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Section 4 Disorders of Bone and Mineral Metabolism

Bone and Mineral

Metabolism in Health

and Disease F. Richard Bringhurst, Henry M. Kronenberg,

Eva S. Liu, Marc N. Wein BONE STRUCTURE AND METABOLISM Bone is a dynamic tissue that is remodeled constantly throughout life. The arrangement of compact and cancellous bone provides strength and density suitable for both mobility and protection. Compact or cortical bone forms the roughly cylindrical shell of long bones; cancel lous or trabecular bone forms the plate-like meshwork that internally supports the cortical shell. In addition, bone provides a reservoir for calcium, magnesium, phosphorus, sodium, and other ions necessary for homeostatic functions. Bone also hosts and regulates hematopoiesis by providing niches for hematopoietic cell proliferation and differen tiation. The skeleton is highly vascular and receives ~10% of the cardiac output. Remodeling of bone is accomplished by two distinct cell types: osteoblasts produce bone matrix, and osteoclasts resorb the matrix. The activities of these cells are coordinated by osteocytes, long-lived regulatory cells embedded within bone matrix. The extracellular components of bone consist of a solid mineral phase in close association with an organic matrix, of which 90–95% is type I collagen (Chap. 425). The noncollagenous portion of the organic matrix is heterogeneous and contains serum proteins such as albumin as well as many locally produced proteins, whose functions are incompletely understood. Those proteins include cell attachment/ signaling proteins such as thrombospondin, osteopontin, and fibronectin; calcium-binding proteins such as matrix gla protein and osteocalcin; and proteoglycans such as biglycan and decorin. Some of the proteins organize collagen fibrils; others influence mineralization and binding of the mineral phase to the matrix. The mineral phase is made up of calcium and phosphate and is best

characterized as a poorly crystalline hydroxyapatite. The mineral phase of bone is deposited initially in intimate relation to the collagen fibrils and is laid down in specific locations in the “holes” between the collagen fibrils. This architectural arrangement of mineral and matrix results in a two-phase material well suited to withstand mechanical stresses. The organization of collagen influences the amount and type of mineral phase formed in bone. Although the primary structures of type I collagen in skin and bone tissues are similar, there are differences in posttranslational modifications and distribution of intermolecular cross-links. The holes in the packing structure of the collagen are larger in mineralized collagen of bone and dentin than in unmineralized col lagens such as those in tendon. Single amino acid substitutions in the helical portion of either the α1 (COL1A1) or α2 (COL1A2) chains of type I collagen disrupt the organization of bone in the disease, osteo genesis imperfecta. The severe skeletal fragility associated with this group of disorders highlights the importance of the fibrillar matrix in the structure of bone (Chap. 425). Osteoblasts synthesize and secrete the organic matrix and regu late its mineralization. They are derived from cells of mesenchymal origin (Fig. 421-1A). Osteoblast precursors derive from the perios teum, the bone marrow, or the hypertrophic chondrocytes at the end of the growth plate. Active osteoblasts are found on the surface of newly forming bone. As an osteoblast secretes matrix, which then is mineralized, the cell may become an osteocyte, still connected with its nutrient supply through a series of canaliculi. Osteocytes account for the vast majority of the cells in bone. They are thought to be the

mechanosensors that communicate signals to surface osteoblasts and osteoclasts and their progenitors through the canalicular network and thereby serve as master regulators of bone formation and resorption. Osteocytes also secrete fibroblast growth factor 23 (FGF23), a major hormonal regulator of phosphate metabolism (see below). Mineraliza tion of the matrix, both in trabecular bone and in osteones of compact cortical bone (Haversian systems), begins soon after the matrix is secreted (primary mineralization) but is not completed for several weeks or even longer (secondary mineralization). Although this min eralization takes advantage of the high concentrations of calcium and phosphate, already near saturation in serum, mineralization is a care fully regulated process that is dependent on the activity of osteoblastderived alkaline phosphatase, which probably works by hydrolyzing inhibitors of mineralization, such as pyrophosphate.

CHAPTER 421 Genetic studies in humans and mice have identified several key genes that control osteoblast development. Runx2 is a transcription factor expressed specifically in chondrocyte (cartilage cells) and osteo blast progenitors as well as in hypertrophic chondrocytes and mature osteoblasts. Runx2 regulates the expression of several important osteo blast proteins, including osterix (SP7) (another transcription factor needed for osteoblast maturation), osteopontin, bone sialoprotein, type I collagen, osteocalcin, and receptor-activator of nuclear factor (NF)-κB (RANK) ligand. Runx2 expression is regulated in part by bone morphogenic proteins (BMPs). Runx2-deficient mice are devoid of osteoblasts, whereas mice with a deletion of only one allele (Runx2 +/–) exhibit a delay in formation of the clavicles and some cranial bones. The latter abnormalities are similar to those in the human disorder cleidocranial dysplasia, which is also caused by heterozygous inactivat ing mutations in Runx2. The paracrine signaling molecule, Indian hedgehog (Ihh), also plays a critical role in osteoblast development, as evidenced by Ihh-deficient mice that lack osteoblasts in the type of bone formed on a cartilage mold (endochondral ossification). Signals

originating from members of the wnt family of paracrine factors are also important for osteo blast proliferation and differentiation. Osteocytes regulate osteoblasts partly by secreting a potent inhibitor of wnt signaling called sclerostin. Numerous other growth-regulatory factors affect osteoblast function, including the three closely related transforming growth factor βs, fibro blast growth factors (FGFs) 2 and 18, platelet-derived growth factor, and insulin-like growth factors (IGFs) I and II. Hormones such as para thyroid hormone (PTH) and 1,25-dihydroxyvitamin D [1,25(OH)2D] activate receptors expressed by osteoblasts to assure mineral homeo stasis and influence a variety of bone cell functions. Osteoclasts that resorb bone (see below) also regulate osteoblasts by releasing growth factors from bone matrix and by synthesizing proteins that can directly regulate osteoblastogenesis. Resorption of bone is carried out mainly by osteoclasts, multinucle ated cells that are formed by fusion of cells derived from the common precursor of macrophages and osteoclasts. Thus, these cells derive from the hematopoietic lineage, quite different from the mesenchymal lineage cells that become osteoblasts. Multiple factors that regulate osteoclast development have been identified (Fig. 421-1B). Factors produced by osteocytes, osteoblasts, and marrow stromal cells allow cells of the osteoblast lineage to control osteoclast development and activity. Macrophage colony-stimulating factor (M-CSF) plays a critical role during several steps in the pathway and ultimately leads to fusion of osteoclast progenitor cells to form multinucleated, active osteoclasts. RANK ligand, a member of the tumor necrosis factor (TNF) family, is expressed on the surface of osteocytes, osteoblasts, and stromal fibro blasts. In a process involving cell-cell interactions, RANK ligand binds to the RANK receptor on osteoclast progenitors, stimulating osteoclast differentiation and activation. Alternatively, a soluble decoy receptor, referred to as osteoprotegerin (OPG), can bind RANK ligand and inhibit osteoclast differentiation. Several growth factors and cytokines (including interleukins 1, 6, and 11; TNF; and interferon γ) modulate osteoclast differentiation and function. Most hormones that influence osteoclast function do not target these cells directly but instead target cells of the osteoblast lineage to increase production of M-CSF and RANK. Both PTH and 1,25(OH)2D increase osteoclast number and

Osteoblast differentiation Chondrocyte Adipocyte Skeletal progenitors PART 12 Endocrinology and Metabolism Ihh, BMPs Pre-OB OB OB progenitor Osx Runx2 A Regulation of osteoclast differentiation Stromal/Osteoblast/ osteocyte 1, 25(OH)D IL6 M-CSF RANK ligand RANK Osteoclast precursor Mature osteoclasts that secrete acid and proteases”

B FIGURE 421-1 Pathways regulating development of (A) osteoblasts and (B) osteoclasts. A. Osteoblast lineage cells. Osteoblast progenitors are mesenchymal cells that are found in the perichondrium/periosteum, the bone marrow (where they also support hematopoietic stem cells and can become marrow adipocytes), and the growth plate (where late hypertrophic chondrocytes can die or become osteoblast precursors in the marrow). These progenitors can become chondrocytes early in development or in response to fracture postnatally. In response to Indian hedgehog (Ihh) and bone morphogenetic proteins (BMPs), these precursors become committed to osteoblast differentiation and are regulated by a series of transcription factors, with early essential factors, Runx2 and then osterix (SP7), shown here. On the bone surface, these cells express large amounts of collagen I and cell surface alkaline phosphatase, a crucial regulator of mineralization. Osteoblasts are relatively short-lived and subsequently either die or become osteocytes buried in bone matrix or quiescent bone-lining cells. To track the osteoblast (OB) lineage, we use CreERt mice driven by the Osx and collagen1 gene promotors. During OB differentiation, Osx is starting to

be expressed early on in pre-OBs, while col1 is expressed later in OB development. It can therefore be expected that Osx- and col1-CreERt mouse lines will mark osteoblastic cells at different stages of differentiation. B. Regulation of osteoclast production. Osteoclast progenitors, derived from the hematopoietic lineage, respond to signals from cells of the osteoblast lineage to increase their number and activity. IL, interleukin; M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; PTH, parathyroid hormone. activity by this indirect mechanism. Calcitonin, in contrast, binds to its receptor on the basal surface of osteoclasts and directly inhibits osteo clast function. Estradiol has multiple cellular targets in bone, including osteoclasts, immune cells, and osteoblasts; actions on all these cells serve to decrease osteoclast number and bone resorption. Osteoclast-mediated resorption of bone takes place in scalloped spaces (Howship's lacunae) where the osteoclasts are attached through a specific αvβ3 integrin to components of the bone matrix. The osteo clast forms a tight seal to the underlying matrix and secretes protons, chloride, and proteinases into a confined space that has been likened to an extracellular lysosome. The active osteoclast surface forms a ruffled border that contains a specialized proton pump ATPase that secretes acid that solubilizes the mineral phase. Carbonic anhydrase (type II isoenzyme) within the osteoclast generates the needed pro tons. The bone matrix is resorbed in the acid environment adjacent

Lining cell Apoptosis Mature OB Osteocyte Collagen 1 Osteocalcin R PTH RANK OPG to the ruffled border by proteases, such as cathepsin K, that act at low pH. A distinct process, called osteocytic osteolysis, also causes bone resorption. Using a molecular machinery similar to that in osteoclasts, osteocytes dissolve mineral and matrix from the bone surrounding osteocytes. PTH and its relative, parathyroid hormone–related peptide (PTHrP), stimulate osteocytic osteolysis. The relative contributions of osteoclasts and osteocytes to bone resorption is uncertain. In the embryo and the growing child, bone develops mostly by replacing previously calcified cartilage (endochondral bone forma tion) with subsequent remodeling or, in a few bones, is formed without a cartilage matrix (intramembranous bone formation). Dur ing endochondral bone formation, chondrocytes proliferate, secrete and mineralize a matrix, enlarge (hypertrophy), and then either die or differentiate into precursors of osteoblasts, lengthening bone and

Osteoclast precursor Osteoclast Active osteoclast Lining cells Resting bone surface Resorption Reversal Activation Osteocyte ~3 weeks ~3 months FIGURE 421-2 Schematic representation of bone remodeling. The cycle of bone remodeling is carried out by the basic multicellular unit (BMU), which consists of a group of osteoclasts and osteoblasts. In cortical bone, the BMUs tunnel through the tissue, whereas in cancellous bone, they move across the trabecular surface. The process of bone remodeling is initiated by the recruitment of osteoclast precursors, perhaps to sites of microdamage. These precursors fuse to form multinucleated, active osteoclasts that mediate bone resorption. Osteoclasts adhere to bone and subsequently remove it by acidification and proteolytic digestion. As the BMU advances, osteoclasts leave the resorption site, and osteoblasts, derived from marrow precursors and previously inactive bone lining cells, move in to cover the excavated area and begin the process of new bone formation by secreting osteoid, which eventually is mineralized into new bone. After osteoid mineralization, osteoblasts flatten and form a layer of lining cells over new bone, become osteocytes, or die. providing the matrix and factors that stimulate endochondral bone for mation. This program is regulated by both local factors, such as IGF-I and -II, Ihh, PTHrP, BMPs, and FGFs, and systemic hormones, such as growth hormone, glucocorticoids, and estrogen. New bone, whether formed in infants or in adults during repair, has

a relatively high ratio of cells to matrix and is characterized by coarse fiber bundles of collagen that are interlaced and randomly dispersed (woven bone). In adults, the more mature bone is organized with fiber bundles regularly arranged in parallel or concentric sheets (lamel lar bone). In long bones, deposition of lamellar bone in a concentric arrangement around blood vessels forms the Haversian systems. Growth in length of bones is dependent on proliferation of cartilage cells and the endochondral sequence at the growth plate. Growth in width and thickness is accomplished by formation of bone at the peri osteal surface and by resorption at the endosteal surface, with the rate of formation exceeding that of resorption. In adults, after the growth plates of cartilage close through the actions of estrogen, growth in length and endochondral bone formation cease. Even in adults, how ever, remodeling of bone (within Haversian systems as well as along the surfaces of trabecular bone) continues throughout life. In adults, ~4% of the surface of trabecular bone (such as iliac crest) is involved in active resorption, whereas 10–15% of trabecular surfaces are covered with osteoid, unmineralized new bone formed by osteoblasts. Radioiso tope studies indicate that as much as 18% of the total skeletal calcium is deposited and removed each year. Thus, bone is an active metabolizing tissue that requires an intact blood supply. The cycle of bone resorption and formation is a highly orchestrated process, directed by osteocytes and carried out by the basic multicellular unit, which is composed of a group of osteoclasts and osteoblasts (Fig. 421-2). The response of bone to fractures, infection, and interruption of blood supply and to expanding lesions is relatively limited. Dead bone must be resorbed, and new bone must be formed, a process carried out in association with growth of new blood vessels into the involved area. In injuries that disrupt the organization of the tissue, such as a fracture, in which apposition of fragments is poor or when motion exists at the fracture site, progenitor stromal cells recapitulate the endochondral bone formation of early development and form carti lage that is replaced by bone and, variably, fibrous tissue. When there is good apposition with fixation and little motion at the fracture site, repair occurs predominantly by formation of new bone without other mediating tissue. Remodeling of bone occurs along lines of force generated by mechanical stress. The signals from these mechanical stresses are sensed by osteocytes, which transmit signals to osteoclasts and osteo blasts or their precursors. One such signal made by osteocytes is sclerostin, an inhibitor of wnt signaling. Mechanical forces, as well as

parathyroid hormone, suppress scleros tin production and thus increase bone formation by osteoblasts. Expanding lesions in bone such as tumors induce resorption at the surface in contact with the tumor by producing ligands such as PTHrP that stimulate osteoclast differen tiation and function. Thus, bone plastic ity reflects the interaction of cells with each other and with the environment.

Osteoblast precursors Bone remodeling unit Osteoblast Osteoid Cement line Bone formation Mineralization Bone and Mineral Metabolism in Health and Disease
CHAPTER 421 Measurement of the products of osteoblast and osteoclast activity can assist in the diagnosis and management of bone diseases. Osteoblast activity can be assessed by measuring serum bonespecific alkaline phosphatase. Similarly, osteocalcin, a protein secreted from osteoblasts, is made virtually only by osteoblasts. Measurement of an aminoterminal fragment of procollagen I is also an effective index of bone forma tion. Osteoclast activity can be assessed by measurement of products of collagen degradation. Collagen molecules are covalently linked to each other in the extracellular matrix through the formation of hydroxypyridinium cross-links (Chap. 425). After digestion by osteoclasts, these crosslinked peptides can be measured both in

urine and in blood. CALCIUM METABOLISM Over 99% of the 1–2 kg of calcium present normally in the adult human body resides in the skeleton, where it provides mechanical stability and serves as a reservoir when needed to maintain extracellular fluid (ECF) calcium concentration (Fig. 421-3). Skeletal calcium accretion first becomes significant during the third trimester of fetal life, accelerates throughout childhood and adolescence, reaches a peak in early adult hood, and gradually declines thereafter at rates that rarely exceed 1–2% per year. These slow changes in total skeletal calcium content contrast with relatively high daily rates of closely matched fluxes of calcium into and out of bone (~250–500 mg each), a process mediated by coupled activity of osteoblasts, osteoclasts, and osteocytes. Another 0.5–1% of skeletal calcium is freely exchangeable (e.g., in chemical equilibrium) with that in the ECF. 0.4–1.5 g 1000–2000 g 0.25–0.5 g 0.25–0.5 g ECF 1–2 g 0.25–0.5 g 0.1–0.2 g 8–10 g 7.9–9.7 g Intestine Bone 0.3–1 g Kidney 0.15–.3 g FIGURE 421-3 Calcium homeostasis. Schematic illustration of calcium content of extracellular fluid (ECF) and bone as well as of diet and feces; magnitude of calcium flux per day as calculated by various methods is shown at sites of transport in intestine, kidney, and bone. Ranges of values shown are approximate and were chosen to illustrate certain points discussed in the text. In conditions of calcium balance, rates of calcium release from and uptake into bone are equal.

The concentration of ionized calcium in the ECF must be main tained within a narrow range because of the critical role calcium plays in a wide array of cellular functions, especially those involved in neuromuscular activity, secretion, and signal transduction. Intracel lular cytosolic free calcium levels are ~100 nmol/L and are 10,000-fold lower than ionized calcium concentration in the blood and ECF (1.1–1.3 mmol/L). Cytosolic calcium does not play the structural role played by extracellular calcium; instead, it serves a signaling func tion. The steep chemical gradient of calcium from outside to inside the cell promotes rapid calcium influx through various membrane calcium channels that can be activated by hormones, metabolites, or neurotransmitters, swiftly changing cellular function. In blood, total calcium concentration is normally 2.2–2.6 mM (8.5–10.5 mg/dL), of which ~50% is ionized. The remainder is bound ionically to negatively charged proteins (predominantly albumin and immunoglobulins) or loosely complexed with phosphate, citrate, sulfate, or other anions. Alterations in serum protein concentrations directly affect the total blood calcium concentration even if the ionized calcium concentra tion remains normal. An algorithm to correct for protein changes adjusts the total serum calcium (in mg/dL) upward by 0.8 times the deficit in serum albumin (g/dL) or by 0.5 times the deficit in serum immunoglobulin (in g/dL). Notably, such corrections provide only rough approximations of actual free calcium concentrations, however, and may be misleading, particularly during acute illness. Acidosis also alters ionized calcium by reducing its association with proteins. Accordingly, the best practice is to measure blood ionized calcium directly by a method that employs calcium-selective electrodes in acute settings during which calcium abnormalities might occur.

PART 12 Endocrinology and Metabolism Control of the ionized calcium concentration in the ECF ordinarily is accomplished by adjusting the rates of calcium movement across intestinal and renal epithelia and into and out of bone. These adjust ments are mediated mainly via changes in blood levels of the hormones PTH and 1,25(OH)2D. Acting via binding to calcium-sensing receptors (CaSRs) on the surface of parathyroid cells, blood ionized calcium sup presses PTH secretion by reducing levels of PTH mRNA, promoting the cleavage of PTH to inactive peptides, and suppressing release of PTH-containing granules from parathyroid cells. 1,25(OH)2D inhibits PTH production in the parathyroid by an incompletely understood mechanism of negative feedback (Chap. 422).

Normal dietary calcium intake in the United States varies widely, ranging from 10 to 37 mmol/d (400–1500 mg/d). A National Academy of Medicine (formerly, Institute of Medicine) analysis recommends a daily allowance of 25–30 mmol (1000–1200 mg) for most adults. Intes tinal absorption of ingested calcium involves both active (transcellular) and passive (paracellular) mechanisms. Passive calcium absorption is nonsaturable and approximates 5% of daily calcium intake, whereas active absorption involves apical calcium entry via specific ion chan nels (TRPV5 in the kidney's distal tubule and TRPV6 in the intestine), whose expression is controlled principally by 1,25(OH)2D. This active transport mechanism normally accounts for absorption of 20–70% of dietary calcium. Active gastrointestinal calcium transport occurs mainly in the proximal small bowel (duodenum and proximal jejunum), although some active calcium absorption occurs in most segments of the small intestine. Optimal rates of calcium absorption require gastric acid. This is especially true for weakly dissociable calcium supplements such as calcium carbonate. In fact, large boluses of calcium carbonate are poorly absorbed because of their neutralizing effect on gastric acid. In achlorhydric subjects and for those individuals taking drugs that inhibit gastric acid secretion, or with diminished acid secretion follow ing bariatric surgery, supplements should be taken with meals to opti mize their absorption. Use of calcium citrate may be preferable in these circumstances. Calcium absorption may also be blunted in disease states such as pancreatic or biliary insufficiency, in which ingested calcium remains bound to unabsorbed fatty acids or other food constituents. At high levels of calcium intake, synthesis of 1,25(OH)2D is reduced; this decreases the rate of active intestinal calcium absorption. The opposite occurs with dietary calcium restriction. Some calcium, ~2.5–5 mmol/d (100–200 mg/d), is excreted as an obligate component of intestinal secretions and is not regulated by calciotropic hormones.

The feedback-controlled hormonal regulation of intestinal absorp tive efficiency results in a relatively constant daily net calcium absorp tion of ~5–10 mmol/d (200–400 mg/d) despite large changes in daily dietary calcium intake. This daily load of absorbed calcium is excreted by the kidneys in a manner that is also tightly regulated by the con centration of ionized calcium in the blood. Approximately 8–10 g/d of calcium is filtered by the glomeruli, of which only 2–3% appears in the urine. Most filtered calcium (65%) is reabsorbed in the proximal tubules via a passive, paracellular route that is coupled to concomitant NaCl reabsorption and not specifically regulated. The cortical thick ascending limb of Henle's loop (cTAL) reabsorbs roughly another 20% of filtered calcium, also via a paracellular mechanism. Calcium reabsorption in the cTAL requires a tight-junctional proteins called paracellin-1 and Claudin14 and is inhibited by increased blood con centrations of calcium or magnesium, acting via the CaSR, which is highly expressed on basolateral membranes in this nephron segment. Operation of the renal CaSR provides a mechanism, independent of those engaged directly by PTH or 1,25(OH)2D, by which serum ion ized calcium can control renal calcium reabsorption. Finally, ~10% of filtered calcium is reabsorbed in the distal convoluted tubules (DCTs) by a highly regulated transcellular mechanism. Calcium enters the luminal surface of the cell through specific apical calcium channels (TRPV5). It then moves across the cell in association with a specific calcium-binding protein (calbindin-D28k) that buffers cytosolic cal cium concentrations from the large mass of transported calcium. Basolateral Ca2+-ATPases and Na+/Ca2+ exchangers actively extrude calcium and thereby maintain the transcellular calcium gradient. All these processes are stimulated directly or indirectly by PTH and 1,25(OH)2D. The DCT is also the site of action of thiazide diuretics, which lower urinary calcium excretion by inducing sodium depletion and thereby augmenting proximal calcium reabsorption. Conversely, dietary sodium loads, or increased distal sodium delivery caused by loop diuretics or saline infusion, induce

calciuresis. The homeostatic mechanisms that normally maintain a constant serum ionized calcium concentration may fail at extremes of calcium intake or when the hormonal systems or organs involved are compro mised. Thus, even with maximal activity of the vitamin D–dependent intestinal active transport system, sustained calcium intake <5 mmol/d (<200 mg/d) cannot provide enough net calcium absorption to replace obligate losses via the intestine, the kidney, sweat, and other secre tions. In this case, increased blood levels of PTH and 1,25(OH)2D activate osteoclastic bone resorption to obtain needed calcium from bone, which leads to progressive bone loss and negative calcium bal ance. Increased PTH and 1,25(OH)2D also enhance renal calcium reabsorption, and 1,25(OH)2D enhances calcium absorption in the gut. At very high calcium intakes (>100 mmol/d [>4 g/d]), passive intestinal absorption continues to deliver calcium into the ECF despite maximally downregulated intestinal active transport and renal tubular calcium reabsorption. This can cause severe hypercalciuria, nephrocal cinosis, progressive renal failure, and hypercalcemia (e.g., “milk-alkali syndrome”). Deficiency or excess of PTH or vitamin D, intestinal disease, and renal failure represent other commonly encountered chal lenges to normal calcium homeostasis (Chap. 422). PHOSPHORUS METABOLISM Although 85% of the ~600 g of body phosphorus is present in bone mineral, phosphorus is also a major intracellular constituent both as the free anion(s) and as a component of numerous organophosphate compounds, including structural proteins, enzymes, transcription fac tors, carbohydrate and lipid intermediates, high-energy stores (ATP [adenosine triphosphate], creatine phosphate), and nucleic acids. Unlike calcium, phosphorus exists intracellularly at concentrations close to those present in ECF (e.g., 1–2 mmol/L). In cells and in the ECF, phosphorus exists in several forms, predominantly as $H_2PO_4^-$ or $NaHPO_4^-$, with perhaps 10% as HPO_4^{2-}. This mixture of anions will be referred to here as “phosphate.” In serum, ~12% of phosphorus is bound to proteins. Concentrations of phosphates in blood and ECF generally are expressed in terms of elemental phosphorus, with the normal range in adults being 0.75–1.45 mmol/L (2.5–4.5 mg/dL).

Because the volume of the intracellular fluid compartment is twice that of the ECF, measurements of ECF phosphate may not accurately reflect phosphate availability within cells that follows even modest shifts of phosphate from one compartment to the other. Phosphate is widely available in foods and is absorbed efficiently (65%) by the small intestine even in the absence of vitamin D. However, gut phosphate absorptive efficiency may be enhanced (to 85–90%) via active transport mechanisms that are stimulated by 1,25(OH)2D. These mechanisms involve activation of Na^+/PO_4^{2-} co-transporters, such as Npt2b, that move phosphate into intestinal cells against an unfavorable electrochemical gradient. Daily net intestinal phosphate absorption varies widely with the composition of the diet but is generally in the range of 500–1000 mg/d. Phosphate absorption can be inhibited by large doses of calcium salts or by sevelamer hydrochloride (Renagel), strategies commonly used to control levels of serum phosphate in chronic kidney disease. Aluminum hydroxide antacids also reduce phosphate absorption but are used less commonly because of the potential for aluminum toxicity. Low serum phosphate stimulates renal proximal tubular synthesis of 1,25(OH)2D, perhaps by suppressing blood levels of FGF23 (see below). Serum phosphate levels vary by as much as 50% on a normal day. This reflects the effect of food intake but also an underlying circadian rhythm that produces a nadir between 7 and 10 A.M. Carbohydrate administration, especially as IV dextrose solutions in fasting subjects, can decrease serum phosphate by >0.7 mmol/L (2 mg/dL) in common clinical settings including treatment of ketoacidosis or metabolic or respiratory alkalosis. Because of this wide variation in serum phos phate, it is best to perform measurements in the basal, fasting state. Control of serum phosphate is

determined mainly by the rate of renal tubular reabsorption of the filtered load, which is ~4–6 g/d. Because intestinal phosphate absorption is highly efficient, urinary excretion is not constant but varies directly with dietary intake. The fractional excretion of phosphate (ratio of phosphate to creatinine clearance) is generally in the range of 10–15%. The proximal tubule is the principal site at which renal phosphate reabsorption is regulated. This is accomplished by changes in the levels of apical expression and activity of specific Na+/PO4 2– co-transporters (NaPi-2a and NaPi-2c) in the proximal tubule. Levels of these transporters at the apical surface of these cells are reduced rapidly by PTH, a major hormonal regulator of renal phosphate excretion. In addition, the circulating hormone FGF23 can inhibit phosphate reabsorption by a similar mechanism. FGF23 is synthesized by osteocytes. Activating FGF23 mutations cause the rare disorder autosomal dominant hypophosphatemic rickets (ADHR). In contrast to PTH, FGF23 reduces synthesis of 1,25(OH)2D, which may worsen the resulting hypophosphatemia by lowering intestinal phosphate absorption. Renal reabsorption of phosphate is responsive to changes in dietary intake such that experimental dietary phosphate restriction leads to a dramatic lowering of urinary phosphate within hours, preceding any decline in serum phosphate (e.g., filtered load). This physiologic renal adaptation to changes in dietary phosphate availability occurs independently of PTH and may be mediated in part by changes in levels of serum FGF23. Findings in FGF23-deficient mice suggest that FGF23 normally acts to lower blood phosphate and 1,25(OH)2D levels. In turn, elevation of blood phosphate and 1,25(OH)2D increases blood levels of FGF23. Renal phosphate reabsorption is impaired by hypocalcemia, hypo magnesemia, and severe hypophosphatemia. Phosphate clearance is enhanced by ECF volume expansion and impaired by dehydration. Phosphate retention is an important pathophysiologic feature of renal insufficiency (Chap. 322). ■

■HYPOPHOSPHATEMIA Causes Hypophosphatemia can occur by one or more of three primary mechanisms: (1) inadequate intestinal phosphate absorption, (2) excessive renal phosphate excretion, and (3) rapid redistribution of phosphate from the ECF into bone or soft tissue (Table 421-1). Because phosphate is so abundant in foods, inadequate intestinal absorption is almost never observed now that aluminum hydroxide antacids, which

TABLE 421-1 Causes of Hypophosphatemia I. Reduced renal tubular phosphate reabsorption A. PTH/PTHrP-dependent

1. Primary hyperparathyroidism
2. Secondary hyperparathyroidism a. Vitamin D deficiency/resistance b. Calcium starvation/malabsorption c. Bartter’s syndrome d. Autosomal recessive renal hypercalciuria with hypomagnesemia
3. PTHrP-dependent hypercalcemia of malignancy
4. Familial hypocalciuric hypercalcemia B. PTH/PTHrP-independent Bone and Mineral Metabolism in Health and Disease
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5. Excess FGF23 or other “phosphatonins” a. X-linked hypophosphatemic rickets (XLH) b. Autosomal recessive hypophosphatemia (ARHP) c. Autosomal dominant hypophosphatemic rickets (ADHR) (DMP1, ENPP1 deficiency) d. Tumor-induced osteomalacia syndrome (TIO) e. McCune-Albright syndrome (fibrous dysplasia) f. Epidermal nevus syndrome
6. Intrinsic renal disease a. Fanconi’s syndrome(s) b. Cystinosis c. Wilson’s disease d. NaPi-2a or NaPi-2c mutations

7. Other systemic disorders a. Poorly controlled diabetes mellitus b. Alcoholism c. Hyperaldosteronism d. Hypomagnesemia e. Amyloidosis f. Hemolytic-uremic syndrome g. Renal transplantation or partial liver resection h. Rewarming or induced hyperthermia
8. Drugs or toxins a. Ethanol b. Acetazolamide, other diuretics c. High-dose estrogens or glucocorticoids d. Heavy metals (lead, cadmium, saccharated ferric oxide) e. Toluene, N-methyl formamide f. Cisplatin, ifosfamide, foscarnet, rapamycin II. Impaired intestinal phosphate absorption A. Aluminum-containing antacids B. Sevalamer III. Shifts of extracellular phosphate into cells A. Intravenous glucose B. Insulin therapy for prolonged hyperglycemia or diabetic ketoacidosis C. Catecholamines (epinephrine, dopamine, albuterol) D. Acute respiratory alkalosis E. Gram-negative sepsis, toxic shock syndrome F. Recovery from starvation or acidosis G. Rapid cellular proliferation
9. Leukemic blast crisis
10. Intensive erythropoietin, other growth factor therapy IV. Accelerated net bone formation A. After parathyroidectomy B. Treatment of vitamin D deficiency, Paget's disease C. Osteoblastic metastases Abbreviations: PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide.

bind phosphate in the gut, are no longer widely used. Fasting or starva tion, however, may result in depletion of body phosphate and predis pose to subsequent hypophosphatemia during refeeding, especially if this is accomplished with IV glucose alone.

Chronic hypophosphatemia usually signifies the presence of a per sistent renal tubular phosphate-wasting disorder. Excessive activation of PTH/PTHrP receptors in the proximal tubule, as a result of primary or secondary hyperparathyroidism or because of the PTHrP-mediated hypercalcemia syndrome in malignancy (Chap. 422), is a common cause of renal hypophosphatemia. Familial hypocalciuric hypercalce mia and Jansen's metaphyseal chondrodysplasia are rare examples of genetic disorders in this category (Chap. 422). PART 12 Endocrinology and Metabolism Several genetic and acquired diseases cause PTH/PTHrP receptorindependent tubular phosphate wasting with associated rickets and osteomalacia. All these diseases manifest severe hypophosphatemia; renal phosphate wasting, sometimes accompanied by aminoaciduria; inappropriately low blood levels of 1,25(OH)2D; low-normal serum levels of calcium; and evidence of impaired cartilage or bone miner alization (osteomalacia). Analysis of these diseases in patients without generalized proximal tubular defects (Fanconi syndrome) led to the discovery of the hormone FGF23, which is an important physiologic regulator of phosphate metabolism. FGF23 decreases phosphate reab sorption in the proximal tubule and also suppresses the 1α-hydroxylase responsible for synthesis of 1,25(OH)2D. FGF23 is synthesized by cells of the osteoblast lineage, primarily osteocytes. High-phosphate diets increase FGF23 levels, and low-phosphate diets decrease them. ADHR was the first disease linked to abnormalities in FGF23. ADHR results from activating mutations in the gene that encodes FGF23. These mutations alter a cleavage site that ordinarily allows for inactivation of intact FGF23. Several other genetic disorders lead to elevated FGF23, hypophosphatemia, and osteomalacia. The most common of these is X-linked hypophosphatemic rickets (XLH), which results from inactivating mutations in an endopeptidase termed PHEX (phosphateregulating gene with homologies to endopeptidases on the X chromo some) that is expressed most abundantly on the surface of osteocytes and mature osteoblasts. Patients with XLH usually have high FGF23 levels, and ablation of the FGF23 gene reverses the hypophosphatemia found in the mouse version of XLH. How inactivation of PHEX leads to increased levels of FGF23 has not been determined. Two

rare auto somal recessive hypophosphatemic syndromes associated with elevated FGF23 are due to inactivating mutations of dentin matrix protein 1 (DMP1) and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), respectively, both of which normally are highly expressed in bone and presumably regulate FGF23 production. An unusual hypophosphatemic disorder, tumor-induced osteomalacia (TIO), is an acquired disorder in which tumors, usually of mesenchymal origin, secrete FGF23. The hypophosphatemic syndrome resolves completely within hours to days after successful resection of the responsible tumor. Such tumors typically express large amounts of FGF23 mRNA, and patients with TIO usually exhibit elevations of FGF23 in their blood. Neutralizing antibodies against FGF23 can be used to treat hypophos phatemia in patients with XLH and TIO. Dent's disease is an X-linked recessive disorder caused by inac tivating mutations in CLCN5, a chloride transporter expressed in endosomes of the proximal tubule; features include hypercalciuria, hypophosphatemia, and recurrent kidney stones. Renal phosphate wasting is common among poorly controlled diabetic patients and alcoholics, who therefore are at risk for iatrogenic hypophosphatemia when treated with insulin or IV glucose, respectively. Diuretics and certain other drugs and toxins can cause defective renal tubular phos phate reabsorption (Table 421-1). In hospitalized patients, hypophosphatemia is often attributable to massive redistribution of phosphate from the ECF into cells. Insulin therapy for diabetic ketoacidosis is a paradigm for this phenomenon, in which the severity of the hypophosphatemia is related to the extent of antecedent depletion of phosphate and other electrolytes (Chap. 416). The hypophosphatemia is usually greatest at a point many hours after initiation of insulin therapy and is difficult to predict from baseline measurements of serum phosphate at the time of presentation, when

prerenal azotemia can obscure significant phosphate depletion. Other factors that may contribute to such acute redistributive hypophospha temia include antecedent starvation or malnutrition, administration of IV glucose without other nutrients, elevated blood catecholamines (endogenous or exogenous), respiratory alkalosis, and recovery from metabolic acidosis. Hypophosphatemia also can occur transiently (over weeks to months) during the phase of accelerated net bone formation that fol lows parathyroidectomy for severe primary hyperparathyroidism or during treatment of vitamin D deficiency or lytic Paget's disease. This is referred to as "hungry bone syndrome" and is most prominent in patients who preoperatively have evidence of very high bone turnover (e.g., elevated serum levels of alkaline phosphatase). Osteoblastic metastases can also lead to this syndrome. Clinical and Laboratory Findings The clinical manifestations of severe hypophosphatemia reflect a generalized defect in cellular energy metabolism because of ATP depletion, a shift from oxidative phos phorylation toward glycolysis, and associated tissue or organ dysfunc tion. Acute, severe hypophosphatemia occurs mainly or exclusively in hospitalized patients with underlying serious medical or surgical illness and preexisting phosphate depletion due to excessive urinary losses, severe malabsorption, or malnutrition. Chronic hypophospha temia tends to be less severe, with a clinical presentation dominated by musculoskeletal complaints such as bone pain, osteomalacia, pseudo fractures, and proximal muscle weakness or, in children, rickets and short stature. Neuromuscular manifestations of severe hypophosphatemia are variable but may include muscle weakness, lethargy, confusion, dysar thria, dysphagia, oculomotor palsies, nystagmus, ataxia, hyporeflexia, impaired sphincter control, paresthesia, generalized or GuillainBarré–like ascending paralysis, seizures, coma, and even death. Serious sequelae such as paralysis and seizures are likely only at phosphate concentrations <0.25 mmol/L (<0.8 mg/dL). Rhabdomyolysis may develop during rapidly progressive hypophosphatemia. The diagnosis of

hypophosphatemia-induced rhabdomyolysis may be overlooked, as up to 30% of patients with acute hypophosphatemia (<0.7 mM) have creatine phosphokinase elevations that peak 1–2 days after the nadir in serum phosphate, when the release of phosphate from injured myocytes may have led to a near normalization of circulating levels of phosphate. Respiratory failure and cardiac dysfunction, which are reversible with phosphate treatment, may occur at serum phosphate levels of 0.5–0.8 mmol/L (1.5–2.5 mg/dL). Renal tubular defects, including tubular acidosis, glycosuria, and impaired reabsorption of sodium and calcium, may occur. Hematologic abnormalities correlate with reduc tions in intracellular ATP and 2,3-diphosphoglycerate and may include erythrocyte microspherocytosis and hemolysis; impaired oxyhemo globin dissociation; defective leukocyte chemotaxis, phagocytosis, and bacterial killing; and platelet dysfunction. TREATMENT Hypophosphatemia Severe hypophosphatemia (<0.75 mmol/L [<2 mg/dL]), particu larly in the setting of underlying phosphate depletion, consti tutes a dangerous electrolyte abnormality that should be corrected promptly. Unfortunately, the cumulative deficit in body phosphate cannot be predicted directly from knowledge of the circulating level of phosphate, and therapy must be approached empirically. The threshold for IV phosphate therapy and consequently the dose of phosphate to be administered should reflect consideration of renal function, the likely severity and duration of the underlying phosphate depletion, and the presence and severity of symptoms consistent with those of hypophosphatemia. In adults, phosphate may be safely administered IV as neutral mixtures of sodium or potassium phosphate salts at initial doses of 0.2–0.8 mmol/kg of elemental phosphorus over 6 h (e.g., 10–50 mmol over 6 h), with doses >20 mmol/6 h reserved for those who have serum levels

TABLE 421-2 Intravenous Therapy for Hypophosphatemia CONSIDER Likely severity of underlying phosphate depletion Concurrent parenteral glucose administration Presence of neuromuscular, cardiopulmonary, or hematologic complications of hypophosphatemia Renal function (reduce dose by 50% if serum creatinine >220 µmol/L [>2.5 mg/dL]) Serum calcium level (correct hypocalcemia first; reduce dose by 50% in hypercalcemia) Guidelines RATE OF INFUSION, MMOL/H DURATION, H TOTAL ADMINISTERED, MMOL SERUM PHOSPHORUS, MM (MG/DL) <0.8 (<2.5)

<0.5 (<1.5)

<0.3 (<1)

Note: Rates shown are calculated for a 70-kg person; levels of serum calcium and phosphorus must be measured every 6–12 h during therapy; infusions can be repeated to achieve stable serum phosphorus levels >0.8 mmol/L (>2.5 mg/dL); most formulations available in the United States provide 3 mmol/mL of sodium or potassium phosphate. <0.5 mmol/L (1.5 mg/dL) and normal renal function. A suggested approach is presented in Table 421-2. Serum levels of phosphate and calcium must be monitored closely (every 6–12 h) throughout treatment. It is important to avoid a serum calcium-phosphorus product >50 mg2/dL2 to reduce the risk of heterotopic calcification. Hypocalcemia, if present, should be corrected before administer ing IV phosphate. Less severe hypophosphatemia, in the range of 0.5–0.8 mmol/L (1.5–2.5 mg/dL), usually can be treated with oral phosphate in divided doses of 750–2000 mg/d as elemental phos phorus; higher doses can cause bloating and diarrhea. Management of chronic hypophosphatemia requires knowledge of the cause(s) of the disorder. Hypophosphatemia related to the secondary hyperparathyroidism of vitamin D deficiency usually responds to treatment with vitamin D and calcium alone. XLH, ADHR,

TIO, and related renal tubular disorders usually are man aged with divided oral doses of phosphate, often with calcium and 1,25(OH)2D supplements to bypass the block in renal 1,25(OH)2D synthesis and prevent secondary hyperparathyroidism caused by suppression of ECF calcium levels. Care must be taken to be sure that oral calcium and phosphate are not administered at the same time, to avoid precipitation before absorption. Thiazide diuretics may be used to prevent nephrocalcinosis in patients who are man aged this way. Complete normalization of hypophosphatemia is generally not possible in these conditions. Burosumab, a human monoclonal antibody that inhibits FGF23, has been approved for the treatment of XLH and TIO. It corrects hypophosphatemia, improves bone pain, and heals fractures in both adults and children. Optimal therapy for TIO is surgical removal of the responsible tumor, which may be localized by radiographic skeletal survey or bone scan (many are located in bone) or by radionuclide scanning using sestamibi or labeled octreotide. Successful treatment of TIOinduced hypophosphatemia with octreotide has been reported in a small number of patients. Burosumab treatment can be used to treat hypophosphatemia in patients with TIO in whom tumors cannot be localized or removed. ■ ■HYPERPHOSPHATEMIA Causes When the filtered load of phosphate and glomerular fil tration rate (GFR) are normal, control of serum phosphate levels is achieved by adjusting the rate at which phosphate is reabsorbed by the proximal tubular NaPi-2 co-transporters. Hyperphosphatemia, defined in adults as a fasting serum phosphate concentration >1.8 mmol/L (5.5 mg/dL), usually results from impaired glomerular filtration, hypo parathyroidism, excessive delivery of phosphate into the ECF (from bone, gut, or parenteral phosphate therapy), or a combination of these

TABLE 421-3 Causes of Hyperphosphatemia I. Impaired renal phosphate excretion A. Renal insufficiency B. Hypoparathyroidism

1. Developmental
2. Autoimmune
3. After neck surgery or radiation
4. Activating mutations of the calcium-sensing receptor C. Parathyroid suppression Bone and Mineral Metabolism in Health and Disease
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5. Parathyroid-independent hypercalcemia a. Vitamin D or vitamin A intoxication b. Sarcoidosis, other granulomatous diseases c. Immobilization, osteolytic metastases d. Milk-alkali syndrome
6. Severe hypermagnesemia or hypomagnesemia D. Pseudohypoparathyroidism E. Acromegaly F. Tumoral calcinosis G. Heparin therapy II. Massive extracellular fluid phosphate loads A. Rapid administration of exogenous phosphate (intravenous, oral, rectal) B. Extensive cellular injury or necrosis
7. Crush injuries
8. Rhabdomyolysis
9. Hyperthermia
10. Fulminant hepatitis
11. Cytotoxic therapy
12. Severe hemolytic anemia C. Transcellular phosphate shifts
13. Metabolic acidosis
14. Respiratory acidosis factors (Table 421-3). The upper limit of normal serum phosphate concentrations is higher in children and neonates (2.4 mmol/L [7 mg/ dL]). It is useful to

distinguish hyperphosphatemia caused by impaired renal phosphate excretion from that which results from excessive deliv ery of phosphate into the ECF (Table 421-3). In chronic renal insufficiency, reduced GFR leads to phosphate retention. Hyperphosphatemia, and progressive loss of nephron func tion, in turn further impairs renal synthesis of 1,25(OH)2D, increases FGF23 levels, and stimulates PTH secretion and parathyroid gland hypertrophy both directly and indirectly (by lowering blood ionized calcium levels). Thus, hyperphosphatemia is a major cause of the secondary hyperparathyroidism of renal failure (Chaps. 322 and 422). Hypoparathyroidism leads to hyperphosphatemia via increased expression of NaPi-2 co-transporters in the proximal tubule. Hypo parathyroidism, or parathyroid suppression, has multiple potential causes, including autoimmune disease; developmental, surgical, or radiation-induced absence of functional parathyroid tissue; vitamin D intoxication or other causes of PTH-independent hypercalcemia; cellu lar PTH resistance (pseudohypoparathyroidism or hypomagnesemia); infiltrative disorders such as Wilson's disease and hemochromatosis; and impaired PTH secretion caused by hypermagnesemia, severe hypomagnesemia, or activating mutations in the CaSR. Hypocalcemia may also contribute directly to impaired phosphate clearance, as cal cium infusion can induce phosphaturia in hypoparathyroid subjects. Increased tubular phosphate reabsorption also occurs in acromegaly, during heparin administration, and in tumoral calcinosis. Tumoral cal cinosis is caused by a rare group of genetic disorders in which FGF23 is processed in a way that leads to low levels of active FGF23 in the blood stream. This may result from mutations in the FGF23 sequence or via inactivating mutations in the GALNT3 gene, which encodes a galac tosaminyl transferase that normally adds sugar residues to FGF23 that slow its proteolysis. A similar syndrome results from FGF23 resistance due to inactivating mutations of the FGF23 co-receptor Klotho. These

abnormalities cause elevated serum 1,25(OH)2D, parathyroid suppres sion, increased intestinal calcium absorption, and focal hyperostosis with large, lobulated periarticular heterotopic ossifications (especially at shoulders or hips) and are accompanied by hyperphosphatemia. In some forms of tumoral calcinosis, serum phosphorus levels are normal.

When large amounts of phosphate are delivered rapidly into the ECF, hyperphosphatemia can occur despite normal renal function. Examples include overzealous IV phosphate therapy, oral or rectal administra tion of large amounts of phosphate-containing laxatives or enemas (especially in children), extensive soft tissue injury or necrosis (crush injuries, rhabdomyolysis, hyperthermia, fulminant hepatitis, cytotoxic chemotherapy), extensive hemolytic anemia, and transcellular phos phate shifts induced by severe metabolic or respiratory acidosis. PART 12 Endocrinology and Metabolism Clinical Findings The clinical consequences of acute, severe hyperphosphatemia are due mainly to the formation of widespread calcium phosphate precipitates and resulting hypocalcemia. Thus, tetany, seizures, accelerated nephrocalcinosis (with renal failure, hyper kalemia, hyperuricemia, and metabolic acidosis), and pulmonary or cardiac calcifications (including development of acute heart block) may occur. The severity of these complications relates to the elevation of serum phosphate levels, which can reach concentrations as high as 7 mmol/L (20 mg/dL) in instances of massive soft tissue injury or tumor lysis syndrome. TREATMENT Hyperphosphatemia Therapeutic options for management of severe hyperphosphatemia are limited. Volume expansion may enhance renal phosphate clear ance. Aluminum hydroxide antacids

or sevelamer may be helpful in chelating and limiting absorption of offending phosphate salts pres ent in the intestine. Hemodialysis is the most effective therapeutic strategy and should be considered early in the course of severe hyperphosphatemia, especially in the setting of renal failure and symptomatic hypocalcemia. MAGNESIUM METABOLISM Magnesium is the major intracellular divalent cation. Normal concen trations of extracellular magnesium and calcium are crucial for normal neuromuscular activity. Intracellular magnesium forms a key complex with ATP and is an important cofactor for a wide range of enzymes, transporters, and nucleic acids required for normal cellular function, replication, and energy metabolism. The concentration of magne sium in serum is closely regulated within the range of 0.7–1 mmol/L (1.5–2 meq/L; 1.7–2.4 mg/dL), of which 30% is protein-bound and another 15% is loosely complexed to phosphate and other anions. One-half of the 25 g (1000 mmol) of total body magnesium is located in bone, only one-half of which is insoluble in the mineral phase. Almost all extraskeletal magnesium is present within cells, where the total concentration is 5 mM, 95% of which is bound to proteins and other macromolecules. Because only 1% of body magnesium resides in the ECF, measurements of serum magnesium levels may not accurately reflect the level of total body magnesium stores. Dietary magnesium content normally ranges from 6 to 15 mmol/d (140–360 mg/d), of which 30–40% is absorbed, mainly in the jejunum and ileum. Intestinal magnesium absorptive efficiency is stimulated by 1,25(OH)2D and can reach 70% during magnesium deprivation. Urinary magnesium excretion normally matches net intestinal absorp tion and is ~4 mmol/d (100 mg/d). Regulation of serum magnesium concentrations is achieved mainly by control of renal magnesium reabsorption. Only 20% of filtered magnesium is reabsorbed in the proximal tubule, whereas 60% is reclaimed in the cTAL and another 5–10% in the DCT. Magnesium reabsorption in the cTAL occurs via a paracellular route that requires both a lumen-positive potential, cre ated by NaCl reabsorption, and tight-junction proteins encoded by members of the Claudin gene family. Magnesium reabsorption in the cTAL is increased by PTH but inhibited by hypercalcemia or hyperma gnesemia, both of which activate the CaSR in this nephron segment.

■ ■HYPOMAGNESEMIA Causes Hypomagnesemia usually signifies substantial depletion of body magnesium stores (0.5–1 mmol/kg). Hypomagnesemia can result from intestinal malabsorption; protracted vomiting, diarrhea, or intestinal drainage; defective renal tubular magnesium reabsorption; or rapid shifts of magnesium from the ECF into cells, bone, or third spaces (Table 421-4). Dietary magnesium deficiency is unlikely except possibly in the setting of alcoholism. Rare genetic disorders that cause selective intestinal magnesium malabsorption have been described (primary infantile hypomagnesemia types 1 and 2). Another rare TABLE 421-4 Causes of Hypomagnesemia I. Impaired intestinal absorption A. Hypomagnesemia with secondary hypocalcemia (TRPM6 mutations) B. Malabsorption syndromes C. Vitamin D deficiency D. Proton pump inhibitors II. Increased intestinal losses A. Protracted vomiting/diarrhea B. Intestinal drainage, fistulas III. Impaired renal tubular reabsorption A. Genetic magnesium-wasting syndromes

1. Gitelman’s syndrome
2. Bartter’s syndrome
3. Claudin 16 or 19 mutations
4. Potassium channel mutations (Kv1.1, Kir4.1)
5. Na+,K+-ATPase γ-subunit mutations (FXYD2) B. Acquired renal disease
6. Tubulointerstitial disease
7. Postobstruction, ATN (diuretic phase)

8. Renal transplantation C. Drugs and toxins
9. Ethanol
10. Diuretics (loop, thiazide, osmotic)
11. Cisplatin
12. Pentamidine, foscarnet
13. Cyclosporine
14. Aminoglycosides, amphotericin B
15. Cetuximab D. Other
16. Extracellular fluid volume expansion
17. Hyperaldosteronism
18. SIADH
19. Diabetes mellitus
20. Hypercalcemia
21. Phosphate depletion
22. Metabolic acidosis
23. Hyperthyroidism IV. Rapid shifts from extracellular fluid A. Intracellular redistribution
24. Recovery from diabetic ketoacidosis
25. Refeeding syndrome
26. Correction of respiratory acidosis
27. Catecholamines B. Accelerated bone formation
28. Post-parathyroidectomy
29. Treatment of vitamin D deficiency
30. Osteoblastic metastases C. Other
31. Pancreatitis, burns, excessive sweating
32. Pregnancy (third trimester) and lactation Abbreviations: ATN, acute tubular necrosis; SIADH, syndrome of inappropriate antidiuretic hormone.

inherited disorder (hypomagnesemia with secondary hypocalcemia) is caused by mutations in the gene encoding TRPM6, a protein that, with TRPM7, forms a channel important for both intestinal and distaltubular renal transcellular magnesium transport. Malabsorptive states, often compounded by vitamin D deficiency, can critically limit magne sium absorption and produce hypomagnesemia despite the compensa tory effects of secondary hyperparathyroidism and of hypocalcemia and hypomagnesemia to enhance cTAL magnesium reabsorption. Diarrhea or surgical drainage fluid may contain ≥5 mmol/L of magne sium. Proton pump inhibitors (omeprazole and others) may produce hypomagnesemia by an unknown mechanism that does not involve renal wasting of magnesium. Several genetic magnesium-wasting syndromes have been described, including inactivating mutations of genes encoding the DCT NaCl co-transporter (Gitelman’s syndrome), proteins required for cTAL Na-K-2Cl transport (Bartter’s syndrome), claudin 16 or claudin 19 (autosomal recessive renal hypomagnesemia with hypercalciuria), a DCT Na+,K+-ATPase γ-subunit (autosomal dominant renal hypo magnesemia with hypocalciuria), DCT K+ channels (Kv1.1, Kir4.1), and a mitochondrial gene encoding a tRNA. Activating mutations of the CaSR can cause hypomagnesemia as well as hypocalcemia. ECF expansion, hypercalcemia, and severe phosphate depletion may impair magnesium reabsorption, as can various forms of renal injury, including those caused by drugs such as cisplatin, cyclosporine, ami noglycosides, and pentamidine as well as the epidermal growth factor (EGF) receptor inhibitory antibody cetuximab (EGF action is required for normal DCT apical expression of TRPM6) (Table 421-4). A rising blood

concentration of ethanol directly impairs tubular magnesium reabsorption, and persistent glycosuria with osmotic diuresis leads to magnesium wasting and probably contributes to the high frequency of hypomagnesemia in poorly controlled diabetic patients. Magnesium depletion is aggravated by metabolic acidosis, which causes intracel lular losses as well. Hypomagnesemia due to rapid shifts of magnesium from ECF into the intracellular compartment can occur during recovery from diabetic ketoacidosis, starvation, or respiratory acidosis. Less acute shifts may be seen during rapid bone formation after parathyroidectomy, with treatment of vitamin D deficiency, or with osteoblastic metastases. Large amounts of magnesium may be lost with acute pancreatitis, extensive burns, or protracted and severe sweating and during preg nancy and lactation. Clinical and Laboratory Findings Hypomagnesemia may cause generalized alterations in neuromuscular function, including tetany, seizures, muscle weakness, ataxia, nystagmus, vertigo, depression, irri tability, and psychosis. Patients are usually asymptomatic when serum magnesium concentrations are >0.5 mmol/L (1 meq/L; 1.2 mg/dL), although the severity of symptoms may not correlate well with serum magnesium levels. Cardiac arrhythmias may occur, including sinus tachycardia, other supraventricular tachycardias, and ventricular arrhythmias. Electrocardiographic abnormalities may include pro longed PR or QT intervals, T-wave flattening or inversion, and ST straightening. Sensitivity to digitalis toxicity may be enhanced. Other electrolyte abnormalities often seen with hypomagnesemia, including hypocalcemia (with hypocalciuria) and hypokalemia, may not be easily corrected unless magnesium is administered as well. The hypocalcemia may be a result of concurrent vitamin D defi ciency, although hypomagnesemia can cause impaired synthesis of 1,25(OH)2D, cellular resistance to PTH, and, at very low serum mag nesium (<0.4 mmol/L [<0.8 meq/L; <1 mg/dL]), defects in PTH secre tion; these abnormalities are reversible with therapy. TREATMENT Hypomagnesemia Mild, asymptomatic hypomagnesemia may be treated with oral magnesium salts (MgCl2, MgO, Mg[OH]2) in divided doses total ing 20–30 mmol/d (40–60 meq/d). Diarrhea may occur with larger doses. More severe hypomagnesemia should be treated

parenterally, preferably with IV MgCl2, which can be administered safely as a continuous infusion of 50 mmol/d (100 meq Mg2+/d) if renal function is normal. If GFR is reduced, the infusion rate should be lowered by 50–75%. Use of IM MgSO4 is discouraged; the injections are painful and provide relatively little magnesium (2 mL of 50% MgSO4 supplies only 4 mmol). MgSO4 may be given IV instead of MgCl2, although the sulfate anions may bind calcium in serum and urine and aggravate hypocalcemia. Serum magne sium should be monitored at intervals of 12–24 h during therapy, which may continue for several days because of impaired renal con servation of magnesium (only 50–70% of the daily IV magnesium dose is retained) and delayed repletion of intracellular deficits, which may be as high as 1–1.5 mmol/kg (2–3 meq/kg).

 It is important to consider the need for calcium, potassium, and phosphate supplementation in patients with hypomagnesemia. Vitamin D deficiency frequently coexists and should be treated with oral or parenteral vitamin D or 25(OH)D (but not with 1,25(OH)2D, which may impair tubular magnesium reabsorp tion, possibly via PTH suppression). In severely hypomagnesemic patients with concomitant hypocalcemia and hypophosphatemia, administration of IV magnesium alone may worsen hypophos phatemia, provoking neuromuscular symptoms or rhabdomy olysis, due to rapid stimulation of previously suppressed PTH secretion. This is avoided by administering both calcium and magnesium. ■ ■HYPERMAGNESEMIA Causes Hypermagnesemia is rarely seen in the absence of renal insufficiency as normal kidneys can

excrete large amounts (250 mmol/d) of magnesium. Mild hypermagnesemia due to exces sive reabsorption in the cTAL occurs with CaSR mutations in familial hypocalciuric hypercalcemia and has been described in some patients with adrenal insufficiency, hypothyroidism, or hypothermia. Massive exogenous magnesium exposures, usually via the gastrointestinal tract, can overwhelm renal excretory capacity and cause life-threatening hypermagnesemia (Table 421-5). A notable example of this is pro longed retention of even normal amounts of magnesium-containing cathartics in patients with intestinal ileus, obstruction, or perforation. Extensive soft tissue injury or necrosis also can deliver large amounts of magnesium into the ECF in patients who have suffered trauma, shock, sepsis, cardiac arrest, or severe burns. Further, infusion of magnesium in pregnant women with eclampsia can lead to hypocalcemia. Clinical and Laboratory Findings The most prominent clinical manifestations of hypermagnesemia are vasodilation and neuromuscu lar blockade, which may appear at serum magnesium concentrations

> 2 mmol/L (>4 meq/L; >4.8 mg/dL). Hypotension that is refractory to vasopressors or volume expansion may be an early sign. Nausea, lethargy, and weakness may progress to respiratory failure, paralysis, TABLE 421-5 Causes of Hypermagnesemia I. Excessive magnesium intake A. Cathartics, urologic irrigants B. Parenteral magnesium administration II. Rapid mobilization from soft tissues A. Trauma, shock, sepsis B. Cardiac arrest C. Burns III. Impaired magnesium excretion A. Renal failure B. Familial hypocalciuric hypercalcemia IV. Other A. Adrenal insufficiency B. Hypothyroidism C. Hypothermia

and coma, with hypoactive tendon reflexes, at serum magnesium levels

> 4 mmol/L. Other findings may include gastrointestinal hypomotility or ileus; facial flushing; pupillary dilation; paradoxical bradycardia; prolongation of PR, QRS, and QT intervals; heart block; and, at serum magnesium levels approaching 10 mmol/L, asystole.

Hypermagnesemia, acting via the CaSR, causes hypocalcemia and hypercalciuria due to both parathyroid suppression and impaired cTAL calcium reabsorption. TREATMENT Hypermagnesemia PART 12 Endocrinology and Metabolism Successful treatment of hypermagnesemia generally involves iden tifying and interrupting the source(s) of magnesium and employing measures to increase magnesium clearance from the ECF. Use of magnesium-free cathartics or enemas may be helpful in clearing ingested magnesium from the gastrointestinal tract. Vigorous IV hydration should be attempted, if appropriate. Hemodialysis is effective and may be required in patients with significant renal insufficiency. Calcium, administered IV in doses of 100–200 mg over 1–2 h, has been reported to provide temporary improvement in signs and symptoms of hypermagnesemia. VITAMIN D ■ ■SYNTHESIS AND METABOLISM 1,25-Dihydroxyvitamin D [1,25(OH)2D] is the major steroid hormone involved in regulation of mineral ion homeostasis. Vitamin D and its metabolites are hormones and hormone precursors rather than vitamins, since in the proper biologic setting, they can be synthesized endogenously (Fig. 421-4). In response to ultraviolet radiation of the skin,

a photochemical cleavage results in the formation of vitamin D from 7-dehydrocholesterol. Cutaneous production of vitamin D is decreased by melanin and high solar protection factor sunblocks, which effectively impair skin penetration by ultraviolet light. The increased use of sunblocks in North America and Western Europe and a reduction in the magnitude of solar exposure of the general popula tion over the past several decades has led to an increased reliance on dietary sources of vitamin D. In the United States and Canada, these sources largely consist of fortified cereals and dairy products, in addi tion to fish oils and egg yolks. Vitamin D from plant sources is in the form of vitamin D2, whereas that from animal sources is vitamin D3. These two forms have equivalent biologic activity and are activated equally well by the vitamin D hydroxylases in humans. Vitamin D enters the circulation, whether absorbed from the intestine or synthe sized cutaneously, bound to vitamin D–binding protein, an α-globulin synthesized in the liver. Vitamin D is subsequently 25-hydroxylated in the liver by a cytochrome P450 oxidase in the mitochondria and microsomes. The activity of this hydroxylase is not tightly regulated, and the resultant metabolite, 25-hydroxyvitamin D [25(OH)D], is the major circulating and storage form of vitamin D. Approximately 88% of 25(OH)D circulates bound to the vitamin D–binding protein, 0.03% is free, and the rest circulates bound to albumin. The half-life of 25(OH) D is ~2–3 weeks, with that of 25(OH)D2 being shorter than that of 25(OH)D3 due to a lower affinity of vitamin D–binding protein for the former. The half-life of 25(OH)D is also greatly shortened when vita min D–binding protein levels are reduced, as can occur with increased urinary losses in the nephrotic syndrome. The second hydroxylation, required for the formation of the mature hormone, occurs in the kidney (Fig. 421-5). The 25-hydroxyvitamin D-1α-hydroxylase (encoded by the CYP27B1 gene) is a tightly regu lated cytochrome P450–like mixed-function oxidase expressed in the proximal convoluted tubule cells of the kidney. PTH and hypophospha temia are the major inducers of this microsomal enzyme in the kidney, whereas calcium, FGF23, and the enzyme’s product, 1,25(OH)2D, repress it. The 25-hydroxyvitamin D-1α-hydroxylase is also present in numerous other cell types, where it is not subject to hormonal

Vitamin D Skin 7-Dehydrocholesterol Gut Vitamin D Liver 25(OH)D Kidney 1,25(OH)2D FIGURE 421-4 Vitamin D synthesis and activation. Vitamin D is synthesized in the skin in response to ultraviolet radiation and also is absorbed from the diet. It is then transported to the liver, where it undergoes 25-hydroxylation. This metabolite is the major circulating form of vitamin D. The final step in hormone activation, 1α-hydroxylation, occurs in the kidney. regulation. It is expressed in epidermal keratinocytes, but keratinocyte production of 1,25(OH)2D is not thought to contribute to circulating levels of this hormone. In addition to being present in the trophoblastic layer of the placenta, the 1α-hydroxylase is produced by macrophages associated with granulomas and lymphomas. In these latter pathologic states, the activity of the enzyme is induced by interferon γ and TNF-α but is not regulated by calcium or 1,25(OH)2D; therefore, hypercalce mia, associated with elevated levels of 1,25(OH)2D, may be observed. Treatment of sarcoidosis-associated hypercalcemia with glucocorti coids, ketoconazole, or chloroquine reduces 1,25(OH)2D production and effectively lowers serum calcium. In contrast, chloroquine has not been shown to lower the elevated serum 1,25(OH)2D levels in patients with lymphoma. The major pathway for inactivation of vitamin D metabolites is an additional hydroxylation step by the vitamin D 24-hydroxylase, an enzyme that is expressed in most tissues. 1,25(OH)2D is the major inducer of this enzyme; therefore, this hormone promotes its own inactivation, thereby limiting its biologic effects. FGF23 also induces this hydroxylase, thereby reducing circulating 1,25(OH)2D levels by increasing its inactivation, as well as by impairing its synthesis. Muta tions of the gene encoding this enzyme (CYP24A1) can lead to infan tile

hypercalcemia, and in those less severely affected, long-standing hypercalciuria, nephrocalcinosis, and nephrolithiasis can occur. Polar metabolites of 1,25(OH)2D are secreted into the bile and reabsorbed via the enterohepatic circulation. Impairment of this recir culation, which is seen with diseases of the terminal ileum, leads to accelerated losses of vitamin D metabolites.

Vitamin D3 Vitamin D-25 hydroxylase – Liver 25(OH)D3 25(OH)D-1αhydroxylase and other factors Pi – Kidney / + – /

2D H) 1,25(OH)2D3 (O

1, PTH – PTH Bone Parathyroid glands

C

a2

-

C Intestine H al P ci O fi

2– ca

2– O ti P on H +

a2 C Blood calcium FIGURE 421-5 Schematic representation of the hormonal control loop for vitamin D metabolism and function. A reduction in the serum calcium below ~2.2 mmol/L (8.8 mg/dL) prompts a proportional increase in the secretion of parathyroid hormone (PTH) and so mobilizes additional calcium from the bone. PTH promotes the synthesis of 1,25(OH)2D in the kidney, which in turn stimulates the mobilization of calcium from bone and intestine and regulates the synthesis of PTH by negative feedback. ■ ■ACTIONS OF 1,25(OH)2D 1,25(OH)2D mediates its biologic effects by binding to a member of the nuclear receptor superfamily, the vitamin D receptor (VDR). This receptor belongs to the subfamily that includes the thyroid hormone receptors, the retinoid receptors, and the peroxisome proliferator– activated receptors; however, in contrast to the other members of this subfamily, only one VDR isoform has been isolated. The VDR binds to target DNA sequences as a heterodimer with the retinoid X receptor, recruiting a series of coactivators that modify chromatin and approxi mate the VDR to the basal transcriptional apparatus, resulting in the induction of target gene expression. The mechanism of transcriptional repression by the VDR varies with different target genes but has been shown to involve either interference with the action of activating transcription factors or the recruitment of novel proteins to the VDR complex, resulting in transcriptional repression. The affinity of the VDR for 1,25(OH)2D is approximately three orders of magnitude higher than that for other vitamin D metabo lites. Metabolites resulting from the 24-hydroxylation of vitamin D, including 1,24,25 trihydroxyvitamin D3 (1,24,35(OH)3D3) and 24,25 dihydroxyvitamin D3 (24,25(OH)D3) have biologic effects that mimic 1,25(OH)2D. In normal physiologic circumstances, these other

metabolites are not thought to play significant roles in stimulating receptor-dependent actions. However, in states of vitamin D toxicity, the markedly elevated levels of 25(OH)D may lead to hypercalcemia by interacting directly with the VDR and by displacing 1,25(OH)2D from vitamin

D–binding protein, resulting in increased bioavailability of the active hormone.

The VDR is expressed in a wide range of cells and tissues. The molecular actions of 1,25(OH)2D have been studied most extensively in tissues involved in the regulation of mineral ion homeostasis. This hormone is a major inducer of calbindin 9K, a calcium-binding pro tein expressed in the intestine, which is thought to play an important role in the active transport of calcium across the enterocyte. The two major calcium transporters expressed by intestinal epithelia, TRPV5 and TRPV6 (transient receptor potential vanilloid), are also vitamin D responsive. By inducing the expression of these and other genes in the small intestine, 1,25(OH)2D increases the efficiency of intes tinal calcium absorption, and it also has been shown to have several important actions in the skeleton. The VDR is expressed in osteoblasts and regulates the expression of several genes in this cell. These genes include the bone matrix proteins osteocalcin and osteopontin, which are upregulated by 1,25(OH)2D, in addition to type I collagen, which is transcriptionally repressed by 1,25(OH)2D. Both 1,25(OH)2D and PTH induce the expression of RANK ligand in osteoblasts, which promotes osteoclast differentiation and increases osteoclast activity, by binding to RANK on osteoclast progenitors and mature osteoclasts. This is the mechanism by which 1,25(OH)2D induces bone resorption. 1,25(OH)2D regulates phosphate homeostasis, primarily by inducing the expression of FGF23 in osteocytes. The skeletal features associated with VDR-knockout mice (rickets, osteomalacia) are largely corrected by increasing calcium and phosphorus intake, underscoring the impor tance of vitamin D action in the gut. Bone and Mineral Metabolism in Health and Disease
CHAPTER 421 The VDR is expressed in the parathyroid gland, and 1,25(OH)2D has been shown to have antiproliferative effects on parathyroid cells and to suppress the transcription of the parathyroid hormone gene. These effects of 1,25(OH)2D on the parathyroid gland are an important part of the rationale for current therapies directed at preventing and treating hyperparathyroidism associated with renal insufficiency and complica tions of chronic oral phosphate therapy. The VDR is also expressed in tissues and organs that do not play a role in mineral ion homeostasis. Notable in this respect is the obser vation that 1,25(OH)2D has an antiproliferative effect on several cell types, including keratinocytes, breast cancer cells, and prostate cancer cells. The effects of 1,25(OH)2D and the VDR on keratinocytes are particularly intriguing, since the VDR is primarily a transcriptional repressor in these cells. Alopecia is seen in humans and mice with mutant VDRs but is not a feature of vitamin D deficiency; thus, the effects of the VDR on the hair follicle are ligand-independent. Vitamin D action is also important for regulating the normal maturation of the bone-tendon attachment site, called the enthesis. ■ ■VITAMIN D DEFICIENCY The mounting concern about the relationship between solar exposure and the development of skin cancer has led to increased reliance on dietary sources of vitamin D. Although the prevalence of vitamin D deficiency varies, the third National Health and Nutrition Examination Survey (NHANES III) revealed that vitamin D deficiency is prevalent throughout the United States, with the prevalence being >29% in obese children. The clinical syndrome of vitamin D deficiency can be a result of deficient production of vitamin D in the skin, lack of dietary intake, accelerated losses of vitamin D, impaired vitamin D activation, or resis tance to the biologic effects of 1,25(OH)2D (Table 421-6). The elderly and nursing home residents are particularly at risk for vitamin D defi ciency, since both the efficiency of vitamin D synthesis in the skin and the absorption of vitamin D from the intestine decline with age. The presence of terminal ileal disease also results in impaired enterohepatic circulation of vitamin D metabolites. While intestinal malabsorption of dietary fats and short bowel syndrome, including that associated with intestinal bypass surgery, lead to vitamin D deficiency,

the cause of vitamin D deficiency in obese individuals is poorly understood.

TABLE 421-6 Causes of Impaired Vitamin D Action Vitamin D deficiency Impaired cutaneous production Dietary absence Malabsorption (short gut syndrome, Impaired 1α-hydroxylation Hypoparathyroidism Ketoconazole 1α-Hydroxylase mutation FGF23 excess Oncogenic osteomalacia Hypophosphatemic rickets Fibrous dysplasia Chronic kidney disease Target organ resistance Vitamin D receptor mutation Phenytoin Other Obesity gastric bypass) Accelerated loss of vitamin D Increased metabolism (barbiturates, phenytoin, rifampin) Impaired enterohepatic circulation Nephrotic syndrome CYP3A4 mutation Impaired 25-hydroxylation Liver disease, isoniazid 25-Hydroxylase mutation PART 12 Endocrinology and Metabolism In addition to intestinal diseases, accelerated inactivation of vitamin D metabolites can be seen with drugs that induce hepatic cytochrome P450 mixed-function oxidases such as barbiturates, phenytoin, and rifampin. Gain-of-function mutations in CYP3A4 accelerate the oxi dation and inactivation of vitamin D metabolites, thus resulting in decreased serum levels of 25OHD and 1,25(OH)2D. This form of rickets is autosomal recessive and presents during early childhood and can be treated with high doses of calcitriol or vitamin D. Impaired 25-hydrox ylation, associated with severe liver disease or isoniazid, is an uncom mon cause of vitamin D deficiency. A mutation in the gene responsible for 25-hydroxylation has been identified in a few kindreds. Increased circulating FGF23 levels impair 1α-hydroxylation, preventing the pro duction of 1,25(OH)2D. High levels of FGF23 are seen in those with genetic disorders associated with hypophosphatemic rickets, the most common of which is X-linked hypophosphatemia, and are prevalent in populations with profound renal dysfunction. Thus, therapeutic inter ventions should be considered in patients whose creatinine clearance is <0.5 mL/s (30 mL/min). Mutations in the renal 1α-hydroxylase are the basis for the genetic disorder pseudovitamin D–deficiency rickets (also called vitamin D–dependent rickets type I). This autosomal recessive disorder presents with the syndrome of vitamin D deficiency in the first year of life. Patients present with growth retardation, rickets, and hypo calcemic seizures. Serum 1,25(OH)2D levels are low despite normal 25(OH)D levels and elevated PTH levels. Treatment with vitamin D metabolites that do not require 1α-hydroxylation for activity results in disease remission, although lifelong therapy is required. A second autosomal recessive disorder, hereditary vitamin D–resistant rickets (also called vitamin D-dependent rickets type II), a consequence of vitamin D receptor mutations, is a greater therapeutic challenge. These patients present in a similar fashion during the first year of life, but alopecia often accompanies the disorder, demonstrating a functional role of the VDR in the keratinocyte stem cell population required for hair follicle regeneration. Serum levels of 1,25(OH)2D are dramatically elevated in these individuals both because of increased production due to stimulation of 1α-hydroxylase activity as a consequence of second ary hyperparathyroidism and because of impaired inactivation since induction of the 24-hydroxylase by 1,25(OH)2D requires an intact VDR. Since the receptor mutation results in hormone resistance, daily calcium and phosphate infusions may be required to bypass the defect in intestinal mineral ion absorption. Regardless of the cause, the clinical manifestations of vitamin D deficiency are largely a consequence of impaired intestinal calcium absorption. Mild to moderate vitamin D deficiency is asymptomatic, whereas long-standing vitamin D deficiency results in hypocalcemia accompanied by secondary hyperparathyroidism, impaired miner alization of the skeleton (osteopenia on x-ray or decreased bone mineral density), and proximal myopathy. Vitamin D deficiency also has been shown to be associated with an increase in overall mortal ity, including cardiovascular causes. In the absence of an intercurrent illness, the hypocalcemia associated with long-standing vitamin D deficiency rarely presents with acute symptoms of hypocalcemia such

as numbness, tingling, and seizures. However, the concurrent devel opment of hypomagnesemia, which impairs parathyroid function, or the administration of potent bisphosphonates, which impair bone resorption, can lead to acute symptomatic hypocalcemia in vitamin D– deficient individuals. Rickets and Osteomalacia In children, before epiphyseal fusion, vitamin D deficiency results in growth retardation associated with an expansion of the growth plate known as rickets. Three layers of chondrocytes are present in the normal growth plate: the reserve zone, the proliferating zone, and the hypertrophic zone. Rickets associated with impaired vitamin D action is characterized by expansion of the hypertrophic chondrocyte layer. The expansion of the growth plate is a consequence of impaired apoptosis of the late hypertrophic chondro cytes, an event that precedes replacement of these cells by osteoblasts during endochondral bone formation. Investigations in murine models demonstrate that hypophosphatemia, which in vitamin D deficiency is a consequence of secondary hyperparathyroidism, is a key etiologic factor in the development of the rachitic growth plate. Impaired actions specific to vitamin D also contribute to the expansion of the hypertro phic layer in the rachitic growth plate. The hypocalcemia and hypophosphatemia that accompany vitamin D deficiency result in impaired mineralization of bone matrix proteins, a condition known as osteomalacia. Osteomalacia is also a feature of long-standing hypophosphatemia, which may result from renal phosphate wasting, or chronic use of etidronate or phosphate-binding antacids. This hypomineralized matrix is biomechanically inferior to normal bone; as a result, patients with osteomalacia are prone to bow ing of weight-bearing extremities and skeletal fractures. Vitamin D and calcium supplementation have been shown to decrease the incidence of hip fracture among ambulatory nursing home residents in France, suggesting that undermineralization of bone contributes significantly to morbidity in the elderly. Proximal myopathy is a striking feature of severe vitamin D deficiency both in children and in adults. Rapid reso lution of the myopathy is observed upon vitamin D treatment. Although vitamin D deficiency is the most common cause of rickets and osteomalacia, many disorders lead to inadequate mineralization of the growth plate and bone. Calcium deficiency without vitamin D defi ciency, the disorders of vitamin D metabolism previously discussed, and hypophosphatemia can all lead to inefficient mineralization. Even in the presence of normal calcium and phosphate levels, chronic aci dosis and drugs such as bisphosphonates can lead to osteomalacia. The inorganic calcium/phosphate mineral phase of bone cannot form at low pH. Bisphosphonates bind to and prevent hydroxyapatite crystal growth. Since alkaline phosphatase is necessary for normal mineral deposition, probably because the enzyme can hydrolyze inhibitors of mineralization such as inorganic pyrophosphate, genetic inactivation of the alkaline phosphatase gene (hereditary hypophosphatasia) also can lead to osteomalacia in the setting of normal calcium and phos phate levels. Diagnosis of Vitamin D Deficiency, Rickets, and Osteomalacia

The most specific screening test for vitamin D deficiency in otherwise healthy individuals is a serum 25(OH)D level. Although the normal ranges vary, levels of 25(OH)D <37 nmol/L (<15 ng/mL) are associ ated with increasing PTH levels and lower bone density. The National Academy of Medicine has defined vitamin D sufficiency as a vitamin D level >50 nmol/L (>20 ng/mL), although higher levels may be required to optimize intestinal calcium absorption in the elderly and those with underlying disease states, including obesity. Vitamin D deficiency leads to impaired intestinal absorption of calcium, resulting in decreased serum total and ionized calcium values. This hypocalcemia results in secondary hyperparathyroidism, a homeostatic response that initially maintains serum calcium levels at the expense of the skeleton. Due to the PTH-induced increase in bone turnover, alkaline phosphatase levels are often increased. In addition to increasing bone resorption, PTH decreases urinary calcium excretion while promoting phos phaturia. This results in

hypophosphatemia, which exacerbates the mineralization defect in the skeleton. With prolonged vitamin D defi ciency resulting in osteomalacia, calcium stores in the skeleton become

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Revision #1
Created 2026-01-06 16:35:26 UTC by Omar Ayman
Updated 2026-01-06 16:35:26 UTC by Omar Ayman