

Review Article



Proceedings of the 2016 Santa Fe Bone Symposium: New Concepts in the Management of Osteoporosis and Metabolic Bone Diseases

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Abstract

The Santa Fe Bone Symposium is an annual meeting of healthcare professionals and clinical researchers that details the clinical relevance of advances in knowledge of skeletal diseases. The 17th Santa Fe Bone Symposium was held in Santa Fe, New Mexico, USA, on August 5–6, 2016. The program included plenary lectures, oral presentations by endocrinology fellows, meet-the-professor sessions, and panel discussions, all aimed to provide ample opportunity for interactive discussions among all participants. Symposium topics included recent developments in the translation of basic bone science to patient care, new clinical practice guidelines for postmenopausal osteoporosis, management of patients with disorders of phosphate metabolism, new and emerging treatments for rare bone diseases, strategies to enhance fracture healing, and an update on Bone Health Extension for Community Healthcare Outcomes, using a teleconferencing platform to elevate the level of knowledge of healthcare professionals in underserved communities to deliver best practice care for skeletal diseases. The highlights and important clinical messages of the 2016 Santa Fe Bone Symposium are provided herein by each of the faculty presenters.

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Introduction

The 17th Santa Fe Bone Symposium was held August 5–6, 2016, in Santa Fe, New Mexico, USA. This annual event convenes scientists, researchers, physicians, and other healthcare professionals to exchange current concepts in the care of skeletal disorders based on advances in basic science and clinical investigation. Presentations and discussions are directed to the application of the best available medical evidence to clinical practice, with appropriate regard to limitations of applying clinical trial data to the care of individual patients. The agenda for the 2-day symposium provided many opportunities for interaction of all participants. Plenary presentations were complemented by oral case presentations by endocrinology fellows, meet-the-professor sessions, and open-topic panel discussions. Progress of the University of New Mexico Bone Health ECHO (Extension for Community Healthcare Outcomes; <http://echo.unm.edu/>) program was also presented.

The contents of earlier Santa Fe Bone Symposia have been made available in peer-reviewed journals (1–10), monographs in print and electronic formats (11–15), online slide presentations (16–18), and audiovisual webcasts. Here we present the highlights of the 17th annual Santa Fe Bone Symposium with the goal of assisting healthcare providers in applying the best available medical evidence to the care of their patients with skeletal diseases.

Translation of Basic Bone Science to Clinical Practice

John P. Bilezikian, MD

The recent development of drugs to treat osteoporosis has taken advantage of advances in basic bone science. In a remarkably short space of time, discoveries of new pathways of cell and molecular biology, as they relate specifically to bone elements, have inspired these developments. In some cases, discoveries have been initiated by an appreciation of rare human experiments of nature. The bisphosphonates represent an outlier in this discussion because an understanding of their biochemical actions to inhibit specific enzymatic steps in the mevalonic acid pathway came after they were recognized to be effective antiresorptive agents (19). We now know that by inhibiting this pathway, the bisphosphonates disrupt important anchoring proteins of osteoclast, rendering these cells either generally dysfunctional or frankly apoptotic (20).

The RANK-RANK Ligand-OPG Pathway: Discovery Research Leading to the Development of Denosumab

The osteocyte is the most abundant bone cell, serving as a master signaling agent to the other major bone cells, the osteoblast and the osteoclast. Receptor activator of

nuclear factor- κ B ligand (RANKL), a product of the osteocyte, is a direct activator of the mature osteoclast and a powerful stimulator of the development of the lineage pathway leading to the maturation of osteoclasts (21). Appreciation of the balance between this important ligand and its natural inhibitor, osteoprotegerin, led to the development of a fully human monoclonal antibody to RANKL, known as denosumab. Denosumab powerfully binds RANKL and thus prevents its interaction with its cognate receptor, RANK, on osteoclasts (22). As a result, the population of osteoclasts rapidly falls to the point where transiliac bone biopsies typically show few, if any, osteoclasts, and clinically powerful inhibition of bone resorption is evident (23). Denosumab has been shown in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM), the pivotal clinical trial leading to this drug's registration, to significantly reduce new vertebral, non-vertebral, and hip fractures over 3 years of administration (24). Follow-up data, extending well beyond the 3-year clinical trial period, have shown that the anti-fracture effects are sustained and may in fact become more pronounced over time at non-vertebral sites (25). More recently, it has been shown that when the regimen of twice yearly subcutaneous injection of denosumab is stopped, there is not only a rapid reversal of suppressed bone turnover markers and a decline of bone mineral density (BMD) of the lumbar spine, but also an increase in the incidence of vertebral fractures (26). These findings have led experts to recommend that denosumab should not be stopped without initiating sequential effective anti-fracture therapy to preserve bone mass and architecture (27).

Cathepsin K: Development of an Effective and Safe Cathepsin K Inhibitor—Not Meant to be?

Over the past 10 years, great enthusiasm has been generated over the clinical potential of an inhibitor of cathepsin K, an osteoclastic enzyme, to become another major treatment of osteoporosis. In preclinical and early clinical trials, it was evident that an inhibitor of this powerful enzyme prevents the osteoclast from resorbing bone, but would not impair other key functions of the osteoclast, such as its functional linkage to the osteoblast (28). Clinical trials clearly demonstrated that a cathepsin K inhibitor known as odanacatib rapidly reduced the incidence of new vertebral, non-vertebral, and hip fractures (29). The interesting property of this drug of permitting the osteoblast to be more functional than with traditional antiresorptive agents was also promising. However, a careful evaluation of an apparent imbalance between drug and placebo arms of the phase III clinical trial with regard to cardiovascular events was recently confirmed, showing a significantly higher incidence of stroke in patients receiving odanacatib compared with those receiving placebo (30). This observation led to the discontinuance of the development of odanacatib as a treatment for osteoporosis.

Sclerostin: Development of a Sclerostin Inhibitor

Yet another pathway recently recognized to be very important in skeletal metabolism has led to another promising new treatment for osteoporosis. This story begins with appreciation of 2 rare high bone mass disorders, sclerosteosis and van Buchem's disease. In these disorders, the *SOST* gene that codes for sclerostin, an inhibitor of the canonical Wnt signaling pathway, is disrupted, leading to the absence, or markedly reduced levels, of sclerostin (31). By interfering with the interaction between Wnt ligands and their receptors, low-density lipoprotein receptor-related protein 5 and 6 on the osteoblast cell membrane, sclerostin prevents access of cytoplasmic beta-catenin to the nucleus, thereby inhibiting osteoblastic bone formation (32). The therapeutic compound developed as a result of this information is a humanized monoclonal antibody known as romosozumab. By inhibiting sclerostin, the functional brake on the Wnt signaling pathway is released, and bone formation is enabled. Interestingly, romosozumab is also associated with a concomitant inhibition of bone resorption, speaking to the interdependence of the osteoclast and osteoblast. The results of a major clinical trial found that romosozumab, at a dose of 210 mg monthly by subcutaneous injection, is associated with a significant reduction in new vertebral and clinical fractures (33). Statistical analysis including the entire cohort did not show a reduction in non-vertebral fractures, but in a *post hoc* analysis in which patients from Latin America were excluded (there was a preplanned analysis showing an interaction between study sites by geography), there was a significant reduction in non-vertebral fractures in those patients provided romosozumab as compared with those provided placebo.

Osteoanabolic Therapy: Creative Drug Development Based on Osteoanabolic Actions of Parathyroid Hormone

The well-known drug teriparatide reduces vertebral and non-vertebral fractures by stimulating osteoanabolic actions (34). The effect appears to be limited, at least in part, by an increase in bone resorption that follows the initial stimulation of bone formation (35). The quest for an analog of teriparatide that would be associated with a more selective action to stimulate bone formation has led to the development of abaloparatide. This drug is a closer analog of the 1–34 sequence of parathyroid hormone-related protein than teriparatide. Although sharing intense sequence homology with parathyroid hormone-related protein over the first 22 residues, substituents strategically placed thereafter render abaloparatide more selective as an osteoanabolic agent, and less so as a stimulator of resorption. As a result, the daily subcutaneous dose was employed at up to 4-fold higher than teriparatide (80 µg for abaloparatide vs 20 µg for teriparatide). The results of the pivotal clinical trial in which abaloparatide was studied in

a blinded comparison with placebo and in an open-label comparison with teriparatide showed clear beneficial anti-fracture effects in that abaloparatide significantly reduced new vertebral and non-vertebral fractures in comparison with placebo (36). The drug compared favorably with teriparatide in terms of non-vertebral fractures and apparent time-to-effect. There were fewer instances of hypercalcemia and hypercalciuria with abaloparatide, even though the dose was 4-fold higher than with teriparatide.

This presentation has highlighted the rapid translation of basic bone science to clinical application. What is remarkable about this discussion is not only that such translation can occur and, in some cases, successfully, but also how rapidly this “bench-to-bedside” or “bedside-to-bench” transition has been occurring.

The Year in Osteoporosis: Comments on Selected Papers Published From July 2015 to June 2016

Michael R. McClung, MD

A review of clinical papers about osteoporosis published between July 2015 and June 2016 was undertaken, and those considered as being of special interest or importance were chosen for presentation at the Santa Fe Bone Symposium. Some of those selections are highlighted here.

BMD testing is an important tool to identify patients at high risk for fracture and those who would benefit from therapy. The test must be performed and interpreted correctly and reported clearly to take full advantage of the technology. The International Society for Clinical Densitometry (ISCD) provided a description of best practices for dual-energy X-ray absorptiometry (DXA) measurement and reporting, a valuable reference document for facilities and individuals performing DXA examinations (37).

A review by Black and Rosen thoughtfully summarized the current management of postmenopausal osteoporosis (38). They pointed out that our treatments, when given to the right patients, effectively reduce fracture risk. They also emphasized that these benefits far outweigh the uncommon serious side effects of therapy, at least during the first years of treatment. The importance of this paper was not only in the clear message, but in its publication in the *New England Journal of Medicine*, read by many physicians who do not routinely read bone journals. A companion editorial in the *Journal of Bone and Mineral Research* by Drs. Khosla and Shane recounted the early success of implementing fracture protection therapy between 1995 and 2008 and then the marked drop-off in the use of osteoporosis drugs in the United States, including a marked decline in the proportion of patients who receive therapy after hip fracture (39). Citing a “crisis” in our field, the authors echoed the call of Black and Rosen for the use of proven osteoporosis medications in the right patients. Consistent with the information provided in these papers, a report from Japan noted that BMD measurement

was performed in only 8.7% of patients age 50 years and older who had experienced a wrist fracture (40). Although 70% of those tested met criteria for treatment, therapy was begun in only 13.4% of the patients. These results are troubling given new data from the Women's Health Initiative documenting that an incident wrist fracture in a postmenopausal woman was associated with a 50% increase in the risk of hip and spine fracture and a 78%–88% increased risk of humerus and other upper extremity fractures (41).

More encouraging news about osteoporosis management came from the United Kingdom, where the proportion of patients receiving treatment after hip fracture increased from 7% in 2000 to 46% in 2010 (42). This improvement, although still not optimal, coincided with the establishment of fracture liaison services for secondary fracture prevention in that country, providing further evidence of the value of such programs.

One reason for the poor acceptance of and persistence with osteoporosis treatments is concern about the risk of atypical femoral shaft fractures (AFF) with bisphosphonates. A comprehensive review of the effects of bisphosphonate therapy provided details about the incidence and epidemiology of known and potential risks of therapy, putting these risks in perspective compared with the protection provided from fragility fracture (43). Using the Danish national database, the risk of hip fracture and of subtrochanteric or femoral shaft fractures in patients receiving long-term alendronate therapy was assessed (44). Compared with the incidence of fractures in patients who had used alendronate for 3–5 years, a persistent decrease in hip fracture risk of about 30% was observed in patients receiving alendronate for more than 10 years. In contrast, the risk of the much less common subtrochanteric or femoral shaft fractures remained constant with long-term therapy. Because hip fracture risk decreases by 40%–50% during the first 3 years of therapy with alendronate (45,46), these results may have substantially underestimated the absolute benefit of alendronate therapy. However, these data suggest that the fracture protection benefits of alendronate continue to far exceed any risk over a treatment interval of at least 10 years.

Another reason for the declining use of osteoporosis therapy is uncertainty about the management of patients on long-term treatment. An American Society for Bone and Mineral Research Task Force published guidelines, based on available evidence, for long-term bisphosphonate therapy (47). The Task Force demonstrated that, in patients with osteoporosis, the protective benefits of bisphosphonates outweigh the risks of AFF and osteonecrosis of the jaw (ONJ). A clear algorithm for identifying patients in whom temporary interruption of therapy could be considered was provided. The authors also emphasized that patients who remained at high fracture risk after 3–5 years of therapy should continue to be treated with either bisphosphonates or another osteoporosis medication. Unfortunately, because this was published in the *Journal of Bone and Mineral*

Research, a journal not commonly read by primary care providers, many physicians do not know of these guidelines.

More information about the benefits and risk of calcium intake came from the Melbourne Collaborative Cohort Study (48). In a cohort of more than 41,000 men and women age 50–69 years, risks of overall mortality, cardiovascular disease, stroke, and fracture were significantly lower among subjects in the upper quartile of daily calcium intake (average 1348 ± 316 mg) compared with those in the lowest quartile (473 ± 91 mg). These results do not address whether there are cardiovascular risks to providing calcium supplements to older patients.

As predicted by the drug's pharmacology, the effect of denosumab on markers of bone remodeling rapidly return to and then rise above baseline in the first few months after stopping therapy. Reports of 5 patients who experienced severe and/or multiple vertebral fractures within a few months of discontinuing denosumab raised the question of whether an interval of excess fracture risk exists upon stopping this therapy (27). However, the risk of clinical and vertebral fracture was similar. Comparison of fracture risk between patients in the denosumab phase III fracture trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months trial and its extension) who discontinued either denosumab or placebo showed consistent results (26).

In summary, this year's clinical osteoporosis literature was characterized by refinements in our understanding of patient management. No major drug treatment trials had been published. However, since the meeting, the results of phase III fracture trials with romosozumab and abaloparatide have been published as presented by Dr. Bilezikian (33,36). Additionally, we have learned that development of odanacatib has been halted because of an increased risk of stroke (30). These results, and the availability of the novel osteoanabolic treatments, will provide new strategies for osteoporosis management and raise more interesting clinical questions to be addressed.

AACE/ACE Clinical Practice Guidelines on the Diagnosis and Management of Postmenopausal Osteoporosis—2016

Pauline M. Camacho, MD

The 2016 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Clinical Practice Guidelines on Postmenopausal Osteoporosis (49) encapsulates significant updates in the diagnosis and treatment of osteoporosis since the 2010 version. Among the updates are an accompanying treatment algorithm and patient decision tools that can be used in practice. The 2016 Guidelines maintain that osteoporosis should be diagnosed based on the presence of a fragility fracture, in the absence of other metabolic bone disorders. Lumbar spine, femoral neck, and total hip (and 1/3 radius as an alternate site) *T*-scores of -2.5 or lower

also can define osteoporosis. In addition, patients with *T*-score between -1.0 and -2.5 who have a fracture risk (using the World Health Organization fracture risk assessment) that meets or exceeds the country-specific treatment threshold may also be diagnosed with osteoporosis.

Patients who are diagnosed with osteoporosis should undergo a comprehensive evaluation for causes of secondary osteoporosis. In a prior study, approximately 40% of patients were found to have abnormal findings (50). Deficiency of vitamin D or calcium that is detected during the workup should be corrected before initiation of therapy.

Agents used to prevent or treat osteoporosis belong to 2 drug classes: antiresorptive (anti-catabolic) and anabolic (bone forming). Antiresorptive agents include bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), an RANKL inhibitor (denosumab), a selective estrogen receptor modulator (raloxifene), calcitonin, and estrogen. The only US Food and Drug Administration-approved anabolic agent is teriparatide.

The initial choice of therapy should be guided by the individual's fracture risk and the presence or absence of prior fragility fractures. Indicators of higher fracture risk include prior fractures, advanced age, frailty, glucocorticoid use, very low *T*-scores, and increased fall risk. Patients who are candidates for treatment who do not have these indicators would be deemed to have "moderate fracture risk." For this group, approved agents with efficacy to reduce hip, non-vertebral, and spine fractures, including alendronate, risedronate, zoledronic acid, and denosumab, are appropriate as initial therapy. Alternate agents (not proven to reduce hip fractures in randomized controlled trials) include ibandronate and raloxifene. For the patients with "higher fracture risk" or in patients with moderate fracture risk who are unable to tolerate oral therapy, teriparatide, denosumab, or zoledronic acid may be considered as initial agent.

Because of the concern about rare adverse events such as ONJ and AFFs, treatment duration was one of the most important aspects of treatment addressed in the guidelines. For patients with moderate fracture risk, the AACE/ACE recommends a drug "holiday" in stable patients after 5 years of oral bisphosphonate and 3 years of intravenous bisphosphonate use. For those who are at higher fracture risk, the recommendation is to continue therapy for up to 10 years for oral bisphosphonates and up to 6 years for intravenous bisphosphonates. During the drug holiday in these patients with higher fracture risk, another agent such as raloxifene or teriparatide could be considered. Drug holidays are not appropriate for non-bisphosphonate drugs, as there is rapid dissipation of therapeutic effect soon after discontinuation.

Teriparatide therapy is generally limited to 24 months of lifetime use. Upon completing a course of therapy with teriparatide, treatment with an antiresorptive agent is highly recommended to maintain or enhance the benefit achieved.

For patients at moderate fracture risk who lose BMD or develop new fractures while on treatment, it is important to

assess compliance with therapy and reevaluate for causes of secondary osteoporosis. If the patient was previously on an oral bisphosphonate, a switch to an injectable antiresorptive could be considered. If the patient was on an injectable antiresorptive, a switch to teriparatide could be considered. For patients who are in the higher fracture risk group who continue to lose BMD or develop recurrent fractures, the following recommendations apply: if denosumab was being used, consider adding teriparatide, and if the patient was on zoledronic acid, consider switching to teriparatide.

The duration of the drug holiday would depend on the individual patient's clinical state. The AACE/ACE recommends ending the drug holiday in the following scenarios: when a fragility fracture occurs, when there is BMD loss beyond the least significant change of the facility, and possibly when bone turnover markers increase to pretreatment levels. Clinically, if there is a significant increase in the patient's fracture risk (e.g., treatment with high-dose glucocorticoids or significant increase in fall risk from a new stroke), therapy should probably also be resumed.

Serum Phosphorus: Why Do You Measure It, When Do You Measure It, and What Do You Do About It?

Paul D. Miller, MD

Phosphorus is an essential element aiding in the regulation of all biological functions; it is ubiquitous throughout all body tissues. The measurement and management of alterations (high or low) in serum phosphorus concentration is not a usual clinical practice consideration, but it should be. Serum phosphorus should ideally be included among other blood chemistries in a comprehensive metabolic panel; however, it is not. Both hypophosphatemia and hyperphosphatemia have implications for altering bone and muscle function. Chronic hyperphosphatemia in the presence of stage III–V chronic kidney disease is the most significant risk factor for vascular calcification and cardiovascular mortality. Chronic hypophosphatemia, especially due to malabsorption or renal loss, may lead to severe myopathy as well as osteomalacia.

Management of a chronically high or low serum phosphorus first depends on the cause of the biochemical abnormality. Phosphorus is an element necessary for all biological and cellular functions. Without phosphorus, for example, there would be no adenosine triphosphate, the molecular unit of currency of intracellular energy transfer. Hypophosphatemia or hyperphosphatemia can be acute or chronic, each having distinct clinical outcomes. Chronic phosphate depletion leads to 2 major clinical defects: severe myopathy and osteomalacia (adult rickets). Normal serum phosphorus typically ranges from 2.5 to 4.5 mg/dL; it is not affected by the serum albumin concentration and does not need to be drawn in a fasting state (51).

Despite the enormous importance of knowing what the serum phosphorus is, many commercial laboratories have

discontinued reporting serum phosphorus with biochemical profiles. As laboratories have added other routine measures such as estimated glomerular filtration rate (GFR), others have been removed. Because clinicians must order a serum phosphorus level separately, circumstances in which this may be clinically helpful include unexplained muscle weakness, fractures, or “bone pain”; elevated parathyroid hormone (PTH), alkaline phosphatase, serum creatinine, calcium, creatine phosphokinase (CPK), low CO₂, and elevated chloride; low or high alkaline phosphatase; nephrolithiasis or nephrocalcinosis; and patients on a high-dose vitamin D or vitamin D metabolites. When serum phosphorus concentrations are either high (>4.5 mg/dL) or low (<2.5 mg/dL), they both may portend an underlying disease with adverse clinical consequences.

Regulation of Serum Phosphorus

Although bone flux (both cellular and mineral surfaces) and gut absorption are important in establishing the filtered load (serum phosphorus × GFR) of phosphorus, it is the renal threshold for phosphate reabsorption in the proximal tubule that is most important in determining the steady-state serum phosphate concentration. Regulation of renal phosphate is mediated by a multitude of factors, including phosphate dietary intake and absorption, serum phosphorus concentration, and the activity of a host of hormones that influence renal tubular phosphorus reabsorption, such as parathyroid hormone, fibroblast growth factor-23 (FGF-23), Klotho, 1,25-(OH)₂-vitamin D, and phosphatonins such as phosphate-regulating gene with homologies to endopeptidases on the X chromosome, FGF 7, secreted frizzled-related protein 4, and matrix extracellular phosphoglycoprotein (52). The need to maintain phosphorus homeostasis is so great for all biological functions that urinary phosphorus often becomes undetectable when there is a very low intake or absorption, even before the appearance of hypophosphatemia. The kidney is so vital in the regulation of serum phosphorus concentration that in the presence of hypophosphatemia, any measurable urine phosphorus suggests there is renal phosphate wasting; the differential diagnosis should then focus on causes of renal phosphate wastage.

The recommended dietary allowance for daily phosphorus consumption for adult women and men is 700 mg/d (53). The actual dietary intake is often nearly double the recommended dietary allowance. Phosphorus is ubiquitous in the food chain, but major sources in the United States are processed foods, fast foods, convenience foods, and heavy red meat consumption. High phosphorus consumption has created concerns in the nutrition-cardiovascular community of a possible link with vascular calcification and hypertension (54).

Although phosphorus balance studies are impractical outside of specialized research centers, the clinician managing a patient with chronic hypophosphatemia or hyperphosphatemia must first decide the mechanism for the disordered serum phosphorus levels.

Chronic Hypophosphatemia

Serum phosphorus concentration persistently below 2.5 mg/dL merits investigation as to its cause. The causes of chronic hypophosphatemia are shown in Table 1 (55). Once the “hungry bone phenomenon” (the high rate of skeletal uptake of phosphorus and calcium in the immediate days following a parathyroidectomy for primary hyperparathyroidism) has been excluded, the 2 other major organ systems involved in phosphorus homeostasis are the gut and the kidney (56).

Malabsorption of phosphorus may occur in the setting of small bowel diseases, especially after surgical resections. Although vitamin D (25 and 1,25) influences phosphorus absorption, it requires a sustained very low level of vitamin D metabolites to result in hypophosphatemia. Phosphorus depletion can be induced in normal human beings by restricting dietary phosphorus combined with the administration of gastrointestinal oral phosphate binders (57).

Table 1

Causes of Hypophosphatemia and Hyperphosphatemia

Hypophosphatemia

Internal redistribution

- Increased insulin secretion, especially refeeding
- Acute respiratory alkalosis
- Hungry bone phenomenon

Decreased intestinal absorption

- Poor intake
- Inhibition of absorption
- GI surgeries
- Vitamin D deficiency or resistance

Increased urine excretion

- Primary or secondary hyperparathyroidism
- Vitamin D deficiency or resistance (hypophosphatemic vitamin D-resistant rickets; XLH)
- Oncologic osteomalacia (FGF-23; TIO)
- Therapies including thiazides, acetazolamide, tenofovir, adefovir dipivoxil
- Renal displacement including plasmapheresis

Hyperphosphatemia

Acute or chronic renal failure

- Hypoparathyroidism
- Pseudohypoparathyroidism
- Hypophosphatasia
- Rhabdomyolysis
- Low production of FGF-23 (associated with hyperostosis)

Abbr: FGF-23, fibroblast growth factor-23; GI, gastrointestinal; TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia.

The key diagnostic test to discriminate between gastrointestinal and renal causes of hypophosphatemia is measurement of the 24-hour urine phosphorus. Any phosphorus in the urine during chronic hypophosphatemia means renal phosphate wasting, requiring evaluation of renal causes of phosphorus loss, listed in Table 1 (55). Once primary hyperparathyroidism has been excluded or corrected, other common causes of renal phosphate wasting to consider are renal tubular acidosis (RTA), X-linked hypophosphatemia (XLH), and tumor-induced osteomalacia (TIO).

Proximal and distal RTA may cause renal phosphate wasting, resulting in systemic metabolic bone disease, osteoporosis, or osteomalacia (58). Acidosis inhibits renal tubular phosphorus reabsorption. Most cases of RTA are associated with low (<19 meq/L) serum bicarbonate, expressed by laboratory reports as CO₂, and elevated serum chloride (>120 meq/L). RTA is a non-anion gap metabolic acidosis, unlike the metabolic acidosis that accompanies diabetic ketoacidosis, the acidosis of severe chronic renal failure, ethylene glycol poisoning, lactic acidosis, or acidosis from aspirin overdose. One form of RTA (incomplete distal RTA) has normal serum electrolytes and can only be diagnosed with an ammonium chloride loading test to see if the urine pH can be lowered below 5.4. Ammonium chloride loading tests should be done by experts in acid-base metabolism who have experience in performing this test.

The consequences of hypophosphatemia depend on its severity and duration. Most symptomatic patients have serum phosphorus below 1.0 mg/dL–1.5 mg/dL (normal range 2.5–4.5 mg/dL). Phosphorus affects all cellular functions, including the underproduction of adenosine triphosphate. Muscle abnormalities associated with hypophosphatemia range from acute rhabdomyolysis to chronic proximal myopathy. Symptoms may be profound but are usually quickly reversible with adequate phosphate replacement.

The skeletal consequences of chronic hypophosphatemia are rickets (in children) and osteomalacia (in adults). Independent of vitamin D levels (25OH or 1,25 OH₂), chronic hypophosphatemia leads to a severe mineralization defect. Patients with osteomalacia may have diffuse constant proximal hip or pelvis pain that is worse at nighttime while in bed. Low trauma fractures, especially non-vertebral fractures, may occur. Typical radiographic findings are linear radiolucent fracture lines, called Looser zones, that follow the course of nutrient arteries in the proximal humerus or femur (Fig. 1) (59,60).

An important clue to the presence of osteomalacia is the elevation of bone-specific alkaline phosphatase (BSAP). There are a broad variety of disease states that can cause an elevated BSAP (Table 2) (5). If the cause of an elevated BSAP is not clear, a total radioisotope bone scan should be performed to look for “hot spots.” If any are seen, then radiographic imaging should be performed to evaluate for disorders such as Paget’s disease of bone and skeletal malignancy.

Quantitative bone histomorphometry with tetracycline double-labeled transiliac bone biopsy is the most

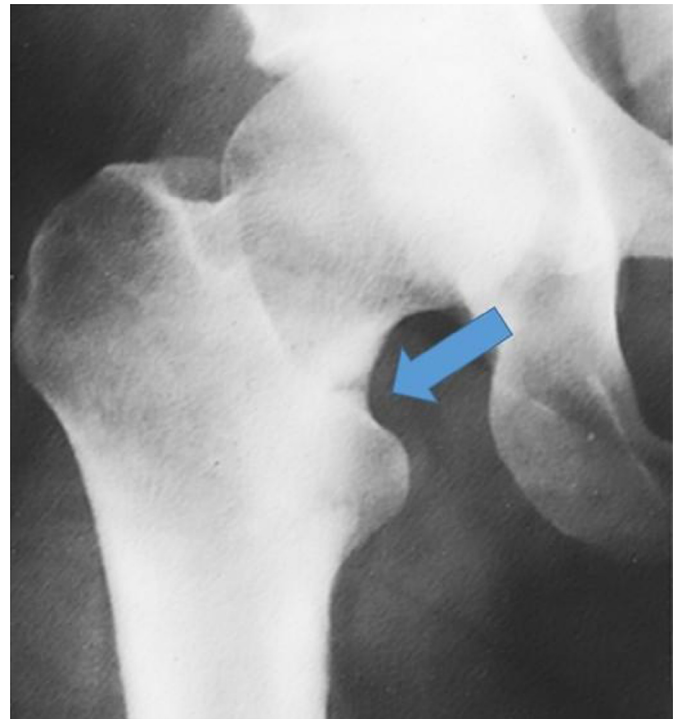


Fig. 1. Looser zone at proximal femur.

sensitive and specific means of diagnosing osteomalacia. Osteomalacia has specific criteria for the diagnosis: osteoid surface of >80%, osteoid thickness >14 microns, and prolonged mineralization lag time (61). Figure 2 shows a bone biopsy specimen with classical features of osteomalacia (62). Because bone biopsies are not readily available in clinical practice settings, it is a fully acceptable standard of care to manage suspected osteomalacia on clinical grounds,

Table 2
Elevated Bone-Specific Alkaline Phosphatase

Severe primary hyperparathyroidism
Hyperthyroidism
Metastatic cancer in bone
Paget’s disease of bone
Recent large bone fracture
Osteomalacia
Severe (<8–10 ng/mL) vitamin D deficiency
Space travel
Immobilization
Treatment with anabolics (teriparatide, abaloparatide, romosozumab, 1–84 PTH)
Treatment with strontium ranelate
High bone turnover osteoporosis
Renal bone disease: either hyperparathyroid disease or osteomalacia

Abbr: PTH, parathyroid hormone.

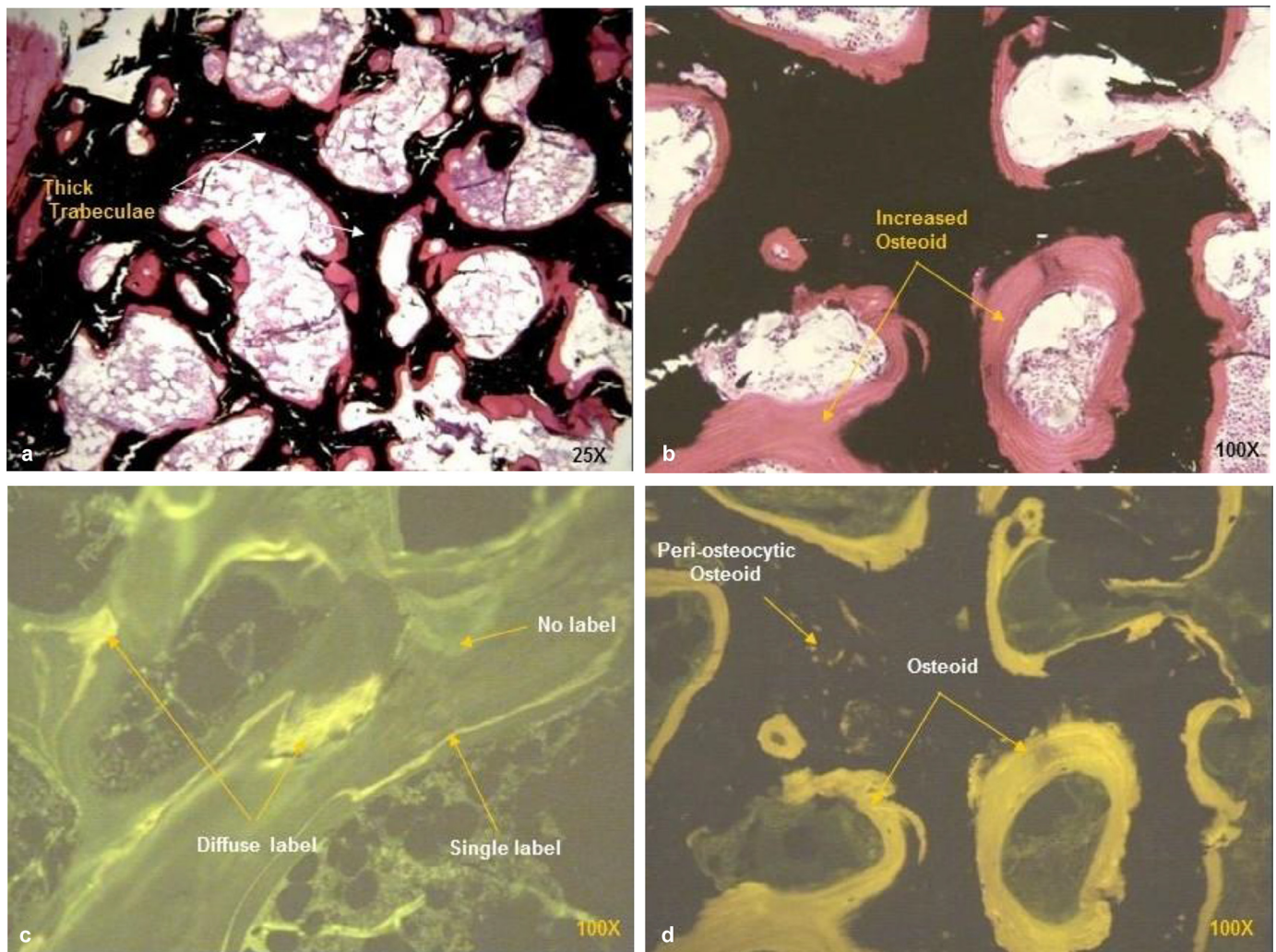


Fig. 2. Bone biopsy of patient with osteomalacia. (A) Von Kossa, hematoxylin-eosin (H&E) stain for calcium and osteoid at 25× resolution. (B) Von Kossa, H&E stain for calcium and osteoid at 100× resolution. (C) Unstained, fluorescent for tetracycline at 100× resolution. (D) Von Kossa, H&E stain and fluorescent for osteoid at 100× resolution.

without a bone biopsy. This approach is justified because osteomalacia always has a cause (Table 3) (63). When the evaluation of hypophosphatemia with an elevated BSAP has eliminated all likely causes other than osteomalacia, a clinician is often faced with a final differential between oncogenic osteomalacia (TIO) and XLH (64).

The clinical presentations and the biochemical profiles of TIO and XLH are identical: proximal constant pain in the hips or pelvis or shoulders (often worse at night); proximal muscle weakness; fractures (including Looser zones) (Fig. 1); and the biochemical profile of hypophosphatemia, phosphaturia, elevated BSAP, elevated FGF-23, normal serum 25-OH-vitamin D, and low 1,25 dihydroxyvitamin D. These biochemical combinations are seen only in severe chronic kidney disease, TIO, or XLH. The clinical challenge is discriminating TIO from XLH. Both are associated with elevated FGF-23 and both are currently treated

Table 3
Causes of Osteomalacia

Severe 25-OHD deficiency (<8 ng/mL)
Chronic hypophosphatemia
Vitamin D-resistant rickets (XLH), low serum PO ₄ , elevated FGF-23, normal 25D but low 1,25 D, phosphaturia
Renal tubular acidosis
Oncogenic osteomalacia (low serum PO ₄ , elevated FGF-23, low 1,25D, phosphaturia [TIO])
Severe chronic kidney disease (multifactorial: elevated sclerostin and FGF-23, low 1,25D)

Abbr: FGF-23, fibroblast growth factor-23; TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia.

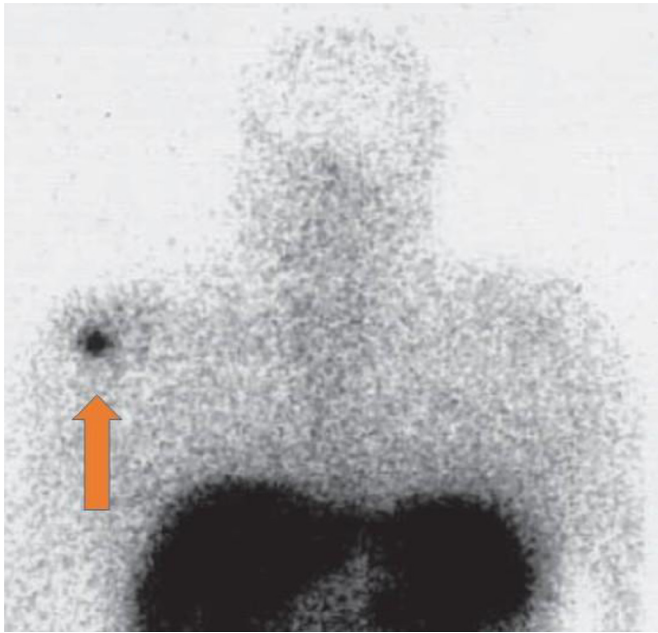


Fig. 3. Small, benign mesenchymal tumor imaged with octreotide scan.

with oral phosphorus replacement and 1,25 dihydroxyvitamin D (calcitriol), with the goal of improving muscle strength and healing the osteomalacia. In the future, treatment may be with a monoclonal antibody to FGF-23, which is currently in development (65). Discrimination between TIO and XLH is often a historic one: TIO usually presents in adulthood, has no genetic component, and is caused by small benign mesenchymal tumors that are the source of the production of FGF-23 (Fig. 3). Once the responsible tumor is removed, the patient is cured and may never again require pharmacological therapy, as the source of excess FGF-23 is gone. This is not the case with hereditary XLH, which often presents early in life and is associated with a chronic lifelong excess production of FGF-23. There seems to be a dysfunctional relationship between FGF-23 and PTH in XLH. Whereas FGF-23 normally suppresses PTH production (both are phosphaturic hormones), with XLH, FGF-23 and PTH are both elevated. The mechanism that drives this abnormal relationship is unknown (66).

Until the causes of chronic hypophosphatemia are clarified, treatment of hypophosphatemia *per se* may be necessary. In asymptomatic patients with serum phosphate less than 2.0 mg/dL (0.64 mmol/L), treatment should begin with oral sodium phosphate or potassium phosphate (250 mg phosphorus), because many of these patients have myopathy and weakness that are not clinically apparent. Phosphorus repletion should be slow, because replacing phosphorus too rapidly induces diarrhea. Most patients will require approximately 1000–1500 mg/d.

Chronic Hyperphosphatemia

There are many causes of chronic elevations of serum phosphorus (Table 1). Most are associated with either acute or chronic renal failure or hypoparathyroidism. One condition associated with hyperphosphatemia, adult hypophosphatasia, merits extra attention, because the prevalence may be higher than previously estimated. Hypophosphatasia is a genetic defect with variable gene expressions leading to the underproduction of osteoblast alkaline phosphatase, with serum total alkaline phosphatase levels typically <40 IU/L (67). In adults, the disease often presents with recurrent metatarsal fractures, mid-shaft femur fractures that may mimic bisphosphonate-associated atypical femur fractures, or abnormal dentition; nephrolithiasis or nephrocalcinosis may also be seen. These patients typically have elevated serum vitamin B6 levels because of the accumulation of this alkaline phosphatase substrate. In a patient with low total alkaline phosphatase, the differential diagnosis should include consideration of other disorders listed in Table 4.

Hypophosphatasia is the one condition where the bone histomorphometry shows osteomalacia, yet the alkaline phosphatase is low rather than elevated, and serum phosphorus may be high rather than low; this is the opposite of what is observed with all other conditions associated with osteomalacia.

Treatment of abnormal bone mineralization associated with hypophosphatasia has been reported in a few case reports using the anabolic agent, teriparatide (68). Teriparatide seems to stimulate the osteoblast to produce alkaline phosphatase, even in this condition. Recently, the Food and Drug Administration approved the enzyme replacement, asfotase alpha, for the treatment of patients with perinatal or infantile- and juvenile-onset hypophosphatasia (67). Specialists in metabolic bone disease are using this agent in adults with hypophosphatasia, especially in those who have suffered recurrent poorly healing fractures. Many questions remain on duration of therapy, monitoring therapy,

Table 4
Causes of Low Serum Alkaline Phosphatase

Hypophosphatasia
Renal adynamic bone disease
Treatment with antiresorptive agents
Hypoparathyroidism
Vitamin D intoxication (perhaps via hypercalcemia and PTH suppression)
Celiac disease
Cardiac bypass
Clofibrate
Cushing's disease
Massive transfusions
Milk alkali syndrome
Vitamin C deficiency
Wilson's disease

and, of course, payment of this expensive yet innovative therapy.

For the hyperphosphatemia of hypoparathyroidism, there is also a new Food and Drug Administration treatment, recombinant human PTH (rhPTH) (1–84), which acts like endogenous PTH to increase renal tubular reabsorption of calcium and induce phosphaturia (69). An advantage of PTH replacement for hypoparathyroidism is that it will not induce hypercalciuria and renal stone formation often seen with conventional calcium and vitamin D therapy while also avoiding hyperphosphatemia that can lead to vascular calcification.

In summary, disorders of phosphorus metabolism are common but often missed, because the commercial laboratory blood chemistry panels do not include serum phosphorus. We should encourage the routine return of serum phosphorus to these reports. Until that time, there are clinical reasons to order a serum phosphorus as outlined here. In the presence of persistent hypo- or hyperphosphatemia, treatment of the underlying disease process is indicated. When the underlining disease cannot be identified and treated, it is important to control the serum phosphorus to avoid the consequences of disordered phosphorus levels. The prevalence of TIO, XLH, and hypophosphatasia is probably higher than previously recognized because of under-recognition of abnormal phosphorus levels and lack of attention to low serum alkaline phosphatase.

Rare Bone Diseases You Should Never Miss

Bart L. Clarke, MD

Patients with rare bone diseases are commonly seen in metabolic bone disease clinics, referred by physicians who may not be familiar with these diseases or may not be comfortable in providing care for them. Understanding the pathophysiology of these rare disorders is very helpful in their management, but can also be very informative regarding targets for therapy of more common bone disorders, such as osteoporosis. Several selected rare bone diseases are briefly described here, with emphasis on their pathophysiology and treatments. It is important to realize that rare bone diseases associated with low BMD may masquerade as osteoporosis, but biochemical tests performed during secondary cause evaluation should help distinguish these disorders from osteoporosis. In some cases, if rare bone diseases are treated as osteoporosis, they may worsen.

Hypoparathyroidism

Hypoparathyroidism is a rare bone disease characterized by low serum calcium, increased serum phosphorus, and inappropriately low levels of parathyroid hormone (70,71). Treating the disorder requires management of hypocalcemia and hyperphosphatemia, as well as avoidance of hypercalciuria, which can lead to nephrocalcinosis, kidney

stones, and chronic kidney disease. This disease is also characterized by posterior subcapsular cataracts and basal ganglia and other intracerebral calcifications (71). These complications are attributed to deposition of calcium-phosphate complexes in soft tissues owing to increased calcium-phosphate product caused by treatment with high-dose calcium and activated vitamin D supplements.

It is estimated that 60–80,000 patients in the United States have hypoparathyroidism, based on analysis of a large insurance claims database (71,72). Of the 8901 cases of hypoparathyroidism identified in the database, 75% were transient and lasted for less than 6 months, whereas 25% were chronic and lasted longer than 6 months (72). The most common cause of hypoparathyroidism was anterior neck surgery.

The Danish National Patient Registry studies estimated the prevalence of postsurgical hypoparathyroidism at 22 of 100,000, and nonsurgical hypoparathyroidism at 2.3 of 100,000 (73,74). Patients with postsurgical hypoparathyroidism had increased risk of depression, other neuropsychiatric diseases, and hospitalization for infections, but did not have increased risk of cataracts, spinal stenosis, overall fractures, gastrointestinal cancers, or mortality (74). Their risk of upper extremity fractures was significantly decreased compared with age- and sex-matched population controls (74). Patients with nonsurgical hypoparathyroidism had higher risk of renal insufficiency, cardiovascular disease, neuropsychiatric complications, infections, seizures, cataracts, and upper extremity fractures, but had reduced risk of malignant diseases and normal mortality (73). Nonsurgical hypoparathyroidism may appear as isolated autoimmune hypoparathyroidism or as an autoimmune polyglandular disorder. It may also be associated with infiltrative disorders or hereditary defects that include abnormalities of PTH biosynthesis, PTH secretion, or parathyroid gland development (75).

Once-daily subcutaneous self-administration of synthetic rhPTH (1–84) was shown to benefit patients with hypoparathyroidism in a multinational phase III randomized placebo-controlled trial, and approved for adjunctive treatment of hypoparathyroidism in the United States in January 2015 (76). Treatment with rhPTH (1–84) lowered or eliminated the need for supplemental calcium and activated vitamin D in 53% of patients, compared with 2% of placebo-treated subjects. Long-term studies of safety and efficacy of rhPTH (1–84) beyond 6 years are not yet available. Hypoparathyroidism compromises patient quality of life, and open-label treatment with rhPTH 1–84 over 5 years improved quality of life measures after 2 months and persisted through 5 years (77).

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a group of rare genetic disorders affecting type 1 collagen, causing skeletal fragility, fractures, and growth deficiency (78). About 85%–90% of patients with these disorders have autosomal

dominant mutations in the COL1A1 and COL1A2 collagen genes, leading to underproduction of the $\alpha 1(I)$ and $\alpha 2(I)$ chains of type I collagen, or poor-quality collagen (79). Since 2006, an increasing number of autosomal recessive mutations in related genes have been reported, which affect the processing of collagen in bone and other tissues, mineralization of bone, or osteoblast differentiation that lead to the same OI phenotype (80). A total of 17 mutations causing this disorder have been described to date, with a prevalence of 1 in 15–20,000 births.

The Sillence classification published in 1979 identified 4 types of OI, based on clinical and radiographic features (81). Sillence type I is mild and due to a quantitative decrease in structurally normal collagen. Lethal type II, severe type III, and moderate type IV all have mutations altering collagen structure, leading to poor-quality collagen.

In addition to growth deficiency and multiple fractures, patients with OI have defective tooth formation, hearing loss, macrocephaly, blue sclerae, scoliosis, barrel chest, and/or joint laxity. Serum and urine mineral metabolism laboratory studies remain within normal limits, although total and/or bone alkaline phosphatase may increase after fracture. Treatment is usually directed at preventing bone loss in patients with multiple fractures using oral or intravenous bisphosphonates, or orthopedic repair after fractures have occurred (78). Denosumab has recently been used to treat OI type VI and children with OI (82,83). Teriparatide has been shown to cause an anabolic response in adults with OI (84).

Hypophosphatasia

Hypophosphatasia is a very rare genetic disorder with insufficient production of tissue-nonspecific isoenzyme of alkaline phosphatase resulting in poorly mineralized bones, osteomalacia or rickets, low BMD, and often muscle weakness (67). The level of tissue-nonspecific isoenzyme of alkaline phosphatase deficiency varies, causing expression of perinatal lethal, perinatal benign, infantile, childhood, and adult forms of the disorder. Odonto-hypophosphatasia is a sixth form, associated with early dental loss, but not fractures.

Depending on the severity of skeletal disease, recurrent fractures, deformities of the extremities, hypoplastic chest leading to respiratory failure, premature tooth loss, and bone pain may occur (85). Hypophosphatasia leads to reduced serum alkaline phosphatase and accumulation of substrates that include urinary phosphoethanolamine, serum inorganic pyrophosphate, and serum pyridoxal-5'-phosphate (B6).

Treatment of pediatric hypophosphatasia is directed at improving mineralization of the bone matrix with asfotase alpha, a bone-targeted alkaline phosphatase approved in the United States in October 2015 (86), and calcium and activated vitamin D replacement in older patients. Bisphosphonates and other potent antiresorptive agents should be avoided in patients with low bone density due to hypophosphatasia with low serum

alkaline phosphatase, as these agents may worsen skeletal hypomineralization.

Hypophosphatemia and Increased Serum FGF-23

A variety of disorders associated with hypophosphatemia are associated with increased FGF-23, leading to skeletal rickets or osteomalacia and growth retardation (87). FGF-23 decreases renal tubular reabsorption of phosphorus and production of 1,25-dihydroxyvitamin D, leading to urinary phosphorus loss and decreased serum phosphorus. Klotho is an obligatory coreceptor for FGF-23 signaling after FGF-23 binds to the FGF receptor 1 in the renal tubule.

A variety of hypophosphatemic disorders have been reported to be caused by increased serum FGF-23. Autosomal dominant hypophosphatemic rickets is due to gain of function mutations in the FGF-23 gene, leading to decreased inactivation of FGF-23. Autosomal dominant hypophosphatemic rickets may improve with iron supplementation, leading to recovery of renal tubular ability to reabsorb phosphorus (88). TIO is caused by FGF-23 overproduction by various tumors (89). XLH is caused by loss of function mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome gene, which produces the enzyme responsible for degradation of FGF-23 (90). Autosomal recessive hypophosphatemic rickets type 1 is due to dentin matrix acidic phosphoprotein 1 gene mutations causing reduced expression of dentin matrix acidic phosphoprotein 1 protein, impaired osteocyte differentiation, and increased FGF-23 production, whereas autosomal recessive hypophosphatemic rickets type 2 is due to ectonucleotide pyrophosphatase/phosphodiesterase 1 gene loss of function mutations causing increased FGF-23 production (91). Increased renal phosphate loss due to increased FGF-23 levels may also be seen in fibrous dysplasia with or without McCune-Albright syndrome, opsismodysplasia, osteoglophonic dysplasia, or epidermal nevus syndrome.

Patients with these disorders are treated with phosphorus and activated vitamin D supplementation. In TIO, tumors are removed surgically as soon as they can be identified. A monoclonal antibody against FGF-23 (KRN23) has been developed to reduce renal tubular phosphate loss by blocking FGF-23 actions at the renal tubule, primarily for the treatment of XLH and TIO (92). Phase I or II data from an XLH trial were published in 2015, with a phase III clinical trial for XLH underway (93). A phase I or II clinical trial for TIO is also underway currently.

Hajdu-Cheney Syndrome

This extremely rare autosomal dominant genetic syndrome, also called acro-osteolysis with osteoporosis and changes in skull and mandible (arthrodentoosteodysplasia), was first reported in 1948 (94). It is characterized by severe and excessive bone resorption leading to osteoporosis and a

wide range of other symptoms (95). Hajdu-Cheney syndrome is caused by heterozygous gain of function mutations in the NOTCH2 gene first identified in 2011 (96,97). Mutations in exon 34 at the C-terminal end of the gene leads to production of a shortened stable Notch2 protein that accumulates because of lack of proteosomal degradation. Subjects have increased bone flexibility and deformities, serpentine tibiae and fibulae, short stature, hypertelorism, low-set ears, delayed acquisition of speech and motor skills, wormian bones, small maxilla, early dental loss, hypoplastic frontal nasal sinuses, joint laxity, cardiovascular defects, polycystic kidneys, and severe osteoporosis due to overactivation of RANKL, leading to increased osteoclastogenesis (98). Treatment with oral or intravenous bisphosphonates is usually given to prevent severe bone loss, but antiresorptive treatment may not prevent acroosteolysis or other skeletal manifestations of the disorder (99).

Pycnodysostosis

This autosomal recessive disorder is due to deficiency of cathepsin K, a lysosomal cysteine protease that leads to decreased collagen degradation by osteoclasts (100). Affected patients have disproportionately short stature, relatively large cranium, fronto-occipital prominence, small facies and chin, obtuse mandibular angle, high-arched palate, dental malocclusion with retained deciduous teeth, proptosis, and beaked and pointed nose (101). The French impressionist painter Henri de Toulouse-Lautrec is thought to have been affected by this disorder (102). The anterior fontanel and other cranial sutures may remain open. Fingers are short and clubbed from acro-osteolysis or aplasia of the terminal phalanges. The thorax is narrow, and patients may have pectus excavatum, kyphoscoliosis, or lumbar lordosis. Sclerae may be blue. Recurrent fractures typically affect the lower extremities and cause genu valgum, with adult height ranging between 4'3" and 4'11". Similar to osteopetrosis, the skeleton becomes uniformly osteosclerotic in childhood, and osteosclerosis increases with age (103). Laboratory studies show normal serum calcium, phosphorus, and alkaline phosphatase, without anemia. There is no established medical therapy for this disorder.

In summary, the selected rare bone diseases described are of interest in that they offer significant insight into the pathophysiology underlying bone loss or increased bone density. Rare bone diseases may lead to bone loss owing to mutations affecting collagen synthesis or processing, decreased alkaline phosphatase activity causing decreased bone mineralization, increased FGF-23 expression causing decreased serum phosphorus and osteomalacia or rickets, or increased Notch2 activity stimulating osteoclast activity and acro-osteolysis. Other rare bone diseases may result in increased bone density due to decreased parathyroid hormone activity leading to low bone turnover and increased mineralization, or mutations causing decreased cathepsin K activity leading to decreased bone resorption by osteoclasts. Greater understanding of these and other rare bone diseases will lead to specific treatments for individuals

affected by them, but also help select targets for therapy for more common bone diseases.

Update on DXA Measurements for Assessment of Skeletal Health

John Shepherd, PhD

There is growing concern that men and women at high risk of hip fracture are not receiving treatment that would lower their risk. An editorial from Khosla and Shane (39) referred to this as a crisis in the treatment of osteoporosis. Despite the availability of many medications proven to reduce fracture risk, they are commonly not taken long enough to achieve the expected benefit. In addition, Overman et al (104) have shown that there has been a steady linear decline in the number of DXA examinations being performed since 2009 that parallels the decreases in DXA reimbursement. Even though the number of DXA examinations has been declining in the United States, this should not be viewed as a reflection on the utility of the technology. Over the past 10 years, we have seen many new features and guidelines for DXA.

The ISCD Position Development Conferences (PDCs) provide guidance on how to use DXA. The most recent PDC was in 2015 and covered the topics of non-BMD measures of fracture risk, including trabecular bone score (TBS), hip geometry, and computed tomography measures (105). The ISCD is continually looking for ways to clarify the diagnosis and monitor bone diseases using densitometry. At the 2016 ISCD annual meeting in Galway, Ireland, as well as at this Santa Fe Bone Symposium, candidate topics were proposed for the next PDC, which include the following: a general review and update of all ISCD Official Positions to ensure they are consistent with current practice; reconsideration of the use of 1/3 radius *T*-score for diagnosing osteoporosis; creation of guidelines for bone assessment in diseases other than osteoporosis, including rare diseases that impact bone health; guidance on the use of the dual hip scan mode; and consensus protocol and guidelines in using DXA for safety monitoring of rare side effects of treatment such as onset of ONJ and AFFs. With respect to safety monitoring, there are scan modes available on both General Electric and Hologic systems for scanning the entire femur to look for radiographic precursors of AFF (beaking and cortical thickening).

Also from the ISCD annual meeting, guidance was proven on potential clinical applications of TBS. This is a gray-level texture metric extracted from DXA spine scan images. TBS provides additional fracture risk information beyond BMD alone (106) and is compatible with the fracture risk assessment tool (107). However, there had not been population reference data available for TBS. Following the release of the National Health and Nutrition Examination Survey TBS data (108), Fan and Shepherd presented reference data values for men and women of 4 ethnicities from age 20–85 years (109). Some general findings

include TBS decreases with age in all sex or ethnicity groups; there were no overall differences by sex, and all combinations of vertebrae produced similar TBS reference curves by age.

Another advancement in DXA analysis technology is software that generates 3-dimensional (3D) representations of the proximal hip from a DXA scan, based on the work by Whitmarsh et al (110,111). A first reporting shows that the finite-element stiffness derived from DXA-based 3D images is similar to the same measures from computed tomography images ($r^2 = 0.85$) (112). The same 3D technique can be used to create 3D lumbar spine images from DXA 2D images. The novelty of this approach is apparent, but the clinical value, besides 3D printing of a patient's spine, is yet to be determined.

There is growing use of DXA to monitor multiple risk factors for falls and hip fracture including sarcopenia, osteosarcopenia, and sarcopenic obesity. Nine definitions of sarcopenia were recently compared (113). The definitions that best predicted falls were based on low lean mass alone and low lean mass plus decreased functional performance. People with osteoporosis and sarcopenia have lower physical performance and higher bone turnover, increasing the risk of falls that can result in fractures (114). Furthermore, older obese women who were also sarcopenic (sarcopenic obesity) have been found to have a 2.6-fold higher risk of difficulty climbing stairs and other daily functional assessments than their peers with healthy body composition (115). In short, DXA can aid in the assessment of overall falls risk and skeletal health of older adults using multiple measures of bone, fat, and lean tissues. Measuring bone for osteoporosis, lean mass for sarcopenia, or percent fat for obesity, in isolation of the other measures, creates an incomplete understanding of personalized falls and fracture risk.

Another publication of note is by Malkov et al (116), who demonstrated that DXA cannot measure muscle density for hip fracture risk assessment, but can report thigh subcutaneous fat. They found that for a given BMD, men with high appendicular lean mass (top 50th percentile) and low subcutaneous fat mass (bottom quartile) have an 8-fold higher risk of hip fracture than those with low appendicular lean mass (bottom 50th percentile) and high subcutaneous fat (top quartile). In women, this effect was not nearly as strong with a 2-fold increased risk of hip fracture in the lowest quartile of hip fat with little or no differences seen by lean mass.

DXA is a potentially useful clinical tool to evaluate and monitor a variety of clinical conditions. However, its use in the United States has been declining in recent years, in part because of large reductions in DXA reimbursement resulting in the closure of many outpatient DXA facilities. Until reimbursement is restored to sustainable levels, we have to think of ways to use DXA as efficiently as possible. One concept is to create a single whole-body scan that provides high-spatial resolution dual hip BMD, lumbar spine BMD, and TBS values equivalent to those measured from

dedicated scans. Because the scan is a whole-body scan, one would also get appendicular lean mass for sarcopenia and percent body fat for obesity. Other metabolic risk factors such as visceral adipose tissue (117), trunk-to-leg volume ratio (118), and thigh subcutaneous fat (116) would also be reported. This one whole-body scan could replace all other DXA scans except for forearm and vertebral fracture assessment, making DXA more cost-effective and time efficient.

In summary, new topics are under consideration by the ISCD for inclusion in the next PDC. DXA can be used for monitoring of safety of osteoporosis treatments by detecting early radiographic signs of atypical femoral fractures. DXA has unique utility for quantifying falls risk using lean mass (sarcopenia) with bone status (osteosarcopenia) and fat status (sarcopenic obesity).

Osteoporosis Treatments for Fracture Healing

Susan Bukata, MD

Fracture healing is a complex process that occurs in multiple stages. Although we are very aware of the various stages involved in fracture healing, the exact biology at each step and the transition between stages have not yet been fully elucidated. It has been a concern of many practitioners that the medications we use to treat osteoporosis may interfere with fracture healing, but current evidence does not show this to be the case. However, we should be cautious in certain situations until more clinical evidence is available. An understanding of the effect of various osteoporosis medications on the fracture healing process may help physicians feel comfortable in counseling their patients to start medications early after a fragility fracture and to continue medications if they have a fragility fracture.

After bone is broken, there is bleeding at the injury site with the release of multiple growth factors and prostaglandins into the clot. Inflammation occurs and osteoclasts are activated to remove bony debris while early blood vessels begin to grow into the area of injury to reestablish a blood flow to the bone. Mesenchymal stem cells are recruited to the injury site and begin the stage of producing cartilaginous matrix known as primary callus or soft callus, which creates mechanical stability at the fracture site. This cartilage callus then becomes mineralized and converted to a hard, bony callus to complete the repair. This bony callus will then remodel until the bone has returned to a near-normal appearance, although this final remodeling stage can take many months depending on the fracture site and the age of the patient. This process of fracture healing resembles chondral bone formation that occurs during bone development and is often known as secondary fracture healing because it goes to a cartilage phase before being transformed into new bone. Most fractures heal this way as there is some mechanical instability at the fracture site that stimulates the formation of the cartilage callus to quickly fill in the gap between the fracture fragment ends. Stress fractures, on the other hand, do not have this and

rely on the process of primary bone healing through which osteoclasts resorb bone at the site of the fracture and introduce primary remodeling to repair the fracture. This relies on the osteoclasts to create cutting cones across the fracture site followed by osteoblastic bone formation to repair the fracture (119). Stress fractures and bone healing that occur with this pattern of primary bone healing may have some issues with certain osteoporosis medications, although definitive clinical data are lacking.

There is no clinical data available regarding estrogen's effect on fracture healing, but it is known to influence both osteoblast and osteoclast functions. Animal models in mice and rats demonstrate similar changes in response to estrogen levels. In ovariectomized animals, the callus shows impaired formation around the periosteal rim and an overall decreased cartilage callus area. Overall, the callus is unstructured and less dense, and the cortex at final healing is thin and porous. Giving estrogen to these animals still results in less callus than in control animals, but it is more compact and dense with an increased trabecular structure and endosteal bone formation along the cortex (120). The selective estrogen receptor modulator raloxifene also does not have any clinical data regarding fracture healing, but in a rat model, raloxifene enhanced bone formation throughout the callus, including both the endosteal and the periosteal portions of the cortex. Both estrogen and raloxifene improved mechanical properties at the fracture site when compared with ovariectomized animals, further emphasizing that even the loss of estrogen (with ovariectomy) changes fracture healing patterns, but still results in a healed fracture (121).

Bisphosphonates primarily affect the activity of osteoclasts. When administered, bisphosphonates will concentrate in the area of highest bone turnover. Radio-labeled bisphosphonates will often concentrate in a fracture site, leading to concerns about their influence on fracture healing. In rodent fracture models, ovariectomized animals treated with a variety of bisphosphonates demonstrated increased fracture callus volume, but because of the increased size of the callus, the callus behaved biomechanically equivalent to a normal callus seen in a control animal (bending and torsional strength are related to the radius of the callus to the third and fourth power respectively, so small increases in the radius result in significant changes in strength). Microscopic subsections of the fracture callus demonstrated decreased strength with less organization, fewer trabeculae, and generally more immature cartilage compared with normal callus (122). In rats given intravenous bisphosphonates either as a single bolus dose or as a divided dose weekly for 5 weeks, the bolus dose again demonstrated increased callus size, but no delay in endochondral ossification and only a slight slowing of hard callus remodeling to bone when compared with controls were observed. The weekly dosing also showed increased callus volume and no delay in endochondral ossification, but remodeling was slow compared with controls, and this delay persisted for an extended period, even after drug was

stopped (123). Clinical data are generally retrospective, and with hip fractures, wrist fractures, and high tibial osteotomies, there appeared to be no difference in time to healing or nonunion rate for patients receiving bisphosphonate compared with either placebo group or no treatment group (124,125). In children with OI, 2 separate studies suggested some evidence of delayed fracture healing in patients with osteotomies of the diaphyseal portions of bone and in more mature children (126). Bisphosphonates have also been shown in a small study of distraction osteogenesis (limb lengthening) and in hypertrophic nonunions to potentially be helpful in completing healing and improving BMD in the newly formed bone (127).

Denosumab is an RANKL inhibitor that also decreases osteoclast function. There are no clinical data currently reported with respect to denosumab and fracture healing. A mouse fracture model demonstrated increased callus volume, delayed callus remodeling, and increased BMD in callus tissue, but did not demonstrate compromise in mechanical properties (128). Patients in clinical trials treated with denosumab have not demonstrated difficulties in healing fractures that occur during these trials. AFFs have occurred in patients during treatment with both bisphosphonates and denosumab, although 10% of AFFs occur in patients who have not taken any osteoporosis medications. AFFs are unique in that they are tension stress fractures and some of the patients with these fractures have demonstrated delays in healing at the fracture site even if the bisphosphonate or denosumab treatment is stopped. The exact etiology of that delay is not currently clear.

Anabolic agents stimulate bone formation through the osteoblast and have the potential not only for normal fracture healing, but also for possibly enhanced fracture healing. Teriparatide is currently the only anabolic agent available for patient treatment. It has been shown to stimulate mesenchymal stem cell recruitment and osteoblast differentiation, vascular endothelial growth factor expression, and signaling pathways similar to prostaglandins that are involved with normal fracture healing. Rodent fracture healing models demonstrated enhanced callus, bone mineral content, BMD, cartilage formation, and increased mechanical strength at the fracture site with teriparatide treatment (129). A clinical trial of teriparatide and wrist fracture healing showed no differences in the time to bridging of 3 or 4 cortices between the 40 µg daily and the control group, but an improvement was observed in the 20 µg group. The 20 µg group showed early callus formation compared with controls (130). A trial with 1–84 PTH and pelvic fractures showed that by 8 weeks, all the PTH-treated patients had healed, but only 4 of the control patients had healed (131). PTH-treated patients had improved pain and return to function. Future anabolic agents working through the Wnt signaling pathways also demonstrate improvements in bone healing in animal models, with no interference in bone healing in human clinical trials. DKK-1 antibody in a mouse model increased callus volume, BMD, bone mineral content, and biomechanical strength, but these

improvements are lost if the treatment is not started immediately after fracture, demonstrating that timing of treatment is essential with this agent (132). Anti-sclerotin antibody in both a rat model and a monkey model demonstrated increased bone mass, increased bone strength, more bone formation, smaller fracture gaps, more advanced remodeling of fracture callus, and increases in trabecular bone volume at fracture healing sites (133). Novel anabolic agents will receive increased attention as they receive approval for clinical use.

Overall, all of the data provided by animal models and clinical trials demonstrate that osteoporosis medications do not interfere with fracture healing. Agents may change the pattern of the fracture healing in the callus itself, but they do not arrest the healing process. Some anabolic agents may enhance fracture healing, but more data are needed. In general, osteoporosis medications can be started immediately following a fracture, with 2 caveats: (1) intravenous bisphosphonates should not be given within the first 2 weeks after a fracture, not necessarily because they interfere with fracture healing, but because medicine given early after the fracture does not provide anti-fracture protection to the remainder of the skeleton, which is the principal goal of treatment with the medication. This is not a fracture healing problem but rather a problem in obtaining adequate treatment for osteoporosis and future fracture prevention; and (2) stress fractures, which rely on primary bone healing, may have some difficulties with healing with bisphosphonates or other agents that severely suppress osteoclast function. Further clinical data are needed, but at this time, it is generally advised to wait for a stress fracture to heal before starting bisphosphonates for osteoporosis treatment.

It is important to start patients on osteoporosis medications as soon as possible after a fragility fracture as they have a clearly demonstrated increased risk of future fracture, and the overall data are reassuring that these medications will not interfere with healing of that fragility fracture.

Update on Bone Health ECHO

E. Michael Lewiecki, MD

Bone Health ECHO, developed at the University of New Mexico Health Sciences Center through the collaboration of the ECHO Institute and the Osteoporosis Foundation of New Mexico, uses a teleconferencing platform to link healthcare professionals in underserved communities with experts in the care of skeletal diseases (134,135). Weekly 1-hour case-based learning sessions with brief didactic presentations have been held since October 6, 2015. By moving knowledge rather than patients, ECHO learners (e.g., physicians, nurse practitioners, physician assistants) can provide better care closer to home at greater convenience and at a lower cost than referral to a specialty center. The Bone Health ECHO concept can be applied to advancing skeletal healthcare knowledge for residents and fellows training at institutions lacking local expertise, for fracture liaison services

coordinators, and for healthcare professionals located anywhere electronic communication is available. ECHO aims to be a force multiplier in the United States and worldwide through replication in many locations to reach greater numbers of healthcare providers who manage many patients. It is very different from telemedicine, which typically involves 1 physician treating 1 patient at a remote location.

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