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Hypercalcemia and Hypocalcemia Calcium is the most abundant mineral in the human body, fulfilling numerous physiological functions. These functions include providing fundamental structure and strength of the skeleton [as the solid hydroxyapatite salt $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$]; cellular signaling and hormone secretion; cardiac pacemaker rhythmicity and contractility; skeletal muscle contractility; immune function; and neural signaling, among others. Given these and other vital biological functions, intracellular and extracellular calcium concentrations are tightly regulated on timescales of milliseconds (intracellular) to minutes-hours (extracellular), with the former very dynamic and the latter very stable as necessary for health. PART 2 Cardinal Manifestations and Presentation of Diseases Serum calcium concentrations are maintained within an exquisitely narrow range through feedback mechanisms that involve parathyroid hormone (PTH) and the vitamin D metabolites 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] and 25-hydroxyvitamin D [$25(\text{OH})\text{D}$]. PTH increases osteocyte production of RANKL, a potent stimulus for osteoclast-mediated bone resorption that mobilizes skeletal calcium. These feedback mechanisms integrate signals between the parathyroid glands, kidney, intestine, and bone to control circulating extracellular calcium (Fig. 57-1; Chap. 421). Disorders of serum calcium concentration are very common, arising from primary or secondary perturbations in the calciotropic functions. Disease manifestations reflect not only the impact of acute calcium changes on organ function, but also the impact of chronic Parathyroid glands

PTH

ECF Ca^{2+}

Kidney

Bone 1,25 $(\text{OH})_2\text{D}$ Intestine FIGURE 57-1 Homeostatic feedback mechanisms maintain extracellular calcium concentrations within a narrow physiologic range, typically 8.5–10.5 mg/dL (2.1–2.6 mM) (reference values vary slightly by lab). A decrease in extracellular (ECF) calcium (Ca^{2+}) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor (CaSR) on parathyroid chief cells. PTH, in turn, increases resorption of calcium from bone (2, left) and distal renal tubule reabsorption of filtered urinary calcium (2, right), and also stimulates renal proximal

tubule 1,25(OH)₂D production (3). Circulating 1,25(OH)₂D acts on the small intestine to increase dietary calcium absorption (4). Collectively, these homeostatic mechanisms defend against life-threatening hypocalcemia and serve to restore serum calcium levels to normal.

compensatory responses that come with clinical consequences (e.g., osteoporosis, nephrocalcinosis). This chapter provides a brief summary of the approach to patients with altered serum calcium levels. See Chap. 422 for a detailed discussion of this topic.

HYPERCALCEMIA

ETIOLOGY The causes of hypercalcemia can be understood based on derangements in the normal feedback mechanisms that regulate serum calcium (Table 57-1). Primary hyperparathyroidism and malignancy are the two most common causes of hypercalcemia, although other diseases must be considered (Table 57-2). Excess PTH production, which is not appropriately suppressed by increased serum calcium concentrations, occurs in primary hyperparathyroidism (pHPT). pHPT is almost always due to a nonmalignant neoplastic disorder of the parathyroid glands (a parathyroid adenoma or parathyroid hyperplasia) that is associated with increased parathyroid cell mass and impaired feedback.

TABLE 57-1 Causes of Hypercalcemia

Excessive PTH production
Primary hyperparathyroidism
Sporadic or familial (e.g., MEN) parathyroid adenoma or hyperplasia
Rarely parathyroid carcinoma
Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
Ectopic PTH secretion (very rare)
FHH (mutations reducing CaSR signaling)
Nongenetic alterations in CaSR function (lithium therapy, rare CaSR inhibitory autoantibodies)
Hypercalcemia of malignancy
Overproduction of PTHrP (many solid tumors)
Lytic skeletal metastases (breast, myeloma)
Excessive 1,25(OH) ₂ D production (by constitutive macrophage CYP27B1 activity)
Granulomatous diseases (many causes: sarcoidosis, tuberculosis, leprosy, fungal infections, foreign body reaction)
Lymphomas (B cell, cutaneous T cell/Sezary syndrome)
Vitamin D intoxication
Ingestion of excessive vitamin D: 25(OH)D
Ingestion of excessive 1,25(OH) ₂ D (calcitriol) or 1- α -hydroxylated vitamin D analogues
Reduced vitamin D catabolism due to CYP24A1 deficiency
Primary increase in bone resorption
Hyperthyroidism
Paget's disease of bone
Immobilization
Ketogenic diet (in treatment of children with refractory epilepsy, uncommon)
Excessive calcium intake
Milk-alkali syndrome
Total parenteral nutrition
Other causes
Endocrine disorders (adrenal insufficiency, pheochromocytoma, acromegaly, VIPoma)
Medications (thiazides, vitamin A, lithium, foscarnet, teriparatide, aromatase inhibitors)
Discontinuation of denosumab with rebound resorption
Recovery phase of rhabdomyolysis with renal failure
Williams-Beuren syndrome
Excessive mammary PTHrP production with pregnancy or lactation (rare)
Pseudohypercalcemia (e.g., calcium-binding IgM in Waldenström's macroglobulinemia)

Abbreviations: CaSR, calcium sensor receptor; FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

TABLE 57-2 Causes of Hypocalcemia

Low Parathyroid Hormone Levels (Hypoparathyroidism)
Parathyroid agenesis
Isolated (genetic: autosomal recessive GCM2 loss of function; X-linked mutations)
Syndromic (e.g., DiGeorge's, HDR, Kearns-Sayre)
Parathyroid destruction
Surgical
Autoimmune (genetic, e.g., APS-1; or acquired, including immune checkpoint inhibitors)
Radiation
Iron or copper overload (hemochromatosis, transfusion-dependent thalassemia, Wilson's disease)
Infiltration by metastases or systemic diseases (sarcoid, IgG4-related disease, Riedel's struma)
Reduced bioactive PTH secretion
Hypomagnesemia (genetic, drug-induced, anti-claudin-16 antibodies)
Severe hypermagnesemia (e.g., obstetric magnesium infusions)
Autosomal dominant hypocalcemia (CaSR activating mutations)
Autoimmune (CaSR activating antibodies; immune checkpoint inhibitor therapy)
Familial isolated hypoparathyroidism (rare PTH gene mutations)
High

Parathyroid Hormone Levels (Secondary Hyperparathyroidism) Vitamin D deficiency or impaired 1,25(OH)₂D production/action Nutritional vitamin D deficiency (poor intake or absorption) Renal insufficiency [phosphate retention, impaired 1,25(OH)₂D production] Excessive intravenous phosphate infusion Vitamin D resistance, including receptor defects Intrinsic small intestine disorders with chronic calcium malabsorption Roux-en-Y bariatric surgery, other causes of short bowel syndrome Celiac disease, Crohn's disease (often with concomitant vitamin D deficiency) Parathyroid hormone resistance Pseudohypoparathyroidism (GNAS mutations or imprinting defects) Congenital PTH receptor mutation syndromes PTH receptor blocking autoantibodies Drugs Alcohol (both acute and chronic ingestion) Calcium chelators (including citrate from massive blood transfusion or FFP) Inhibitors of bone resorption (bisphosphonates, denosumab, plicamycin) Increased vitamin D catabolism (phenytoin, phenobarbital) Phosphate-containing enemas (excessive or with renal disease) Miscellaneous causes Acute pancreatitis Acute rhabdomyolysis Hungry bone syndrome after parathyroidectomy Osteoblastic metastases with marked stimulation of bone formation (prostate cancer) Respiratory or metabolic alkalosis (increased calcium binding to albumin) Refeeding syndrome and its management Pseudohypocalcemia (e.g., low serum albumin with malnutrition, nephrotic syndrome, cirrhosis; gadoversetamide MRI contrast)

Abbreviations: APS-1, autoimmune polyglandular syndrome type 1; CaSR, calcium sensing receptor; FFP, fresh frozen plasma; HDR, hypoparathyroidism, sensorineural deafness, and renal disease; MEN, multiple endocrine neoplasia; MRI, magnetic resonance imaging; PTH, parathyroid hormone. inhibition by calcium. When investigated, genetic causes can be identified in approximately 30% of pHPT cases even in nonfamilial sporadic pHPT, primarily affecting cyclin D1 or menin expression. Moreover, reduced calcium-sensing receptor (CaSR) expression due to CASR chromatin inhibitory H3K27me₃ and H3K9me₃ hypermethylation is observed in about 50% of sporadic parathyroid adenomas. Reduced

CASR protein expression increases both adenoma growth and the basal point for PTH secretion. Inappropriate PTH secretion for the ambient level of serum calcium also occurs in familial hypocalciuric hypercalcemia (FHH). FHH is an autosomal dominant syndrome most commonly involving inactivating mutations in the CASR gene (FHH type 1), with rare families having mutations in other genes encoding proteins necessary for normal CaSR signal transduction. All FHH mutations impair extracellular calcium sensing in both the parathyroid gland and the kidneys, leading to concomitant inappropriate PTH secretion and decreased urinary calcium excretion. In hypercalcemic disorders with normal parathyroid function, PTH levels are suppressed by high serum calcium levels that activate the CaSR to inhibit parathyroid gland PTH production (Fig. 57-1). This is frequently encountered in patients with advanced malignancy. Many solid tumors produce PTH-related peptide (PTHrP). Once processed and secreted, PTHrP shares homology with the first 13 amino acids of PTH and binds the PTH receptor, thus mimicking effects of PTH on bone and kidney to cause hypercalcemia. The hypercalcemia associated with lymphoma or with granulomatous disease (e.g., sarcoidosis, tuberculosis, foreign body reaction) is caused by extrarenal conversion of 25(OH)D to the more potent pro-calcific hormone 1,25(OH)₂D by macrophage CYP27B1 activity. The latter is a feature of local innate immune regulation by vitamin D that operates independent of the normal negative feedback loops outlined in Figure 57-1. In granulomatous disorders, this chronic 1,25(OH)₂D production enhances intestinal calcium absorption, resulting in hypercalcemia and suppressed PTH. Reduced 1,25(OH)₂D catabolism due to genetic deficiency in the inactivating 24-hydroxylase CYP24A1 can also cause hypercalcemia. Unlike the direct actions of 1,25(OH)₂D intoxication, mechanisms of acute vitamin D₃

(cholecalciferol) or vitamin D₂ (ergocalciferol) intoxication relate to acute cellular bioavailability of the 25(OH)D prohormone that is normally stored bound to plasma vitamin D binding protein (DBP). Excessive vitamin D ingestion rapidly displaces this large pool of 25(OH)D normally sequestered by plasma DBP. Although the potency of 25(OH)D for the cellular vitamin D receptor is 500-fold less than 1,25(OH)₂D, acute displacement of 25(OH)D from DBP by excessive exogenous vitamin D exposes tissues to 25(OH)D concentrations sufficient to directly activate the receptor in small intestine, increase transcellular calcium absorption, and drive hypercalcemia. While 1,25(OH)₂D is normally metabolized within a day or two, the longer half-lives of vitamin D and 25(OH)D can prolong hypercalcemia from vitamin D intoxication for several weeks. Disorders that directly increase calcium mobilization from bone, such as thyrotoxicosis, Paget's disease of bone, or osteolytic metastases, also lead to hypercalcemia with suppressed PTH secretion, as does exogenous calcium overload. The latter is most commonly observed in excessive oral ingestion (e.g., milk-alkali syndrome) or during total parenteral nutrition with excessive calcium supplementation. Ketogenic diets used to mitigate refractory seizures in children also increase bone resorption and can cause hypercalcemia. Hypercalcemia associated with prolonged immobilization arises from reduced mechanical loading of bone that increases osteocyte RANKL production and osteoclast-mediated bone resorption. In this setting, particularly with older patients, a previously unrecognized contributor to bone resorption (e.g., pHPT, Paget's disease, or myeloma) may be present and should be considered. Immune checkpoint inhibitors have been rarely associated with either hypercalcemia or hypocalcemia, dependent upon whether the autoimmune immunoglobulin response elicited inhibits or activates the CaSR, respectively.

Hypercalcemia and Hypocalcemia CHAPTER 57 ■ ■ CLINICAL MANIFESTATIONS Mild hypercalcemia (10.5–11.9 mg/dL) is largely asymptomatic and usually recognized only on routine calcium measurements. Some patients may complain of vague neuropsychiatric symptoms, including trouble concentrating, personality changes, or depression. Other common presenting symptoms may include fatigue, proximal muscle weakness, constipation, hyporeflexia, or nephrolithiasis, and bone mineral density may be reduced. Moderate (≥ 12 –14 mg/dL) to severe (≥ 14 mg/dL) hypercalcemia may result in progressive lethargy, stupor, or coma, as well as prominent gastrointestinal symptoms (nausea,

vomiting, anorexia, peptic ulcer, or pancreatitis) and acute renal failure. Hypercalcemia decreases renal concentrating ability in part by down regulating renal collecting duct aquaporin 2, which causes polyuria and volume depletion with frequent prerenal failure. With long-standing hyperparathyroidism, patients may present with bone pain or pathologic fractures and hypertension. Finally, hypercalcemia can result in significant electrocardiographic changes, including bradycardia, atrioventricular block, QRS widening, and short QTc interval.

■ ■ DIAGNOSTIC APPROACH The first step in the diagnostic evaluation of hypercalcemia or hypocalcemia is to ensure that the reported alteration in serum calcium is not due to an abnormal albumin concentration or a similar confounder (pseudohypercalcemia or pseudohypocalcemia; Tables 57-1 and 57-2). About 50% of total serum calcium is ionized, with the remainder bound principally to albumin. Although direct measurements of ionized calcium are possible, these are easily influenced by collection methods that alter calcium binding to albumin (e.g., prolonged tourniquet application during phlebotomy). Thus, it is generally preferable to measure total serum calcium and albumin to “correct” the serum calcium. When serum albumin concentrations are

reduced, a corrected calcium concentration is calculated by adding 0.8 mg/dL to the total calcium level for every decrement in serum albumin of 1.0 g/dL below the albumin reference value of 4.0 g/dL. Conversely, when albumin concentrations are increased, calcium is corrected by subtracting 0.8 mg/dL from the total serum calcium for every increase in serum albumin of 1.0 g/dL above 4.0 g/dL. PART 2 Cardinal Manifestations and Presentation of Diseases A detailed history provides important clues regarding the etiology of hypercalcemia (Table 57-1). Chronic hypercalcemia (many months to several years), often fluctuating between high normal to just above the limits of normal, is most commonly caused by pHPT or by FHH, and occasionally by multiple myeloma. Because of the phosphaturic actions of PTH, the hypercalcemia of pHPT is often accompanied by low serum phosphate or frank hypophosphatemia. Most malignancy-

associated hypercalcemia presents with a more acute course. The history should include review of medications (e.g., thiazides, recent initiation of an aromatase inhibitor), over-the-counter supplements or special diets, personal or family history of nephrolithiasis or other endocrine/metabolic disorders, any previous neck surgery, prior or current malignancy diagnosis, and systemic symptoms suggestive of sarcoidosis, lymphoma, or hyperthyroidism that may be causative or contributory. Once true hypercalcemia is established, the second most important laboratory test in the diagnostic evaluation is a PTH level using a two-site assay for the intact hormone. Serum creatinine should be measured to assess renal function; hypercalcemia can impair renal function, and reduced clearance of inactive PTH fragments may still be detected in some third-generation two-site PTH assays. However, if the PTH level is increased (or "inappropriately normal") in the setting of elevated calcium and low/low-normal phosphorus, the diagnosis is almost always pHPT, particularly if the 24-hour urinary fractional excretion of calcium is elevated (>0.02 ; described below). Genetic analysis is important if early-onset or dominant hereditary pHPT is present with (1) other endocrinopathy suggesting multiple endocrine neoplasia or (2) a lytic-sclerotic tumor of the jaw. In the latter, the inactivating mutations in the tumor suppressor gene CDC73 that cause this syndromic pHPT profoundly increase the lifetime risk for parathyroid carcinoma ($\sim 30\%$). Because individuals with FHH may also present with mildly elevated PTH levels and hypercalcemia, FHH should be considered and excluded because parathyroid surgery is ineffective in this condition. Due to impaired CaSR function in parathyroids and kidney, a calcium/creatinine clearance ratio (calculated as urine calcium/serum calcium divided by urine creatinine/serum creatinine) of <0.01 is suggestive of FHH, particularly when there is a family history of mild, asymptomatic hypercalcemia or recurrent unsuccessful surgeries for "presumed" pHPT. Sequencing of the genes that control CaSR signaling (CASR, GNA11, AP2S1) is now commonly performed for the definitive diagnosis of FHH, particularly if urine calcium studies are inconclusive. Prolonged lithium therapy increases the CaSR set point for negative feedback by calcium and can cause hyperparathyroidism

due to parathyroid hyperplasia or adenoma. Ectopic PTH secretion is extremely rare but has been reported in carcinomas with PTH gene rearrangements; unlike pHPT or parathyroid carcinoma, ectopic PTH secretion does not fluctuate in response to therapeutic correction of hypercalcemia since it is not controlled by a CaSR-sensitive tissue. A suppressed PTH level in the face of hypercalcemia indicates that the hypercalcemia is independent of parathyroid gland function; while many other causes must be excluded (Table 57-1), this is most often due to an underlying malignancy. Although a tumor that causes hypercalcemia is generally overt, a PTHrP level may be needed to establish the diagnosis of hypercalcemia of malignancy. Multiple myeloma must be

evaluated in this setting as well, including measurement of serum free light chains since ~3% of myeloma may be undetected by serum or urine protein electrophoresis with immunofixation. Measurement of serum 25(OH)D is useful for evaluation of both hypercalcemia and hypocalcemia. Hypercalcemia is one of the few settings where a serum 1,25(OH)₂D measurement is useful. In hypercalcemia caused by granulomatous disorders or lymphomas, serum 1,25(OH)₂D levels are either frankly increased or inappropriately normal, in the setting of a low serum PTH. With vitamin D- or 1,25(OH)₂D-mediated hypercalcemia, serum phosphate is frequently elevated or high normal due to increased gastrointestinal absorption and reduced renal excretion. In the vast majority of cases, clinical evaluation in combination with laboratory testing should provide a diagnosis. The very useful mnemonic "VITAMINS TRAP" captures much of the differential for the various disorders listed in Table 57-1: vitamin D, vitamin A intoxication; immobilization; thyrotoxicosis, thiazides, 24-hydroxylase deficiency; Addison's disease, acromegaly, acquired autoimmune; milk-alkali syndrome; inflammation (chronic); neoplasia including multiple myeloma; sarcoidosis; tuberculosis or another granulomatous disease; rhabdomyolysis recovery phase, rebound from denosumab discontinuation; AIDS; PTH (hyperparathyroidism), Paget's disease, parenteral sources, pheochromocytoma, pregnancy-associated PTHrP, and pseudohypercalcemia.

TREATMENT

Hypercalcemia Mild, asymptomatic hypercalcemia does not require immediate therapy beyond assiduous maintenance of adequate oral hydration with close diagnostic follow-up; management is dictated by the underlying cause. By contrast, significant, symptomatic hypercalcemia requires acute intervention to restore normocalcemia independent of the etiology, in addition to treatment of the underlying cause. Initial therapy of significant hypercalcemia begins with volume expansion because hypercalcemia invariably leads to dehydration, as noted above; 4–6 L of intravenous saline may be required over the first 24 h, keeping in mind that underlying comorbidities (e.g., congestive heart failure) will impact the clinical euvolemic set point. Saline infusion improves renal perfusion, urine output, and thus natriuresis, which thereby increases calciuresis. Although loop diuretics can be transiently used to further augment sodium and thus calcium excretion by the distal tubule, loop diuretics should not be initiated until the volume status has been restored to normal. Following intravenous hydration, which helps to most rapidly address hypercalcemia, the mainstays of therapy are intravenous aminobisphosphonates. Aminobisphosphonates are potent inhibitors of osteoclast-mediated bone resorption, the major contributor to severe hypercalcemia in most malignancies and hyperparathyroidism. Zoledronic acid (4 mg intravenously over ~30 min) and pamidronate (60–90 mg intravenously over 2–4 h) are commonly used for the treatment of hypercalcemia of malignancy and parathyroid crisis in adults and are occasionally deployed at lower doses in life-threatening hypercalcemia in children. The onset of intravenous aminobisphosphonate action is within 1–2 days, with normalization of serum calcium levels occurring in 60–90% of patients. To achieve a more rapid albeit transient reduction in bone resorption, calcitonin is routinely implemented as well (4–8 IU/kg

given intramuscularly or subcutaneously every 6 h) during the first 48 hours following admission in conjunction with hydration and aminobisphosphonate infusion. Denosumab (dosed 120 mg subcutaneously on days 1, 8, 15, and 29, then monthly thereafter), an antibody to RANKL, is a potent inhibitor of bone resorption and has been shown to be effective in treating hypercalcemia of malignancy refractory to aminobisphosphonates. Lower doses of denosumab (e.g., 0.3 mg/kg) can be used to treat hypercalcemia patients in the setting of advanced kidney disease, since intravenous aminobisphosphonates are contraindicated with glomerular filtration rate <35 mL/min/1.73 m² and denosumab is cleared by the reticuloendothelial system. In some instances, dialysis may

be required to control severe hypercalcemia, particularly in the settings of anuric acute renal failure or congestive heart failure. When diagnosed, parathyroid carcinoma, a rare cause of hypercalcemia of malignancy driven by PTH, is treated with the CaSR agonist cinacalcet, starting with 30 mg orally twice daily and titrated to normalize serum calcium. Of note, cinacalcet is also used to treat patients with pHPT who are not candidates for parathyroid gland surgery. In patients with vitamin D- or 1,25(OH)₂D-mediated hypercalcemia, glucocorticoids represent foundational pharmacotherapy, as they directly reduce calcium absorption from the small intestine and decrease 1,25(OH)₂D production. Intravenous hydrocortisone (200–400 mg daily) for 3–5 days or oral prednisone (40–60 mg daily) for 7–10 days is used most often, with prolonged taper as guided by serum calcium. However, for severe vitamin D-induced intoxication requiring hospitalization, intravenous hydration and aminobisphosphonates are frequently necessary to rapidly restore normocalcemia. Other drugs, such as ketoconazole, chloroquine, and hydroxychloroquine, decrease 1,25(OH)₂D production but are used infrequently due to side effects. However, for individuals with genetic CYP24A1 deficiency, inhibiting 1,25(OH)₂D synthesis with ketoconazole or fluconazole can help control hypercalcemia and mitigate the toxicity of chronic glucocorticoid administration. For hypercalcemia of thyroid storm, the aggressive management of the underlying thyrotoxicosis, which also includes intravenous glucocorticoid administration in addition to thionamides, usually restores normocalcemia.

HYPOCALCEMIA ■ ■ ETIOLOGY

The causes of hypocalcemia can be differentiated according to whether serum PTH levels are low (hypoparathyroidism) or high (secondary hyperparathyroidism). Although there are many potential causes of hypocalcemia, impaired PTH production and severely impaired intestinal calcium absorption with or without profound vitamin D deficiency are the most common etiologies (Table 57-2) (Chap. 422). Because PTH is the main minute-by-minute defense against hypocalcemia, disorders associated with deficient PTH production may be associated with profound, debilitating, and life-threatening hypocalcemia. In adults, hypoparathyroidism most commonly results from inadvertent damage to all four parathyroid glands during thyroid or parathyroid gland surgery. Hypoparathyroidism is a cardinal feature of autoimmune endocrinopathies (Chap. 400), responsible for about a quarter of hypoparathyroidism. Even late-onset adult idiopathic hypoparathyroidism—unrelated to neck surgery or autoimmune polyglandular syndrome type 1 (APS-1)—frequently exhibits autoimmunity that targets CaSR and other parathyroid antigens. In patients with APS-1, anti-interferon and anti-NALP5 antibodies are frequently present. Hypoparathyroidism may be associated with infiltrative diseases such as sarcoidosis or IgG4-related disease, iron overload (hemochromatosis, transfusion-dependent thalassemia), copper overload (Wilson's syndrome), genetic disorders (e.g., DiGeorge's syndrome), or parathyroid involution following neck irradiation. During the COVID-19 pandemic, via unknown mechanisms, transient hypoparathyroidism and even spontaneous resolution of pHPT were reported. Rare, congenital hypoparathyroidism has been well documented due to inactivating

mutations in GCM2, GATA3, or even the PTH gene itself. Conversely, activating mutations in the CaSR, or in the GNA11 protein that mediates CaSR signaling (autosomal dominant hypocalcemia), also cause congenital hypoparathyroidism. More commonly, impaired PTH secretion may be secondary to magnesium deficiency (via intracellular actions). Hypomagnesemia with hypocalcemia can arise from drug-induced renal loss including chronic alcohol abuse, oncotherapeutics (cisplatin, anti-epidermal growth factor [EGF] antibodies), proton pump inhibitors, or rare autoimmunity that causes tubulointerstitial nephritis with claudin-16 inhibition. Because extracellular magnesium can bind the CaSR with an affinity about one-third that of calcium, severe

hypermagnesemia arising from obstetric magnesium infusions for preeclampsia or preterm labor can also suppress PTH release; this rarely causes symptomatic hypoparathyroidism that must be managed until the magnesium infusion is discontinued.

Hypercalcemia and Hypocalcemia CHAPTER 57 Vitamin D deficiency, impaired 1,25(OH)₂D production due to chronic renal insufficiency, or vitamin D resistance also cause hypocalcemia. However, the degree of hypocalcemia in these disorders is most often not as severe as that seen with hypoparathyroidism; this is because the parathyroids are capable of mounting a compensatory increase in PTH secretion that buffers the extent of hypocalcemia to the detriment of bone. By increasing calcium binding to albumin, both respiratory alkalosis (e.g., hyperventilation) and metabolic alkalosis (e.g., intractable vomiting) can also cause hypocalcemia. When tetany arises with alkalosis, another cause of impaired calcium homeostasis is frequently present. Hypocalcemia may also occur in conditions associated with severe tissue injury such as burns, rhabdomyolysis, tumor lysis, or pancreatitis. The cause of hypocalcemia in these settings may include a combination of hyperphosphatemia, tissue deposition of calcium, and impaired PTH secretion. ■ ■ **CLINICAL MANIFESTATIONS** Patients with hypocalcemia may be asymptomatic if the decreases in serum calcium are relatively mild and chronic, or they may present with life-threatening complications. Moderate to severe hypocalcemia is associated with paresthesias, usually of the fingers, toes, and circumoral regions, and is caused by increased neuromuscular irritability. On physical examination, a Chvostek's sign (twitching of the ipsilateral perioral levator and zygomaticus muscles in response to gentle tapping of the facial nerve, just anterior to the ear or between the corner of the mouth and zygomatic arch) may be elicited, although it is also present in ~10% of normal individuals. As a more definitive sign of neuromuscular irritability and impending tetany, carpal spasm may be induced by inflation of an upper arm blood pressure cuff to 20 mmHg above the patient's systolic blood pressure for 3 min (Trousseau's sign; ipsilateral thumb apposition with wrist flexion). With profound vitamin D insufficiency or hypomagnesemia, proximal myopathy is frequently evident with difficulty rising from a chair while sitting with arms crossed over the chest. Severe hypocalcemia can induce seizures, carpopedal spasm, bronchospasm, laryngospasm, and prolongation of the QTc interval with risk of ventricular tachyarrhythmia (cardiac Torsade) and sudden death. ■ ■ **DIAGNOSTIC APPROACH** In addition to measuring serum calcium, it is important to determine albumin, phosphorus, and magnesium levels. As for the evaluation of hypercalcemia, determining the PTH level is central to the evaluation of hypocalcemia. A suppressed (or "inappropriately low") PTH level in the setting of hypocalcemia establishes impaired PTH secretion (hypoparathyroidism) as the cause of the hypocalcemia. The history will often elicit the underlying cause (e.g., prior neck surgery with parathyroid gland destruction). By contrast, an elevated PTH level (secondary hyperparathyroidism, a compensatory change in response to low calcium) should direct attention to the vitamin D axis or primary disease of the small intestine (e.g., short bowel syndrome due to Roux-en-Y bariatric surgery) as the cause of hypocalcemia. These latter patients are at great risk for hypocalcemia with even modest hypoparathyroidism following neck surgery and can be very difficult to manage. Nutritional vitamin D deficiency is best assessed by obtaining serum