25

Metabolic Bone Diseases

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INTRODUCTION

Orthopaedic surgeons need to have a fundamental understanding of the metabolic bone diseases discussed in this chapter because these diseases compromise bone strength and increase fracture risk, including fragility fractures. A considerable number of patients treated by orthopaedic surgeons, particularly in the population older than 50 years, are at risk for a metabolic bone disease, including those patients who seek elective orthopaedic care, such as joint replacement and spine surgery. Compromised bone strength can contribute to the failure of surgical fixation and stability of the implant-bone interface. Knowledge of the diagnostic modalities and pathophysiology will help orthopaedic surgeons take an active role in the diagnosis and treatment of these diseases and the avoidance of surgical complications.

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SYSTEMIC CALCIUM HOMEOSTASIS

Maintenance of serum calcium concentration is a homeostatic priority because cell membrane signaling and neuromuscular signal transmission are highly sensitive to serum and extracellular calcium concentrations. Cellular responses to several hormones, excitation-contraction coupling in cardiac muscle, and skeletal muscle contraction depend upon calcium concentrations within a narrow physiologic range. To accomplish this homeostatic priority, three organ systems, gastrointestinal, renal, and skeletal, the parathyroids, parathyroid hormone (PTH), and vitamin D ($1,25(OH)_2D$), interact in an elaborate series of physiologic mechanisms to regulate serum calcium concentration.[1] Vitamin D and PTH maintain the concentrations of ionized calcium and phosphate at levels consistent with normal neuromuscular function and within safe range of the solubility product of $CaHPO_4$.

Among the organs supporting serum calcium, bone is unique in that its role as a calcium donor can compromise its structure and lead to fracture. Among the physiologic roles of bone, its role as a calcium donor can take precedence over its structural roles leading to the perspective that the primary function of bone is as the calcium reservoir for serum calcium concentration. Because of the priority to maintain serum calcium concentration, needs for serum calcium or disorders of the integrated physiologic mechanisms to support serum calcium can lead to loss of calcium from bone characterized as metabolic bone diseases, loss of bone mass, structural failure, and fracture. A type of fracture seen with decreased bone density is the fragility fracture defined as a fracture due to a fall from a standing height or with minimal trauma.

CALCIUM

Serum calcium exists in serum in two general forms—ionized and protein bound, binding usually to albumin. Calcium in the ionized form is metabolically active, essential to cell membrane signal transmission. Calcium can also be bound to phosphate in serum and the resulting salts are essential for healthy bone and tooth matrix. However, phosphate binding of calcium in the gastrointestinal tract can prevent calcium absorption and phosphate binding in the serum can exceed the solubility product of calcium phosphate. Decreased serum calcium concentration, due to deficiency or the extra needs of growth, pregnancy, or lactation, stimulates a concerted response by bone, kidney, and gastrointestinal tract, modulated by PTH and vitamin D, to restore and maintain calcium concentration in its physiologic homeostatic range. Elevated vitamin D and PTH stimulate renal tubular reabsorption of calcium, phosphate diuresis, increased intestinal absorption of calcium, and osteolysis. Under these conditions, bone mineral density and mechanical strength may be sacrificed to maintain serum calcium concentration.

VITAMIN D

Vitamin D derives from two sources, calciferol, the major dietary source, and cholecalciferol which derives from 7-dehydrocholesterol. Both are irradiated in the skin which opens their sterol ring structure. Both calciferol and cholecalciferol undergo two hydroxylation steps. The first takes place in the liver and adds a hydroxyl group to the 25 carbon position to form 25(OH)D which is the storage form of vitamin D and the metabolite usually measured in serum. The second hydroxylation step takes place in the kidney at either the 1 or 24 position in the sterol ring. The 1,25(OH)D form is much more metabolically active than is the 24,25(OH)D form. Which position is hydroxylated is largely under the control of PTH and calcium that result in hydroxylation in the 1 position under a hypocalcemic stimulus. The active form of vitamin D, calcitriol ($1,25(OH)_2D$), is a steroid hormone that plays a crucial role in calcium homeostasis, in which it acts to raise serum calcium concentration. It enhances intestinal calcium and phosphate absorption and suppresses PTH secretion. In the kidney, it promotes diuresis of phosphate and stimulates tubular reabsorption of calcium. In bone, it transfers calcium to serum.

PARATHYROID HORMONE

PTH is a peptide hormone secreted by the parathyroid glands under the control of serum ionized calcium concentration. Under conditions of low ionized serum calcium, PTH is secreted and, with intact renal parenchyma, stimulates the production of 1,25(OH)D. Together, these two hormones act to raise serum ionized calcium concentration by increasing the renal tubular reabsorption of calcium, increasing calcium absorption in the small bowel, and mobilizing calcium from bone. PTH also reduces serum phosphate concentration by decreasing the tubular reabsorption of phosphate and promoting a phosphate diuresis. The consequences for bone are decreased mineral density and structural weakness to withstand physiologic stresses. Homeostatic mechanisms are less efficient in responding to hypercalcemia.[2]

KIDNEY

The kidney influences calcium homeostasis by controlling calcium and phosphate diuresis by tubular reabsorption of minerals. Diffusible calcium passes through the glomeruli and both PTH and vitamin D modulate the relative extents of tubular reabsorption of both minerals. Another important contribution of the kidney to calcium homeostasis is the second hydroxylation step of vitamin D. Under the influence of PTH, the second hydroxylation takes place at the 1 position in the sterol ring and results in the much more physiologically active 1,25(OH)D. In these ways, the kidney participates in a feedback loop that acts to raise serum calcium concentration under a hypocalcemic stimulus. Conditions that interfere with the kidney's role in calcium homeostasis can do so through (1) loss of renal parenchyma that results in a failure of the second hydroxylation of vitamin D to its active form and (2) tubular dysfunction resulting in a loss of calcium in the urine (diuresis) exerting a downward pressure on serum calcium concentration. Reductions in both active vitamin D and calcium availability stimulate secondary hyperparathyroidism that results in bone resorption and low bone mineral density.

GASTROINTESTINAL TRACT

Dietary intake of calcium varies widely. Absorption of calcium is regulated by vitamin D and PTH, both of which promote intestinal absorption to raise serum calcium. As vitamin D is fat soluble, it is dependent on intact bile salts for absorption in the proximal duodenum and proximal jejunum. Upper gastrointestinal disorders that interfere with fat digestion and absorption, notably, biliary and pancreatic disorders, can limit vitamin D absorption leading to deficiency.

BONE

Peak bone mass is attained in the third decade of life. Thereafter is a steady loss of bone mineral density (BMD) with an accelerated loss after menopause. Conditions that interfere with the attainment of peak bone mass, such as dietary deficiencies, anorexia, athletic amenorrhea, etc. can lead to age-associated osteoporosis in the later years of life. Physiologic needs for serum calcium that are unmet by other physiologic mechanisms place a downward stress on the calcium reservoir function of bone, leading to skeletal mineral depletion and reducing BMD and bone strength.

Four groups of metabolic bone diseases can lead to decreased bone density—osteoporosis, osteomalacia, renal osteodystrophy, and hyperparathyroidism.[2]

FRACTURE RISK ASSESSMENT AND DIAGNOSIS OF LOW BONE DENSITY

Fractures, especially hip fractures, not only cause mortality and morbidity, but also significantly increase health care costs. In 2005, $17 billion was spent for more than two million fractures in the United States, and the cost is expected to increase.[3] As a fracture is a multifactorial event, it is imperative to assess both skeletal integrity—bone quantity and quality—and the risk of falls when estimating fracture risk. All postmenopausal women, and men aged 50 years or older, should be screened for the risk of osteoporosis. Important clinical risk factors include age ≥65 years, early menopause (age ≤45 years), prior history of fracture, history of parents having a fracture, and a history of malnutrition or eating disorder during adolescence and puberty that potentially prevents the attainment of peak bone mass. Lifestyle factors such as smoking and excessive alcohol intake can also impair bone strength. Attention has been called to the role of falls in fracture risk[4] (**Figure 1**). Many medical conditions and medications can contribute to falls particularly those resulting in visual deficits, such as glaucoma and cataracts, dehydration, postural hypotension, or loss of balance (**Table 1**).

High-risk patients for osteoporosis and fracture (eg, women ≥65 years, men ≥70 years, or younger patients with significant risk factors) should be tested for low bone density.

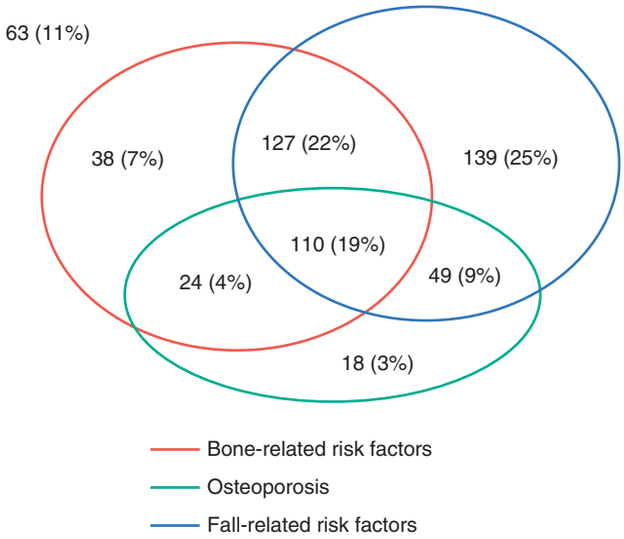

FIGURE 1 Illustration demonstrating the interactions of falls and low bone density in the fracture diathesis. Bone-related and fall-related risk factors interact with low bone density contributing to fractures. (Data from van Helden S, van Geel AC, Geusens PP, et al: Bone and fall-related fracture risks in women and men with a recent clinical fracture. *JBJS* 2008;90[2]:241-248.)

TABLE 1 Risk Factors for Fracture

Bone-Related Risk Factors	Fall-Related Risk Factors
• Fracture history	• > 1 fall last year
• Mother with fracture history	• Psychoactive drugs
• Body mass index (BMI) < 19	• Low level of activities of daily living
• Severe immobility	• Articular symptoms
• Glucocorticoids	• Impaired vision
	• Urinary incontinence
	• Parkinson Disease

Adapted from van Helden S, van Geel AC, Geusens PP, et al: Bone and fall-related fracture risks in women and men with a recent clinical fracture. *JBJS* 2008;90(2):241-248.

The most common method of assessment is dual-energy x-ray absorptiometry (DEXA) in which soft tissue is extracted from the density analysis. Bone mineral density (BMD) is expressed in g/cm^2 and is a planar rather than a volumetric measurement. BMD measured at any skeletal site is a strong predictor of hip or vertebral fracture. The Z-score compares density to an age- and sex-matched cohort; the T-score compares density to a reference group at age 20 years. The current diagnosis of low bone density and decision for treatment are often based on the T-score. Based on World Health Organization criteria, a T-score of −1.0 or above is considered normal, between −1.0 and −2.5 as osteopenia, preferably termed low bone mass, and −2.5 or below is categorized as "osteoporosis." Low BMD in the range of osteopenia or osteoporosis does not indicate a specific disease entity because DEXA does not discriminate between osteoporotic and osteomalacic bone structure. Metabolic bone histopathology can be highly characteristic and often diagnostic (**Figure 2**).

There are a number of helpful tools to assess fracture risk. Among them, the Fracture Risk Assessment Tool, or FRAX, is the most commonly used in clinical practice because it is well validated in large cohort studies and freely available (www.sheffield.ac.uk/FRAX/). FRAX predicts 10-year risks of hip fracture and major osteoporotic fractures (eg, spine, hip, proximal humerus, and distal forearm fracture) using easily accessible clinical risk factors for osteoporosis together with femoral neck bone mineral density in the FRAX calculation.

Measuring BMD using DEXA has inherent limitations because it measures areal BMD (aBMD, g/cm^2) not volumetric BMD (vBMD, g/cm^3). Patients with a smaller bone size, such as women or short individuals, can have lower aBMD despite having the same vBMD compared with age-matched counterparts. Additionally, artifacts from vertebral fractures, arthritic and degenerative changes (eg, sclerosis, osteophytes, osteochondrosis, etc), scoliosis, vascular calcification, laminectomy, and poor positioning can mislead clinicians with spuriously high or low results.

Importantly, DEXA does not assess bone quality, such as geometry, microarchitecture, trabecular connectivity, or bone turnover, which are critical determinants of bone strength. For that reason, large cohort studies have shown that skeletal health

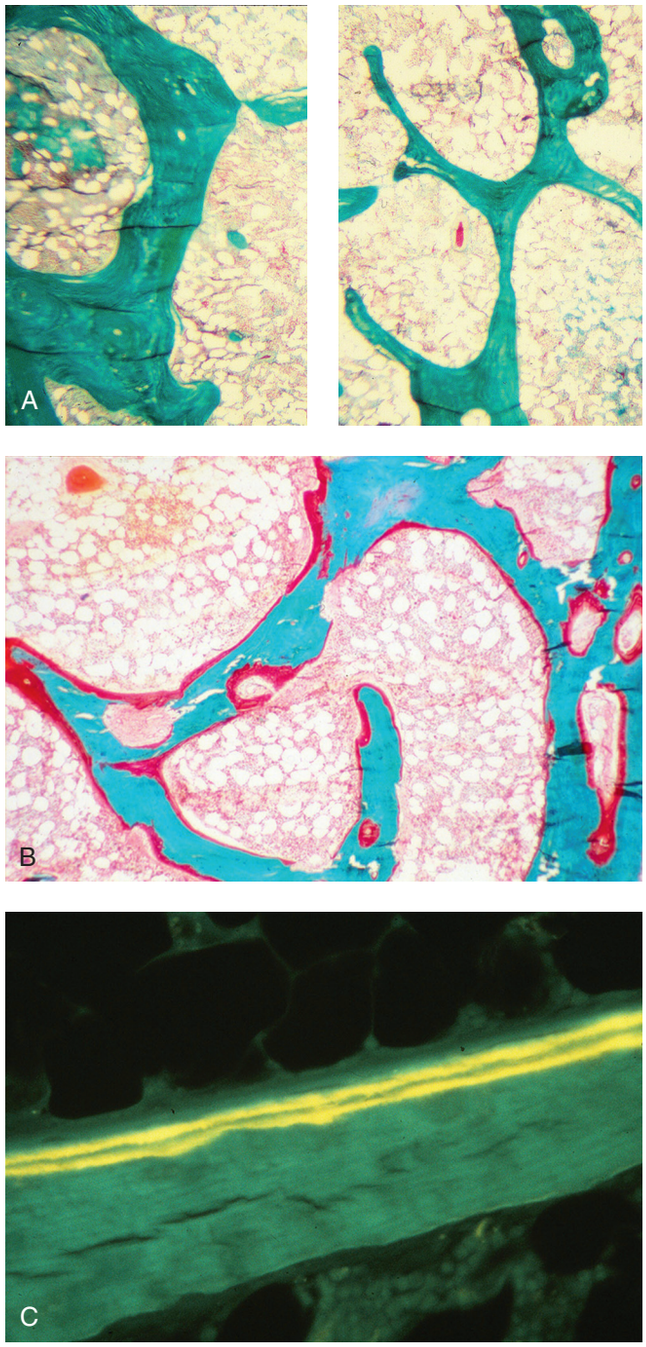

FIGURE 2 Metabolic bone histopathology. **A**, Trabecular morphology. (Left) Normal bone volume and trabecular thickness; (right) low bone volume (density) and thin discontinuous trabeculae. **B**, Osteoid borders. Trichrome stain demonstrating unmineralized osteoid (red) on trabecular surfaces. **C**, Mineralization front. Double tetracycline label is incorporated into the calcification front, fluoresces under ultraviolet light, and reveals the rate of bone formation.

assessment based on BMD alone underestimates the risk of fracture. The Manitoba Bone Density Program cohort showed that more than 60% of fractures in postmenopausal females occurred with normal BMD or low bone mass.[5] Importantly, patients with type 2 diabetes have significantly high risks of fracture despite having normal or even high BMD.[6]

MEASURING BONE QUALITY

Advances in imaging techniques and bioengineering allow the study of bone quality parameters without invasive bone biopsy (**Table 2**). Trabecular bone scoring (TBS) is an indirect measurement of trabecular bone structure. This software analyzes conventional DEXA lumbar spine images and quantifies gray-scale values of each pixel. Dense trabecular structure yields high TBS scores, whereas porous trabecular bone produces a low TBS score. TBS has been validated in postmenopausal women and in older men.[7]

Quantitative ultrasonography (QUS) measures the attenuation of sound waves and the speed of sound through bone tissue and provides information on mechanical properties such as bone stiffness and elasticity. QUS of the calcaneus predicted the risk of osteoporotic fractures and discriminated between patients with or without fragility fractures.[8]

CT-based technologies are capable of assessing skeletal microarchitecture. A reconstructed three-dimensional image of femur or vertebra from low-resolution quantitative volumetric CT (QCT) provides not only vBMD but also geometry and structure. vBMD using QCT has demonstrated better predictive value than aBMD in postmenopausal women receiving long-term glucocorticoids.[9] However, measuring axial bone density using QCT is associated with significant radiation exposure compared with DEXA. High-resolution peripheral QCT (HR-pQCT) has a high spatial resolution up to ~40 μm (thickness of a single trabeculae is 100 to 150 μm and of the cortex is ~500 μm) and separately examines cortical and trabecular compartments. Trabecular connectivity and cortical porosity can be assessed.[10] Evaluating the cortical component provides

TABLE 2 Techniques for Measuring Material Properties of Bone

Techniques	Parameters
• DEXA with trabecular bone Scoring	• DEXA quantifies bone density • TBS assesses trabecular microarchitecture of the lumbar spine
• Quantitative ultrasonography	• Quantifies bone mechanics
• Quantitative CT	• Assesses bone microarchitectures
• High-resolution peripheral QCT	• Assesses microarchitecture and cortical porosity
• Indentation testing	• Measures resistance to plastic deformation

DEXA = dual energy x-ray absorptiometry, TBS = trabecular bone scoring, QCT = quantitative volumetric CT

important insight in understanding the pathophysiology of secondary osteoporosis. For example, patients with type 2 diabetes have normal or high trabecular bone density, but significantly increased cortical porosity that might explain the increased risk of fracture in this group.[11] The major drawback of HR-pQCT is that it examines only peripheral appendicular bone.

Indentation testing permits studying the material properties of bone. A rigid indenter with a depth-sensing indenter tip applies a determined force into smooth and flat areas of interest (tibial midshaft). The resulting impression quantifies resistance to plastic deformation and characterizes mechanical properties with an order of individual trabeculae and osteons. With a higher spatial resolution, nanoindentation can examine bone structures as small as individual lamellae and lacunae (~1 μm).[12]

OSTEOPOROSIS

Osteoporosis is the most common cause of low bone density and is associated with low energy or, fragility, fractures. In the United States alone, 40 million adults suffer from osteoporosis or low bone density.[13] Osteoporosis is characterized by low bone volume, endosteal resorption, cortical thinning and increased porosity, and trabecular thinning and loss of connectivity (**Figure 3**). Deterioration of bone microarchitecture significantly reduces bone strength and increases the risk of fracture. Radiographically, trabecular resorption is characteristic and endosteal resorption is seen as widening of the medullary canal (**Figure 4**).

Once osteoporosis is diagnosed, possible secondary causes should be sought and treated. Vitamin D deficiency (discussed below) is very common and can be diagnosed by measuring the storage form of vitamin D, (25(OH)D). Other conditions can result in low bone density and mimic osteoporosis including prominently the endocrine disorders, hyperparathyroidism, hypercortisolism, hyperthyroidism, diabetes, and hypogonadism. A variety of other conditions including premature menopause, anorexia nervosa, athletic amenorrhea, immobilization, and alcohol abuse can also result in osteoporosis. Other, more rare conditions that include osteoporosis are discussed in Chapter 25. Medications can also contribute to osteoporosis (**Table 3**). Important conditions associated with low bone mass are hormonal therapies, organ transplantation, and immunosuppression.

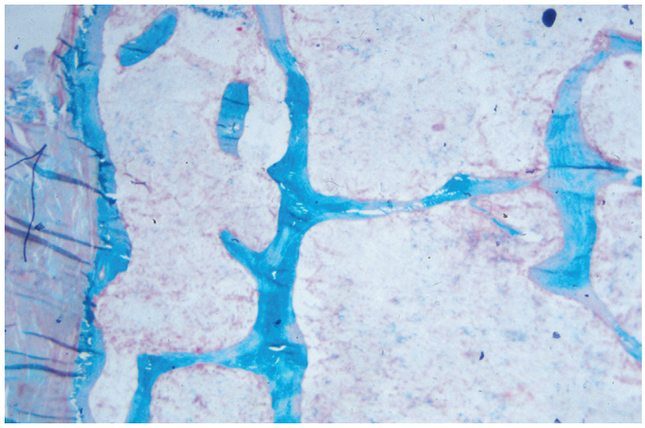

FIGURE 3 Histologic image of osteoporosis histology. Osteoporotic bone exhibits low bone volume, cortical thinning, and thin, discontinuous trabeculae.

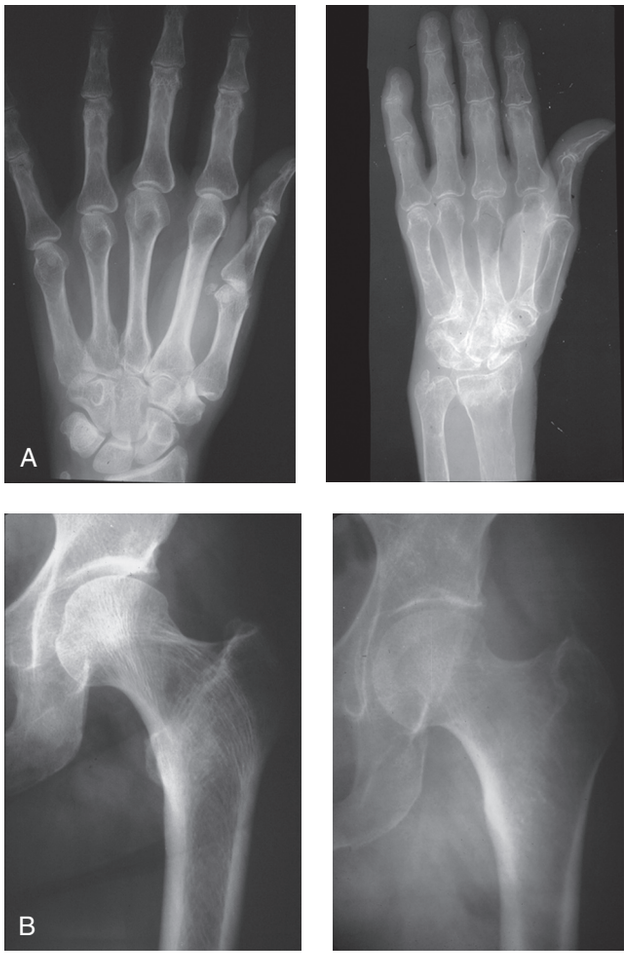

FIGURE 4 Radiographs of osteoporotic bone (**A**) Hand. In normal bone, the two cortices of the third metacarpal of should occupy about ½ the width of the bone (left). Osteoporotic bone exhibits endosteal resorption of the cortices and widening of the medullary canal (right). An incidental distal radius fracture is seen. **B**, Hip. In the normal proximal femur, thick cortices and well-defined trabeculae are seen (left). In the osteoporotic proximal femur, trabeculae are not distinct due to resorption (right).

HORMONAL THERAPY

Adjuvant hormonal therapy for prostate or breast cancer can significantly decrease BMD and increase the risk of fracture. Androgen deprivation treatment using gonadotropin-releasing

TABLE 3 Medications Contributing to Osteoporosis

- Glucocorticoids (≥5 mg/d prednisone or equivalent for ≥3 mo)
- Proton pump inhibitors
- Heparin
- Oral hypoglycemics: thiazolidinedione, SGLT-2 inhibitors
- Anticonvulsants: phenobarbital, phenytoin, carbamazepine
- Immune-modulating agents: methotrexate, tacrolimus, cyclosporine
- Hormonal suppressive agents: GnRH, aromatase inhibitors, tamoxifen
- Thyroid hormone (over treatment)

hormone agonist/antagonists in patients with prostate cancer decreases BMD and increases fracture risk. Loss of bone is noted in multiple skeletal sites including trabecular and cortical bone.[14] Aromatase inhibitors used for breast cancer deprive the skeleton of estrogen and elevate follicle-stimulating hormone (FSH), decreasing BMD and increasing the risk of fracture compared with tamoxifen treatment.[15]

ORGAN TRANSPLANTATION AND IMMUNOSUPPRESSION

End-stage organ failure and organ transplantation-related osteoporosis have gained much attention as survival rates have improved. Transplantation related bone loss occurs mostly in the first 3 to 6 months post-transplant. A significant decline in lumbar spine BMD has been observed (6.8%) during the first 6 months after renal transplantation, which accounts for most of the bone loss (8.8%) over 18 months. BMD in the radial shaft did not show significant bone loss within 6 months,[16] suggesting that trabecular bone is more affected than is cortical bone during the initial posttransplantation period. This acute, rapid and severe bone loss after renal transplantation is caused by multiple factors, including immunosuppressant-induced bone loss, immobilization, vitamin D deficiency, preexisting osteodystrophy, and hyperparathyroidism.[17]

The pattern of acute, rapid, and severe bone loss is also notable in orthotopic liver transplantation.[18] As expected, the decrements in BMD in transplant patients pose a significant risk of fracture that is especially high in the early posttransplant period.[19]

Pretransplant BMD and duration of use of glucocorticoids are the key determinants of the high risk of fracture. Glucocorticoids reduce bone formation primarily by inhibiting osteoblast differentiation and cause apoptosis of osteocytes. Another group of commonly used immunosuppressants, calcineurin inhibitors such as cyclosporine (CsA) and tacrolimus (FK506), also negatively affect bone. They inhibit the activity of the enzyme, calcineurin, which is expressed in osteoblasts and osteoclasts and plays a key role in bone remodeling. Inhibiting calcineurin resulted in increased bone resorption and trabecular bone loss in in vivo study.[20] Patients with cyclosporine monotherapy showed increased osteoclastic activity and decreased osteoblastic bone formation based on histomorphometry.[21] The mammalian target of rapamycin (mTOR) inhibitor, rapamycin, is considered safer, as it does not show significant bone loss compared with cyclosporine.[22] Another immunosuppressant, mycophenolate mofetil (MMF), did not cause bone loss measured by histomorphometric parameters but suppressed osteocalcin levels.[23]

OSTEOPOROSIS PHARMACOTHERAPIES

In osteoporosis, the balance of bone homeostasis favors bone resorption, resulting in bone loss. Therefore, the initial goal is to slow down accelerated resorptive activity with antiresorptive agents and thus restore homeostatic balance of bone formation and resorption to prevent further bone loss. Osteoporosis, however, is characterized by microstructural damage. Therefore, repairing the structural defects is the next goal and anabolic agents, intermittent parathyroid hormone (PTH) administration and PTH-related peptide (PTH-rP) analogue, have reparative effects on bone microarchitecture.

Calcium and Vitamin D Supplements

The importance of vitamin D and calcium for bone health is well established, and deficiencies should be corrected before pharmacotherapy for osteoporosis. Although controversial, the routine use of vitamin D and calcium supplementation has recently been questioned because of a possible increased risk of cardiovascular disease with high calcium intake. Current guidelines advise 1,200 mg of calcium daily (total diet plus supplement) and 800 IU of vitamin D daily for postmenopausal women with osteoporosis.

Estrogen

Estrogens are important in maintaining skeletal homeostasis during growth and development and bone mass during adulthood. Loss of estrogens at menopause causes increased bone remodeling rates and bone loss. Indirectly, estrogens affect the differentiation of osteoclasts by reducing the actions of the receptor activator of nuclear factor-κβ (RANK) system. At menopause, the RANK-RANK ligand (RANKL) system is overactive which stimulates osteoclast development and activity and results in accelerated bone loss. It takes several years for the imbalance caused by the loss of estrogens to reach a new steady state and the rapid bone loss to subside.[24] Hormone replacement therapy had been the mainstay of therapy of postmenopausal osteoporosis for many years but the findings of the Women's Health Initiative study in 2002 marginalized their use. Estrogen with progesterone in women with an intact uterus has been associated with increased risk of breast cancer and cardiovascular events including heart attack and stroke. The use of estrogen alone in women who have had a hysterectomy showed a significantly decreased risk for breast cancer, but the

risk of cardiovascular disease and venous thromboembolism (VTE) persisted. Both estrogen with progesterone and estrogen alone showed a clear reduction in fracture risk from 30% to 70% depending upon anatomic site.[25] While estrogens are effective in relieving menopausal symptoms and preventing perimenopausal bone loss, their use as first-line therapy in osteoporosis is no longer recommended from the risk-benefit perspective.[26]

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are a diverse group of compounds with tissue-specific estrogen receptor agonist or antagonist activity; they are agonists to bone while being antagonists to breast. They decrease bone loss as well as the risk of breast cancer in women. The first SERM developed specifically for osteoporosis treatment was raloxifene, an estrogen agonist in bone and liver. It does not stimulate the endometrium and is a potent antagonist in the breast. In the large Multiple Outcomes of Raloxifene Evaluation (MORE) trial, eight years' follow-up of a total of 7,705 women demonstrated significant increases in BMD at the spine and hip and a significant reduction in vertebral fractures.[27] Their main drawback is perimenopausal symptoms such as hot flashes and an increased risk of VTE.

Diphosphonates

Diphosphonates are the first line of treatment for osteoporosis. Diphosphonates are analogues of pyrophosphate, bind to the surface of hydroxyapatite crystals in bone, and inhibit osteoclastic bone resorption. Their antiresorptive action results from both their affinity for bone mineral and their inhibitory effect on osteoclasts. Not all diphosphonates operate through the same mechanisms. Non-nitrogen-containing diphosphonates such as etidronate or clodronate act as metabolized cytotoxic molecules in the osteoclast that cause loss of mitochondrial membrane potential and apoptosis. Clodronate has been used mainly in the treatment of bone metastases. Nitrogen-containing diphosphonates, such as alendronate, risedronate, ibandronate, and zoledronate are currently used as the first-line treatment for osteoporosis. When internalized by the osteoclast, these compounds inhibit farnesyl diphosphonate synthase, interfering with the formation of the "ruffled border" of osteoclasts that is necessary for forming resorptive pits where bone resorption occurs.[28]

Randomized controlled trials have shown that alendronate (Fosamax), risedronate (Actonel), and zoledronate (Reclast) reduce the risk of vertebral, nonvertebral, and hip fractures, whereas ibandronate (Boniva) showed antifracture efficacy only at vertebral sites.[14,29,30] This difference arises primarily from trial design and the study population. Alendronate and risedronate are available in oral form only; zoledronate is available for intravenous use only; and ibandronate in both forms. Although diphosphonates share several common properties as a drug class, there are chemical, biochemical, and pharmacological differences among them in binding affinities for bone mineral, which may influence their distribution within bone, potency, and duration of action. These differences may be clinically relevant in terms of the onset of fracture reduction, efficacy at different skeletal sites, and the degree and duration of reduction of bone turnover. For example, diphosphonates with higher binding affinity and potential retention, such as alendronate and zoledronate, are associated with greater reduction of bone turnover with longer residual effect after discontinuation. In patients who were treated with alendronate for 5 years, bone turnover markers remained reduced, well below premenopausal levels, for up to 5 years after discontinuation. Following a single infusion of zoledronate, bone turnover markers were suppressed for three or more years. However, in patients treated with a lower binding affinity diphosphonate, such as risedronate, bone turnover markers returned to pretreatment levels within 1 year after discontinuation. No clinical trials have directly compared the clinical efficacy of individual diphosphonates with fractures as an end point.

Diphosphonates are highly effective and safe. GI intolerance (oral diphosphonates), renal impairment (IV diphosphonates), and acute-phase reactions, particularly after the first IV administration, are common. Rare events such as osteonecrosis of the jaw and atypical femur fractures (AFFs) have generated concern although a mechanistic association with diphosphonates has not been fully established. The American Society of Bone and Mineral Research (ASBMR) defined AFFs as stress fractures with specific characteristic radiographic findings. The fracture may have a localized periosteal or endosteal thickening, or an incomplete fracture, of the lateral cortex. The completed fracture is located in the femoral diaphysis, originating at the lateral cortex with a transverse orientation and is noncomminuted.[31] Although the absolute risk of AFFs with diphosphonate use is minimal, the association of prolonged diphosphonate use and an increased risk of AFFs is clear. The age-adjusted incidence rates were 1.78/100,000 per year with less than a 2-year treatment compared with rates of 113.1/100,000 per year with treatment for 8 to 9.9 years.[32] Although antifracture efficacy of the short-term (3 year) diphosphonate treatment clearly outweighs the risk of AFFs, benefit beyond 5 years of diphosphonate use is not clearly shown mainly due to limited long-term data. In 2016, the ASMBR task force offered guidance for long-term diphosphonates and "drug holiday" in terms of risk/benefit assessment. The optimal duration of treatment should be based on individualized fracture risk. The optimal duration of a "drug holiday" has not been clearly defined.[33]

Denosumab

Denosumab (Prolia) is the first drug targeting RANK/RANKL/OPG signaling pathway that controls osteoclast differentiation. Denosumab is a human monoclonal antibody that acts as a "decoy" receptor for RANKL. It blocks RANK-RANKL interaction and thereby inhibits the differentiation and activation of osteoclasts. However, it lacks the bone selectivity of the diphosphonates. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM)

phase III clinical trial, including 7,808 postmenopausal women with osteoporosis, denosumab significantly reduced vertebral, nonvertebral, and hip fractures by 68%, 20%, and 40%, respectively, compared with placebo. Further studies involving over 12,000 patients have confirmed the efficacy and overall safety of denosumab out to 10 years of treatment. Denosumab also increased BMD at the total hip, femoral neck, and lumbar spine and reduced markers of bone turnover to a significantly greater extent than did oral diphosphonates in women who were naïve to diphosphonates or had switched from alendronate to denosumab.[9] However, anabolic claims for denosumab have not been confirmed in histomorphometric studies from postmenopausal women with osteoporosis treated with either denosumab or teriparatide.[34] The effects of denosumab rapidly reverse on discontinuation,[35] so that ensuring compliance is important if benefits are to be sustained.

Unlike diphosphonates that are cleared intact through the kidneys, the clearance of denosumab is not dependent on renal function. Rare cases of osteonecrosis of the jaw and AFFs have been described in patients on denosumab, although, like diphosphonates, no clear mechanism has been uncovered. In the FREEDOM study, serious infections leading to hospitalization were reported more frequently in the denosumab than in the placebo group. Serious skin infections, as well as endocarditis, and infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with denosumab. It is thus prudent to avoid denosumab in patients on concomitant immunosuppressant agents or with impaired immune systems, who may themselves be at increased risk for serious infection.[9]

Calcitonin

Calcitonin is a hormone secreted by the C cells of the thyroid gland. It acts directly on the osteoclast and causes a change in its shape and structure and temporarily ceases its resorptive activity. The injectable form, initially used for the treatment of Paget disease, has been replaced by a nasal spray. The antifracture effects are weak in osteoporotic patients and its use has been superseded by more effective treatments. Recent studies with oral calcitonin have also proved disappointing.[36]

Parathyroid Hormone and Parathyroid Hormone-Related Peptide

Parathyroid hormone 1 to 34, teriparatide (Forteo) and the recently approved PTH-rP analogue, abaloparatide (Tymlos), are the only anabolic agents for osteoporosis treatment. Teriparatide is a recombinant PTH consisting of the first (N-terminus) 34 amino acids, which is the bioactive portion of the hormone. Osteoblasts and preosteoblasts express PTH1R, the receptor for PTH, which is also expressed in renal tubular cells in kidney. Intermittent daily administration of PTH stimulates bone formation at a greater rate than bone resorption, resulting in a net anabolic effect on bone. The anabolic effect of PTH leads to bone formation in cortical and trabecular compartments and reconnection of disrupted trabeculae.

Teriparatide

In osteoporotic women with a history of fractures, daily subcutaneously administered teriparatide decreased the risk of vertebral and nonvertebral fractures and increased the vertebral, femoral, and total body BMD with a median duration of 21 months of treatment. Compared with the placebo group, a 20 µg regimen increased BMD at the lumbar spine by 9% and at the femoral neck by 3%; BMD at the distal radius did not change. Significant improvements in trabecular bone microarchitecture have also been observed. The bone formation marker, N-terminal propeptide of type 1 collagen (P1NP), peaked between 6 and 12 months followed by a plateau at significantly above baseline levels up to 36 months. There was a rise in circulating carboxyl-terminal collagen cross-links (CTX) in later stages suggesting bone resorption. However, two-year histomorphometric data showed that the increase in both resorption and formation in later stage is still anabolic. The "anabolic window" (the period of time when the actions of PTH are maximally anabolic) remains open for at least 2 years.[37] The maximum recommended treatment course is 24 months because of the concern of the risk of osteosarcoma. Rats administered teriparatide at doses 60 times higher than in humans with subcutaneous doses of 20 µg developed osteosarcoma. However, with over 15 years of postmarketing experience and millions of prescriptions, there has been no evidence of an increased clinical risk. At the end of the 2-year course, the patient should be switched to an antiresorptive.

Abaloparatide

Abaloparatide, a PTH-rP analogue, was approved in 2017 by the FDA for the treatment of postmenopausal women with high-risk osteoporosis. It shares 76% amino acid sequence identity with human PTH-rP (1 to 34) and 41% with human PTH (1 to 34). Abaloparatide binds to PTH1R with high selectivity resulting in transient stimulation of the receptor.[38] This leads to greater overall anabolic effect than teriparatide. Daily subcutaneous administration of abaloparatide for 18 months significantly reduced the risk of new vertebral and nonvertebral fractures compared with placebo in a randomized controlled trial (ACTIVE trial). Treatment with abaloparatide was also associated with modestly higher BMD gains, including sites rich in cortical bone, compared with the placebo and teriparatide groups. This is likely due an increased rate of bone mineralization compared with teriparatide. The incidence of hypercalcemia was lower with abaloparatide than with teriparatide. Overall, there were no differences in serious adverse events between the treatment groups.[39] The recommended dosage is 80 µg subcutaneous injection once daily. Like teriparatide, the recommended cumulative use of abaloparatide is limited to 2 years.

Combination and Sequential Treatments

The treatment of osteoporosis is a long process, and many patients will require treatment with more than one type of drug over their lifetime. To date, no substantial evidence

supports the long-term efficacy of the existing treatments. Clinical decision making, therefore, raises several considerations. Which drugs should be used first for treatment and is there any preferred sequence? Also, will any of the drugs interfere with the action of the next? Furthermore, can drugs be used concurrently? As a monotherapy, diphosphonates are the recommended first choice. Denosumab could be considered in certain circumstance such as renal impairment. Recent reports caution against transitioning patients from denosumab to teriparatide because of a notable decline in BMD at the radius and hip. By contrast, when patients on teriparatide are switched to denosumab, BMD continues to increase.[40] Following discontinuation of denosumab, administration of a diphosphonate is recommended to prevent new vertebral fractures.

In summary, diphosphonates only maintain the structure of bone including any accumulated structural or material faults. However, their bone selectivity and effectiveness in reducing the risk of fractures, together with their low cost, has established them as the first line of treatment for osteoporosis. The osteoanabolics, teriparatide and abaloparatide, increase new bone formation, but there is a combined 2-year limit in their use, and the cost remains a consideration. Based on long-term efficacy and safety profile, denosumab has become an attractive option especially for patients with renal impairment. However, compliance is crucial as the rebound risk of fracture was noted with any lapse.

Antiresorptive Drugs and Fracture Healing

There have been concerns that antiresorptive drugs might impair fracture healing, but this has not been borne out in practice. Several animal models showed no impairment of fracture healing unless very high doses of drugs were used. Furthermore, in the major clinical studies with the antiresorptive drugs, there has been no evidence of delayed fracture healing or malunion.[41] Indeed, there is no early stage in fracture healing in which antiresorptive drugs would be expected to act. It is only during the later stages of remodeling of the calcified callus that one would expect antiresorptive drugs to have an impact. In contrast to these concerns, several studies suggested that diphosphonates might enhance fracture repair by stabilizing the fracture callus.

OSTEOMALACIA AND RICKETS

Undermineralized, newly formed bone is the hallmark of both osteomalacia and rickets. On radiographs, bones appear osteopenic and stress fractures with radiodense lines adjacent to regions of radiolucency (called Looser zones or pseudofractures) appear on the concave sides of long bones[42] (**Figure 5**). Characteristic hip fractures resembling slipped femoral capital epiphyses are often present in advanced cases (**Figure 6**). On technetium bone scintigraphy, stress fractures are visible as hot spots (**Figure 7**). In cases of strong clinical suspicion of osteomalacia and negative radiological findings, bone biopsy is diagnostic. It shows widening of osteoid seams due to the lack of mineralization and smudging of tetracycline labels from the slow mineralization rate (**Figure 8**). Deficiencies in calcium or vitamin D represent the prototype of the disease. Vitamin D deficiency leads to malabsorption of calcium and phosphate, resulting in osteomalacia in adults and rickets in children. According to the National Health and Nutrition

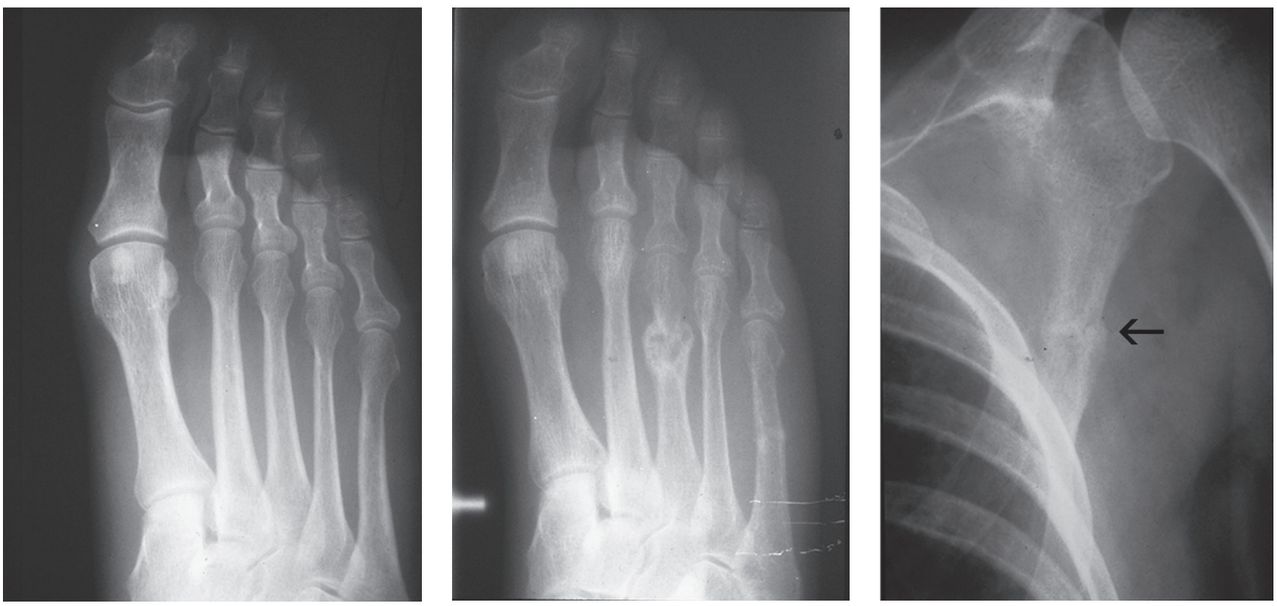

FIGURE 5 Radiographs of stress fractures in osteomalacia. Stress fractures may be seen in osteomalacia that maybe more apparent in the healing phase (left and middle) and on concave bone surfaces known as Looser lines (arrow) (right).

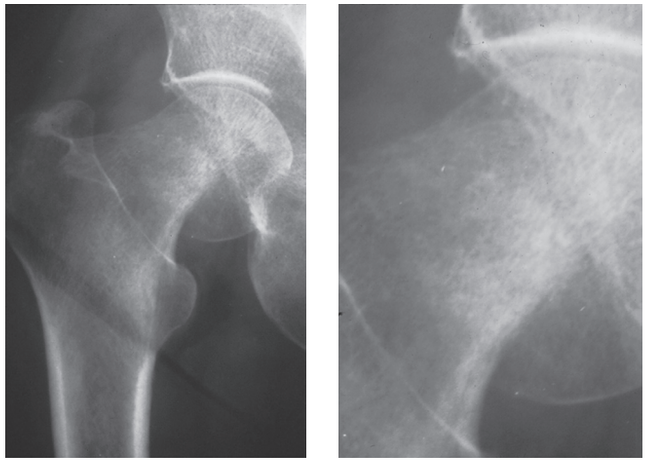

FIGURE 6 Radiographs of osteomalacic hip fractures. Hip fractures in osteomalacic bone may resemble slipped femoral capital epiphyses. They may present with chronic rather than acute bone pain, and deformity may progress over time.

Examination Survey (NHANES) 2005 to 2006 data, the overall prevalence rate of vitamin D deficiency (defined as a serum 25-hydroxyvitamin D [25(OH)D] concentrations ≤20 ng/mL [50 nmol/L]) was 41.6%, with the highest rate seen in blacks (82.1%), followed by Hispanics (69.2%).[43] The diagnosis of vitamin D deficiency is based on measurements of serum 25(OH)D and not on the active metabolite, $1,25(OH)_2D$, which is normal (or high) in most patients. Several criteria for vitamin D deficiency have been proposed, but at this time, the consensus is to supplement vitamin D if serum values are below 30 ng/mL.

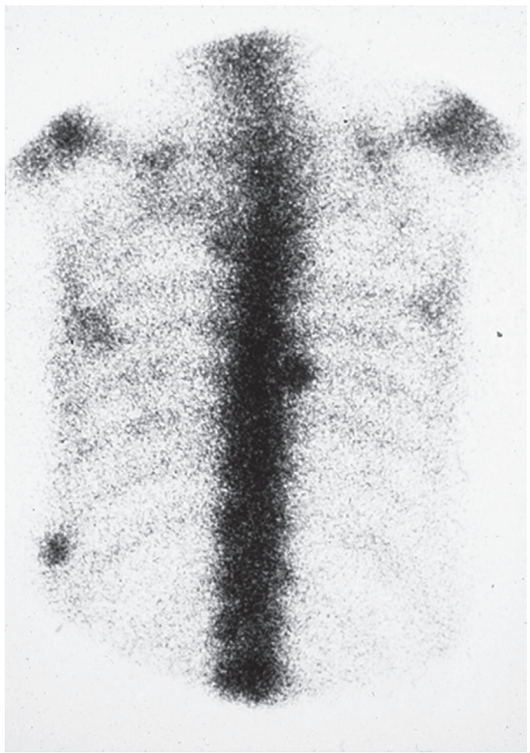

FIGURE 7 Bone scan in osteomalacia. Technetium bone scan demonstrating increased uptake at sites of multiple rib fractures in osteomalacia.

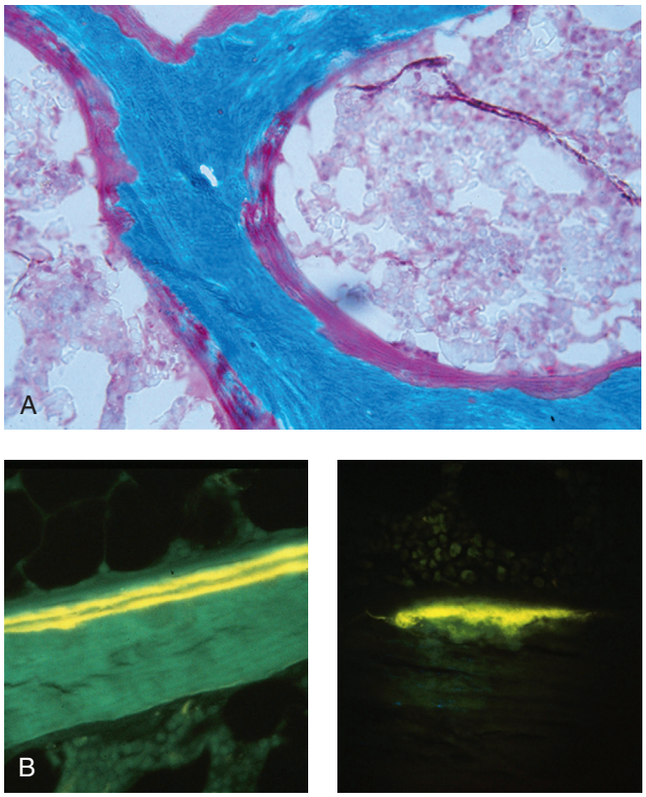

FIGURE 8 Histology and mineralization front in osteomalacia. **A**, Trichrome stain demonstrating unmineralized osteoid borders (red) rimming the length of trabeculae. **B**, In contrast to well-defined bands of double tetracycline labeling in normal bone (left), osteomalacic bone exhibits only a smudge of tetracycline uptake reflecting deficient mineralization (right).

Osteomalacia and vitamin D deficiency can be induced by secondary causes. More common causes of osteomalacia are presented in **Table 4**. The most common secondary causes of osteomalacia are gastrointestinal disorders including celiac disease, hepatobiliary, and pancreatic disease, short bowel syndrome, and some bariatric procedures causing malabsorption of vitamin D; medications such as the anticonvulsants phenobarbital, phenytoin, and carbamazepine can alter hepatic vitamin D metabolism; phosphate-binding antacids can cause hypophosphatemia, metabolic acidosis, and renal osteodystrophy.

Rickets is the pediatric form of osteomalacia. In rachitic children whose epiphyseal plates are still open, defective chondrocyte differentiation and mineralization of the epiphyseal plate are pathophysiologic hallmarks. The lack of mineralization in the provisional zone of calcification results in physeal

TABLE 4 Rare Causes of Osteomalacia

Deficiency	Calcium Vitamin D
Absorptive	Gastric Biliary Enteric
Renal tubular	
Renal osteodystrophy	

Adapted from Mankin HJ: Metabolic bone disease. *JBJS* 1994;76(5):760-788.

cupping and widening and metaphyseal flaring (**Figure 9**). Undermineralization of growing bones can lead to frontal skull bossing, enlarged costochondral junctions (the rachitic rosary), bowing of long bones, and delayed eruption of permanent teeth. Furthermore, in addition to increased fracture risk, bone pain in the legs with proximal muscle weakness and gait instability can be present, together with frequent falling, delayed age of standing or walking, and delayed growth. Hypocalcemic seizures and tetanic spasms in the first year of life may be the initial manifestation of rickets.[44] The diagnosis of nutritional rickets is made on the basis of history, physical examination, and biochemical testing and is confirmed by radiographs. The typical biochemical profile includes low 25(OH)D, low to low-normal serum calcium and phosphate and urinary calcium. PTH, alkaline phosphatase activity, and urine phosphate are usually elevated. However, biochemistry alone cannot differentiate whether the primary cause is vitamin D or dietary calcium deficiency because combined deficiencies are common.

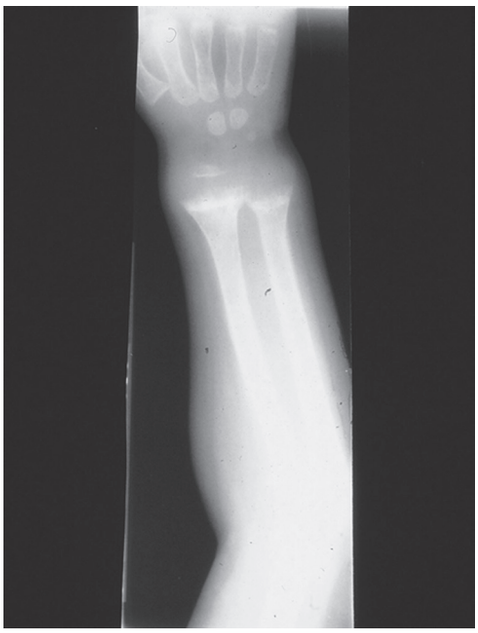

FIGURE 9 Epiphyseal plate in rickets. Radiograph of rachitic epiphyseal plate in the distal radius exhibiting cupping, flaring, and metaphyseal widening associated with deficient mineralization.

Treatment is correction of the vitamin D deficiency. In the United States, the Endocrine Society Clinical Practice Guidelines recommend the use of either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) for the treatment and prevention of vitamin D deficiency. They suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 6 to 8 week or its equivalent of 5,000 IU of vitamin D2 or vitamin D3 daily to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1,000 to 2,000 IU/d.[45]

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is a common endocrine disorder of calcium metabolism characterized by hypercalcemia and elevated concentrations of parathyroid hormone. Most cases occur from a solitary adenoma on one of the four parathyroid glands (80% of cases) or as a multiple gland disorder (15% to 20% of cases). Typically, there are four parathyroid glands, located on the back of the thyroid gland. The presence of a fifth parathyroid gland, usually in the mediastinum, is not uncommon (2% and 6%); parathyroid cancer is rare (<1%).[46]

Elevated serum calcium found in routine biochemical testing of otherwise asymptomatic individuals is the most common presentation. More than half of patients with primary hyperparathyroidism are detected in patients older than 50 years. The disease is mostly sporadic, without a personal or family history of primary hyperparathyroidism or other endocrinopathies.[46] In primary hyperparathyroidism, elevated PTH is associated with elevated serum calcium (except the cases of normocalcaemic primary hyperparathyroidism), bone alkaline phosphatase activity, and a low or low-normal serum phosphate level. Both calcium and phosphate levels are elevated in the urine (**Table 5**). Although vitamin D deficiency is common with primary hyperparathyroidism, active $1,25(OH)_2D$ is close to the upper end of the normal range or elevated. Clinically, the identification of patients with primary hyperparathyroidism at the asymptomatic phase has changed

TABLE 5 Hyperparathyroidism

Physiology	Clinical
1,25 dihydroxy vitamin D production in kidney	
Increase in intestinal calcium absorption	↑ Serum calcium
Increase in tubular reabsorption of calcium	↓ urine calcium
Decrease in tubular reabsorption of phosphate	↑ urine phosphate
Bone resorption	↓ bone density

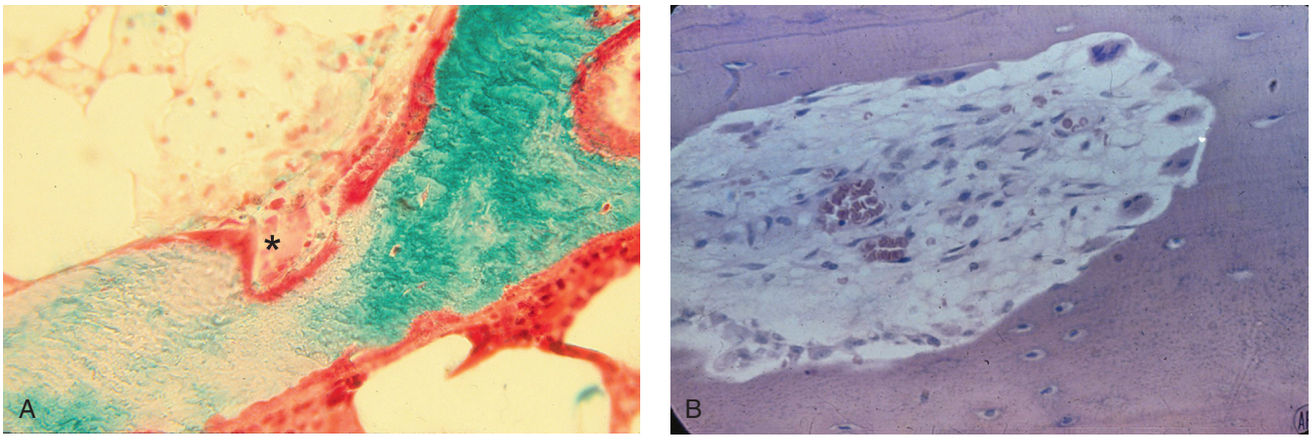

FIGURE 10 Histology of bone resorption in hyperparathyroidism. **A**, Hyperparathyroidism creates porosity in bone by indirectly stimulating osteoclastic resorption (asterisk). **B**, Osteoclastic "cutting cones" create tunneling and porosity.

the clinical phenotype of the disease, and today, fewer patients suffer from severe complications, such as nephrolithiasis or osteitis fibrosa cystica, hallmarks of the skeletal involvement, at the time of the diagnosis. When increased porosity is observed, it is the result of osteoclastic bone resorption (**Figure 10**). Demineralization of bones is mostly cortical, and the radiological features of osteitis fibrosa cystica include salt and pepper degranulation of the skull, tapering of the distal clavicle, subperiosteal resorption of the distal phalanges, bone cysts, and brown tumors. These radiological features can be associated with fractures, skeletal deformities, and bone pain.[46] In advanced cases, there is the risk of proximal muscle weakness, peptic ulcer disease, pancreatitis, hypertension, and atherosclerotic heart disease.

Treatment can be supportive only if patients are asymptomatic, vitamin D levels are within normal range, and hypercalcemia is mild without skeletal or renal involvement. For these patients, an annual assessment of serum calcium and 24-hour urine calcium/creatinine, and BMD measurements every 1 to 2 years is recommended. Symptomatic patients, however, should undergo surgical excision of the parathyroid gland with the adenoma, or excision of 3.5 glands in cases of the hyperplastic glands. After treatment, BMD gradually improves, but it can take several years for complete recovery to occur.[47]

RENAL OSTEODYSTROPHY (CHRONIC KIDNEY DISEASE–MINERAL BONE DISORDER)

Renal osteodystrophy consists of osteomalacia and secondary hyperparathyroidism and refers to alterations in bone morphology associated with chronic kidney disease. Loss of renal parenchyma leads to several physiologic changes affecting bone (**Table 6**). Loss of renal function unifies a spectrum of disparate bone disorders including secondary hyperparathyroidism or osteitis fibrosa (a high-turnover bone disease), osteomalacia (defective mineralization), mixed renal osteodystrophy (hyperparathyroid bone disease with a superimposed mineralization defect), and adynamic bone disease (diminished bone formation and resorption) (**Figure 11**).

The currently used term "Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD)" describes the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of chronic kidney disease. The term renal osteodystrophy has been used exclusively to define the bone pathology associated with chronic kidney disease.[48] The histologic examination is the benchmark and provides type and severity of the bone disease. However, bone biopsy is invasive and, therefore, not commonly done. Bone radiographs can be useful in demonstrating abnormal bone texture and subperiosteal resorption in the fingers, particularly in the radial side of the middle phalanx of the index and middle fingers in osteitis fibrosa cystica (**Figure 12**). Patchy osteosclerosis is also common and accounts for the classic appearance of "rugger jersey" spine (ie, horizontal bands of alternating intensity) and the "salt and pepper" appearance of the skull. However, radiologic features appear late, so individuals with quite marked secondary

TABLE 6 Renal Osteodystrophy

1.	Failure of second hydroxylation (1-α hydroxylation) of vitamin D in the kidney
2.	Hyperphosphatemia decreases serum calcium
3.	Both decrease calcium absorption from the intestine
4.	The result is hypocalcemia, hyperphosphatemia, and hypocalciuria which lead to secondary hyperparathyroidism

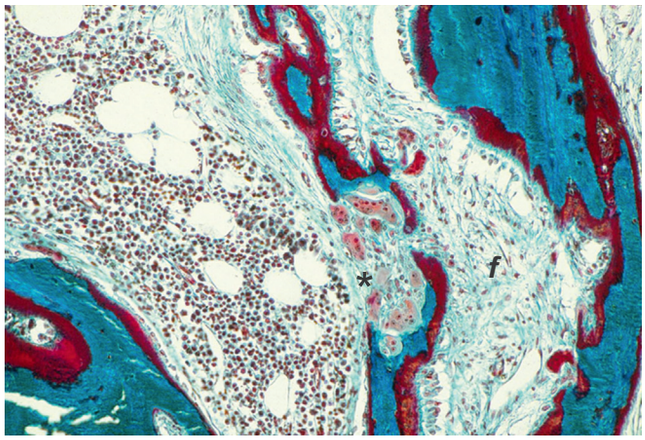

FIGURE 11 Histology in renal osteodystrophy. Osteitis fibrosa cystica comprised of (1) mineralization failure demonstrated by increased osteoid borders (red), (2) secondary hyperparathyroidism with osteoclastic resorption (asterisk), and (3) peritrabecular fibrosis ("f").

hyperparathyroidism may have normal radiographs. The most common phenotype, adynamic or "aplastic" bone disease, is characterized by reduced bone turnover. Many factors contribute to this disease: aging, underlying diabetes, phosphate binders, diphosphonates, and uremia. Aluminum-induced osteomalacia was prevalent when aluminum-containing phosphate binders were used, but currently is relatively infrequent[49] (**Figure 13**).

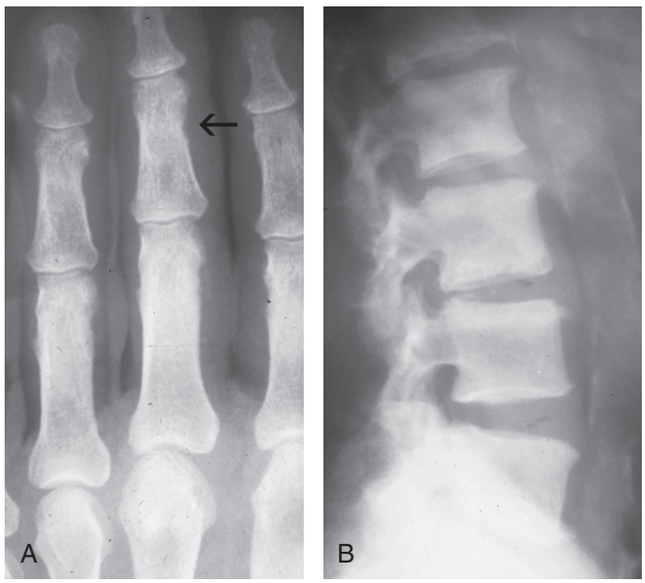

FIGURE 12 Radiographs in renal osteodystrophy. **A**, Subperiosteal resorption of the middle phalanx (arrow). **B**, Focal paradoxical sclerosis manifested by vertebral end plate density termed "rugger jersey spine."

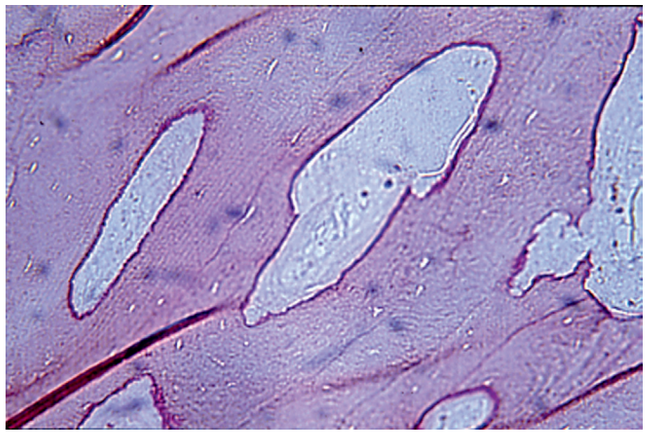

FIGURE 13 Histology of aluminum-associated osteomalacia in renal bone disease. Aluminum deposition (pink stain) at the mineralization front preventing mineralization of osteoid.

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