Kaiser Health News /National Public Radio. 2022 Bill of the Month. Kaiser Family Foundation; 2022. Published byAccess Date: September 14Available from: https://khn.org/news/tag/bill-of-the-month/.
90. CBC News. Tommy Douglas chosen as the Greatest Canadian in 2004. 2004. Date Accessed: September 14, 2022. Available from: https://www.cbc.ca/player/play/1402807530#:~:text=Canada's%20choice%20for%20the%20greatest,29%2C%202004%20on%20The%20National.
91. Reuss-Borst M, Hartmann U, Scheede C, Weiss J. 2012 Prevalence of osteoporosis among cancer patients in Germany: prospective data from an oncological rehabilitation clinic. Osteoporos Int 23(4):1437–1444.
92. Guise TA, Wysolmerski JJ. 2022 Cancer-Associated Hypercalcemia. N Engl J Med 386(15):1443–1451.
93. Stratton J, Hu X, Soulos PR, Davidoff AJ, Pusztai L, Gross CP, et al. 2017 Bone Density Screening in Postmenopausal Women With Early-Stage Breast Cancer Treated With Aromatase Inhibitors. J Oncol Pract 13(5):e505–ee15.
94. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Kainberger F, Kassmann H, Piswanger-Solkner JC, et al. 2008 Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 9(9):840–849.
95. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, et al. 2015 Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 386(9992):433–443.
96. Alibhai SM, Yun L, Cheung AM, Paszat L. 2012 Screening for osteoporosis in men receiving androgen deprivation therapy. JAMA 307(3):255–256.
97. Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA, et al. 2007 Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 25(9):1038–1042.
98. Lipton A, Smith MR, Ellis GK, Goessl C. 2012 Treatment-induced bone loss and fractures in cancer patients undergoing hormone ablation therapy: efficacy and safety of denosumab. Clin Med Insights Oncol 6:287–303.
99. Melton LJ III, Kyle RA, Achenbach SJ, Oberg AL, Rajkumar SV. 2005 Fracture risk with multiple myeloma: a population-based study. J Bone Miner Res 20(3):487–493.
100. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. 2003 Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma - A randomized, double-blind, multicenter, comparative trial. Cancer 98(8):1735–1744.
101. Gupta A, Wang P, Ali SA, Rajkumar SV, Gyawali B, Overton HN, et al. 2020 Use of Bone-Modifying Agents Among Medicare Beneficiaries With Multiple Myeloma. JAMA Oncol 6(2):296–298.
102. Terpos E, Zamagni E, Lentzsch S, Drake MT, Garcia-Sanz R, Abildgaard N, et al. 2021 Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. Lancet Oncol 22(3):e119–ee30.
103. Kyle RA, Rajkumar SV. 2006 Monoclonal gammopathy of undetermined significance. Br J Haematol 134(6):573–589.
104. Ng AC, Khosla S, Charatcharoenwitthaya N, Kumar SK, Achenbach SJ, Holets MF, et al. 2011 Bone microstructural changes revealed by high-resolution peripheral quantitative computed tomography imaging and elevated DKK1 and MIP-1alpha levels in patients with MGUS. Blood 118(25):6529–6534.
105. Drake MT. 2014 Unveiling skeletal fragility in patients diagnosed with MGUS: No longer a condition of undetermined significance? J Bone Miner Res 29(12):2529–2533.
106. Fiscaletti M, Alos N, Ward LM. 2021 Beyond Bone Mineral Density: The Impact of Childhood Cancer and Its Treatment on Bone Structure and Strength. Front Horm Res 54:69–90.
107. Hudson MM, Bhatia S, Casillas J, Landier W. 2021 Section On Hematology/Oncology CSOGASOFPHO. Long-term Follow-up Care for Childhood, Adolescent, and Young Adult Cancer Survivors. Pediatrics 148(3).
108. Roberts AD, Wadhwa R. 2022 Orphan Drug Approval Laws. Treasure IslandFL: StatPearls; 2022.
109. Sanders TI. 1983 The Orphan Drug Act. Prog Clin Biol Res 127:207–215.
110. Mortier GR, Cohn DH, Cormier-Daire V, Hall C, Krakow D, Mundlos S, et al. 2019 Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A 179(12):2393–2419.
111. Tosi LL, Rajah EN, Stewart MH, Gillies AP, Hart TS, Lewiecki EM. 2020 The Rare Bone Disease TeleECHO Program: Leveraging Telehealth to Improve Rare Bone Disease Care. Curr Osteoporos Rep 18(4):344–349.
112. Marom R, Rabenhorst BM, Morello R. 2020 Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol 183(4):R95–R106.
113. Burosumab Collins M. 2018 At Long Last, an Effective Treatment for FGF23-Associated Hypophosphatemia. J Bone Miner Res 33(8):1381–1382.
114. Javaid MK, Boyce A, Appelman-Dijkstra N, Ong J, Defabianis P, Offiah A, et al. 2019 Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis 14(1):139.
115. Hartley I, Zhadina M, Collins MT, Boyce AM. 2019 Fibrous Dysplasia of Bone and McCune-Albright Syndrome: A Bench to Bedside Review. Calcif Tissue Int 104(5):517–529.
116. Seefried L, Dahir K, Petryk A, Hogler W, Linglart A, Martos-Moreno GA, et al. 2020 Burden of Illness in Adults With Hypophosphatasia: Data From the Global Hypophosphatasia Patient Registry. J Bone Miner Res 35(11):2171–2178.
117. Hypophosphatasia Whyte MP. 2017 Enzyme Replacement Therapy Brings New Opportunities and New Challenges. J Bone Miner Res 32(4):667–675.
118. Shapiro JR, Lewiecki EM. 2017 Hypophosphatasia in Adults: Clinical Assessment and Treatment Considerations. J Bone Miner Res 32(10):1977–1980.
119. Khosla S, Cauley JA, Compston J, Kiel DP, Rosen C, Saag KG, et al. 2017 Addressing the Crisis in the Treatment of Osteoporosis: A Path Forward. J Bone Miner Res 32(3):424–430.

120. Lewiecki EM, Wright NC, Curtis JR, Siris E, Gagel RF, Saag KG, et al. 2018 Hip fracture trends in the United States, 2002 to 2015. Osteoporos Int 29(3):717–722.
121. Diez-Perez A, Brandi ML, Al-Daghri N, Branco JC, Bruyere O, Cavalli L, et al. 2019 Radiofrequency echographic multi-spectrometry for the in-vivo assessment of bone strength: state of the art-outcomes of an expert consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Aging Clin Exp Res 31(10):1375–1389.
122. Cortet B, Dennison E, Diez-Perez A, Locquet M, Muratore M, Nogues X, et al. 2021 Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context. Bone 143:115786.
123. Adami G, Arioli G, Bianchi G, Brandi ML, Caffarelli C, Cianferotti L, et al. 2020 Radiofrequency echographic multi spectrometry for the prediction of incident fragility fractures: A 5-year follow-up study. Bone 134:115297.
124. Samelson EJ, Broe KE, Xu H, Yang L, Boyd S, Biver E, et al. 2019 Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study. Lancet Diabetes Endocrinol 7(1):34–43.
125. Mikolajewicz N, Bishop N, Burghardt AJ, Folkestad L, Hall A, Kozloff KM, et al. 2020 HR-pQCT Measures of Bone Microarchitecture Predict Fracture: Systematic Review and Meta-Analysis. J Bone Miner Res 35(3):446–459.
126. van den Bergh JP, Szulc P, Cheung AM, Bouxsein M, Engelke K, Chapurlat R. 2021 The clinical application of high-resolution peripheral computed tomography (HR-pQCT) in adults: state of the art and future directions. Osteoporos Int 32(8):1465–1485.
127. Keaveny TM, Clarke BL, Cosman F, Orwoll ES, Siris ES, Khosla S, et al. 2020 Biomechanical Computed Tomography analysis (BCT) for clinical assessment of osteoporosis. Osteoporos Int 31(6):1025–1048.
128. Adams AL, Fischer H, Kopperdahl DL, Lee DC, Black DM, Bouxsein ML, et al. 2018 Osteoporosis and Hip Fracture Risk From Routine Computed Tomography Scans: The Fracture, Osteoporosis, and CT Utilization Study (FOCUS). J Bone Miner Res 33(7):1291–1301.
129. Boutin RD, Lenchik L. 2020 Value-Added Opportunistic CT: Insights Into Osteoporosis and Sarcopenia. Am J Roentgenol 215(3):582–594.
130. Jang S, Graffy PM, Ziemlewicz TJ, Lee SJ, Summers RM, Pickhardt PJ. 2019 Opportunistic Osteoporosis Screening at Routine Abdominal and Thoracic CT: Normative L1 Trabecular Attenuation Values in More than 20,000 Adults. Radiology 291(2):360–367.
131. Pickhardt PJ, Graffy PM, Zea R, Lee SJ, Liu J, Sandfort V, et al. 2020 Automated Abdominal CT Imaging Biomarkers for Opportunistic Prediction of Future Major Osteoporotic Fractures in Asymptomatic Adults. Radiology 297(1):64–72.
132. Dagan N, Elnekave E, Barda N, Bregman-Amitai O, Bar A, Orlovsky M, et al. 2020 Automated opportunistic osteoporotic fracture risk assessment using computed tomography scans to aid in FRAX underutilization. Nat Med 26 (1):77–82.
133. Bernatz JT, Brooks AE, Squire MW, Illgen RI 2nd, Binkley NC, Anderson PA. 2019 Osteoporosis is Common and Undertreated Prior to Total Joint Arthroplasty. J Arthroplasty 34(7):1347–1353.
134. Kadri A, Binkley N, Hare KJ, Anderson PA. 2020 Bone Health Optimization in Orthopaedic Surgery. J Bone Joint Surg Am 102(7):574–581.
135. Maier GS, Horas K, Seeger JB, Roth KE, Kurth AA, Maus U. 2014 Is there an association between periprosthetic joint infection and low vitamin D levels? Int Orthop 38 (7):1499–1504.
136. Anderson PA, Kadri A, Hare KJ, Binkley N. 2020 Preoperative bone health assessment and optimization in spine surgery. Neurosurg Focus 49(2):E2.
137. Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. 2012 Teriparatide accelerates lumbar posterolateral fusion in women with postmenopausal osteoporosis: prospective study. Spine (Philadelphia, PA 1976) 37(23):E1464–E1468.
138. Inoue G, Ueno M, Nakazawa T, Imura T, Saito W, Uchida K, et al. 2014 Teriparatide increases the insertional torque of pedicle screws during fusion surgery in patients with postmenopausal osteoporosis. J Neurosurg Spine 21 (3):425–431.
139. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. 2007 Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. NEnglJMed 356(18):1809–1822.
140. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster J-Y, et al. 2001 Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441.
141. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. 2016 Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med 375(16):1532–1543.
142. U.S. Department of Health and Human Services. Report to Congress: Current State of Technology-Enabled Collaborative Learning and Capacity Building Models 2019 February 2019 [cited 2022 January 14]. Available from: https://aspe.hhs.gov/system/files/pdf/260691/ECHOAct-ConsolidatedReportToCongress.pdf.
143. Lewiecki EM, Bouchonville MF. 2022 The current role of telehealth in the management of patients with osteoporosis. Expert Rev Endocrinol Metab 17(3):245–254.
144. University of New Mexico School of Medicine. Bone Health 2021 September 25, 2021. Available from: https://hsc.unm.edu/echo/partner-portal/programs/bone-health/.
145. Lewiecki EM, Boyle JF, Arora S, Bouchonville MF 2nd, Chafey DH. 2017 Telementoring: a novel approach to reducing the osteoporosis treatment gap. Osteoporos Int 28(1):407–411.
146. Lewiecki EM, Rochelle R, Bouchonville MF 2nd, Chafey DH, Olenginski TP, Arora S. 2017 Leveraging Scarce Resources With Bone Health TeleECHO to Improve the Care of Osteoporosis. J Endocr Soc 1(12):1428–1434.
147. Lewiecki EM, Rochelle R. 2019 Project ECHO: Telehealth to Expand Capacity to Deliver Best Practice Medical Care. Rheum Dis Clin North Am 45(2):303–314.
148. Belaya Z, Melnichenko G, Golounina O, Tsoriev T, Rozhinskaya L, Dubovitskaya T, et al. 2022 Three-year progress report of Bone Health TeleECHO Moscow: a strategy to improve the care of patients with osteoporosis and other metabolic skeletal diseases in underserved communities of Russia. Osteoporos Int 33(9):2035–2040.