Abnormalities in Calcium Homeostasis

20

Ruben Diaz

Abstract

Calcium plays an important role in a number of physiological processes as diverse as bone formation and turnover, neuronal cell excitability, muscle contractility, and blood clotting. Significant shifts in serum calcium concentration have adverse effects on these physiological functions. In children, maintenance of adequate calcium balance is particularly important since bone deposition and growth is closely linked to the availability of calcium. Higher organisms have developed mechanisms to regulate the extracellular concentration of calcium, normally affected by intermittent changes in calcium absorption in the gut, continuous mineral bone turnover, and calcium losses in the urine. Extracellular calcium levels are set within a very narrow range by the concerted action of several regulatory "calciotropic" hormones on calcium handling by the gastrointestinal tract, bone, and kidney. The abnormal function of calciotropic hormones or the failure of any of these organs to handle calcium properly can cause either hypo-or hypercalcemia.

Keywords

Calcium • Hypercalcemia • Hypocalcemia • Vitamin D • Parathyroid hormone • Phosphate

Calcium plays an important role in a number of physiological processes as diverse as bone formation and turnover, neuronal cell excitability, muscle contractility, and blood clotting. Significant shifts in serum calcium concentration have adverse effects on these physiological functions. In children, maintenance of adequate calcium balance is particularly important since bone deposition and growth is closely linked to the availability of calcium. Higher organisms have developed mechanisms to regulate the extracellular concentration of calcium, normally affected by intermittent changes in calcium absorption in the gut, continuous mineral bone turnover, and calcium losses in the urine.

R. Diaz, M.D., Ph.D. (✉)
Endocrine Division, Saint John of God Hospital,
Passeig Sant Joan de Deu 2, Esplugues de Llobregat
08950, Barcelona, Spain
e-mail: rdiaz@hsjdbcn.org

S. Radovick and M.H. MacGillivray (eds.), *Pediatric Endocrinology: A Practical Clinical Guide, Second Edition*, Contemporary Endocrinology, DOI 10.1007/978-1-60761-395-4_20,

Extracellular calcium levels are set within a very narrow range by the concerted action of several regulatory "calciotropic" hormones on calcium handling by the gastrointestinal tract, bone, and kidney. The abnormal function of calciotropic hormones or the failure of any of these organs to handle calcium properly can cause either hypo- or hypercalcemia.

Calcium is among the most abundant mineral ions in the body. Greater than 98% of total calcium is present as mineral salts in bone but can be mobilized as part of a continuous exchange of calcium between bone and the extracellular compartment during bone remodeling. The remaining fraction of calcium is distributed between the intracellular and extracellular compartments. Calcium in serum exists in three forms: (1) a protein-bound fraction (30–50% of total serum calcium), primarily bound to albumin; (2) complexed with serum anions like phosphate, citrate, and bicarbonate (5–15%); and (3) ionized Ca (Ca^{2+}) (40–60%). Ca^{2+} is the metabolically active form and is the soluble fraction that is tightly regulated. As a result, the concentration of serum Ca^{2+} remains relatively constant with age and dietary intake.

Hormonal Regulation of Serum Ca^{2+}

Parathyroid Hormone

Changes in serum Ca^{2+} are rapidly sensed by the parathyroid glands [1]. There are four paired parathyroid glands, usually positioned in the superior and inferior poles of the thyroid, derived from the 4th and 3rd pharyngeal pouches, respectively. In response to a decrease in serum Ca^{2+}, they secrete parathyroid hormone (PTH), an 84 amino acid polypeptide synthesized and stored in secretory granules. The net effect of PTH on calcium homeostasis is to activate mechanisms that increase serum Ca^{2+} levels [2]. PTH promotes calcium mobilization from bone by osteoblast-mediated activation of bone-resorbing osteoclasts. In the kidney's proximal tubule, PTH activates 1-α-hydroxylase to synthesize calcitriol ($1,25(OH)_2D$) and increases the absorption of sodium, calcium, and bicarbonate while inhibiting phosphate transport and promoting phosphaturia. In the distal tubule, PTH has its most significant effect in the distal convoluted tubule where it activates calcium absorption. In the gut, PTH indirectly promotes, through the action of $1,25(OH)_2D$, the absorption of both calcium and phosphate.

The overall effect of changes in calciotropic hormones on calcium handling by the kidney, gastrointestinal tract, and bone is to maintain the extracellular Ca^{2+} concentration around the normal range (usually 1.12–1.23 mmol/L). This is primarily achieved by the regulation of PTH secretion in parathyroid cells. Ca^{2+} sensing is mediated by a G protein-coupled, calcium-sensing receptor (CaR) [3] expressed in parathyroid cells. Elevations in serum Ca^{2+} activate the CaR which, in turn, mediates the inhibition of PTH secretion by a yet poorly defined mechanism. Although Ca^{2+} is the major regulator of PTH secretion, other calciotropic factors also affect its secretion. The active form of vitamin D, calcitriol, inhibits PTH synthesis, while high serum phosphate has been shown to stimulate PTH secretion [4]. Profound hypomagnesemia inhibits both PTH secretion and action by affecting intracellular signaling function; hypermagnesemia also inhibits PTH secretion, a process likely mediated by the CaR, since magnesium is also a ligand for this receptor [1]. PTH is exquisitely sensitive to degradation both intracellularly in the parathyroid cell and in serum, especially as it traverses the liver and kidney; its serum half-life is less than 8 min. Thus, an accurate measurement of active PTH requires an immunoassay that measures intact PTH, presently achieved by a sandwich immunoradiometric assay (IRMA) or an immunofluorometric assay.

The bioactive site in PTH resides within the first 27 amino acids of the peptide [2]. PTH binds to a G protein-coupled receptor (PTH1R) that activates the production of cAMP and, in some cells, the release of intracellular calcium stores via activation of phospholipase C. This receptor is present in osteoblasts and kidney tubular epithelium, cells that play a direct role in calcium homeostasis. Two additional receptors (PTH2R

and PTH3R) with some homology to the first characterized receptor have been recently described [5], but their role in calcium homeostasis may not be significant.

At least another peptide has been shown to have PTH-like effects. PTH-related protein (PTHrP) was initially characterized for causing hypercalcemia when secreted by some malignant tumors [6]. The amino terminus of this peptide has high homology with the bioactive amino terminus of PTH and binds the PTH receptor. Besides its role as a calciotropic hormone when present in serum in high concentration, PTHrP appears to serve important functions in cartilage formation and the differentiation of several organs where it is expressed during fetal and postnatal development [7]. In the placenta, active transplacental transport of Ca^{2+} appears to be mediated by PTHrP binding to an unidentified receptor [8].

Vitamin D

Vitamin D_3 (cholecalciferol) is produced by photolysis of cholesterol to 7-dehydrocholesterol under UVB irradiation (280–305 nm wavelength) followed by isomerization in the skin [9]. It is hydroxylated to 25-hydroxyvitamin D (25OHD) in the liver, a step that is largely substrate dependent, making 25OHD levels a useful index of vitamin D stores. Its serum half-life is 2–3 weeks. An additional hydroxylation step by a 1-α-hydroxylase in the renal proximal tubule produces the bioactive form of vitamin D, $1,25(OH)_2D$. PTH, hypocalcemia, and hypophosphatemia are the major inducers of 1-α-hydroxylase activity in the proximal tubule. An increase in $1,25(OH)_2D$ production becomes apparent hours after exposure to a stimulus, and the half-life of $1,25(OH)_2D$ is only several hours. The proximal tubule also has 24-hydroxylase activity; hypercalcemia, hyperphosphatemia, and $1,25(OH)_2D$ induce this enzyme, promoting the production of $24,25(OH)_2D$, an inactive metabolite. 1-α-hydroxylation activity is not limited to the proximal tubule. 1-α-hydroxylase is expressed in placenta, a significant source of calcitriol for the fetus, keratinocytes, and activated mononuclear cells. Excess 1-α-hydroxylase activity in mononuclear cells is thought to be responsible for the hypercalcemia and elevation of $1,25(OH)_2D$ levels seen in granulomatous disorders [10].

Vitamin D and its metabolites are transported in serum bound to Vitamin D binding protein (DBP), showing greatest affinity for 25OHD. This protein provides a reservoir of vitamin D metabolites and prevents its rapid clearance in the urine. Megalin, a lipoprotein-like receptor that binds DBP, has been shown to mediate the uptake of vitamin D metabolites in the proximal tubule, suggesting a role for this protein in ensuring 25OHD availability for 1-α-hydroxylation in the kidney [11].

Calcitriol promotes the rise of both calcium and phosphate levels in serum [9]. $1,25(OH)_2D$ binds to vitamin D receptors (VDR), a member of the retinoid family of nuclear receptors, expressed in intestine, distal renal tubular cells, osteoblasts, parathyroid cells, and other tissues not directly involved in calcium homeostasis. In bone, binding to VDR promotes the activation of osteocalcin and alkaline phosphatase production by osteoblasts and the differentiation of osteoclasts precursors, having a net effect in mobilizing calcium and phosphate from bone. In the kidney, $1,25(OH)_2D$ facilitates the action of PTH on distal tubule calcium absorption. The major impact of $1,25(OH)_2D$ is in the small intestine where it promotes the absorption of calcium and phosphate in the duodenum and jejunum.

Calcitonin

Calcitonin is a 32 amino acid peptide produced by thyroid parafollicular C cells and in lesser amounts by other neuroendocrine cells [12]. High Ca^{2+} elicits a rise in calcitonin secretion in parafollicular cells, a process mediated by the same calcium-sensing receptor expressed in parathyroid cells [3]. In almost all instances, calcitonin antagonizes the effect of PTH on bone and kidney, via its binding to a G protein-coupled receptor of the same family as the PTH receptor. Calcitonin has no measurable effects on intestine handling of mineral ions. Paradoxically, calcitonin

levels rise abruptly at birth, despite a drop in serum Ca^{2+} normally seen during the same period, and decrease rapidly after birth [13]. In children older than 3 years, normal serum levels are often below detection unless elicited by hypercalcemia or in the setting of medullary thyroid carcinoma. The role of calcitonin in normal calcium homeostasis is uncertain, since in the absence of parafollicular cells (i.e., thyroidectomy), no significant alterations in calcium homeostasis have been observed; however, it has a pharmacological role in the acute treatment of hypercalcemia and osteoporosis as a promoter of calcium deposition in bone.

Calcium Homeostasis During Fetal and Early Neonatal Period

During fetal development, calcium homeostasis is affected by maternal Ca^{2+} levels [13]. Serum Ca^{2+} in the fetus is set at a higher concentration (≈ 0.25 mmol/L higher) than the mother. There is active transport of calcium across the placenta to sustain this gradient, a process that appears to be mediated by PTHrP (likely the midregion fragment of PTHrP) which is secreted by the fetal parathyroid among other fetal organs during pregnancy. Although the parathyroid glands are present as early as the first trimester in gestation, PTH secretion is normally suppressed during fetal development since fetal serum Ca^{2+} levels remain elevated in utero. In the fetus, bone mass accretion occurs primarily from 24 weeks to full gestation. Maternal serum Ca^{2+} levels and, less significantly, vitamin D status affect the extent of mineralization during this period. The mother is the primary source of vitamin D during this period. Both maternal 25(OH)D and $1,25(OH)_2D$ cross the placenta, while the placenta also produces $1,25(OH)_2D$.

At birth, there is a fall in serum Ca^{2+} levels, reaching a nadir (1–1.17 mmol/L) in the first 24–48 h of life [14]. PTH levels are low at birth but rise with the decrease in serum Ca^{2+}. Serum PTHrP levels decrease rapidly in the first day of life. $1,25(OH)_2D$ levels increase concomitantly with the increase in serum PTH. Milk intake provides the primary source of serum Ca^{2+} during the neonatal period. During the initial neonatal period, intestinal calcium absorption is not significantly regulated by $1,25(OH)_2D$; instead, passive absorption mechanisms enhanced by the presence of lactose in milk predominate at this stage [13]. The intestine progressively develops increased sensitivity and dependency on vitamin D for adequate calcium absorption. Infant's vitamin D levels correlate best with supplementation and sun exposure and not with breast milk intake, regardless of maternal vitamin D status.

Hypocalcemia

Hypocalcemia develops as a consequence of either reduced influx of calcium from the gastrointestinal tract or bone into the extracellular space or the excessive loss of calcium from this space into urine, bone, or stool. Causes of hypocalcemia include abnormalities in calciotropic hormone production and action or improper calcium handling by organs targeted by these hormones (Table 20.1).

Alterations in Calciotropic Hormones Causing Hypocalcemia

Hypoparathyroidism

Lack of adequate PTH production is a frequent cause of hypocalcemia in neonates and early childhood. In hypoparathyroidism, decreased PTH levels cause hypocalcemia and hyperphosphatemia. There are sporadic and familial forms of hypoparathyroidism caused by parathyroid agenesis or dysfunction [15]. When familial, autosomal dominant, autosomal recessive, and X-linked recessive forms of hypoparathyroidism have been described. Mutations of GCM2, a protein linked to parathyroid differentiation, is a recently identified etiology of parathyroid agenesis [16]. In some instances, point mutations of the PTH gene in chromosome 11p15 lead to inappropriate expression of PTH and dyshormonogenesis. A form of autosomal dominant hypoparathyroidism is associated with sensorineural

Table 20.1 Differential diagnosis of hypocalcemia

Alterations in hormonal response
Hypoparathyroidism
Abnormal PTH production
Parathyroid agenesis/dysfunction
Familial forms of isolated PTH deficiency
DiGeorge syndrome
Kenny-Caffey syndrome
Dyshormonogenesis
Acquired hypoparathyroidism
Polyglandular autoimmune disease type I
Mitochondrial myopathies
Disorders of metal ion deposition
Radiation exposure
Idiopathic
Abnormal PTH secretion
Hypomagnesemia
Autosomal dominant hypocalcemia
Critical illness
Peripheral resistance to PTH
Pseudohypoparathyroidism types IA, IB, II
Pseudopseudohypoparathyroidism
Vitamin D
Vitamin D deficiency
Nutritional deficiency
Liver disease
Iatrogenic (e.g., phenobarbital use)
Vitamin D resistance
Hydroxylase deficiencies
Vitamin D receptor dysfunction
Alterations of organs involved in calcium homeostasis
Kidney: Renal failure, renal tubular acidosis
Intestine: Malabsorption
Skeleton: Hungry bone syndrome
Other causes of hypocalcemia
High phosphate load
Tumor lysis syndrome
High phosphate formula
Rhabdomyolysis
Ca sequestration or clearance
Acute pancreatitis
Drugs: Furosemide, calcitonin
Decreased ionized calcium
Exchange blood transfusion
Alkalosis

deafness and renal dysplasia. DiGeorge syndrome and its variants are a more generalized embryological abnormality that occurs either sporadically or with variable autosomal dominant penetrance, involving the development of the third and fourth branchial pouches. This complex malformation is associated with dysmorphic facial features and anomalies of the heart and great vessels with variable defects in thymic and parathyroid gland function often showing dysgenesis of both glands. Deletions and translocations of chromosomes 22q11 and 10p13 have been detected and can be screened in suspected cases [17]. Hypoparathyroidism is also common in patients with Barakat syndrome and Kenny-Caffey syndrome, characterized by medullary stenosis of the long bones, short stature, hyperopia, and basal ganglia calcifications. Hypoparathyroidism has also been reported in a number of mitochondrial myopathies (i.e., Kearns-Sayre syndrome) where PTH secretion appears affected by the intracellular metabolic abnormality [18].

Acquired forms of hypoparathyroidism often occur later in infancy and adolescence. Infiltrative processes such as excess deposition of iron (thalassemia and hemochromatosis) and copper (Wilson's disease) in the parathyroid can impair the secretion of PTH. Exposure to radiation as part of therapy for hyperthyroidism or lymphoma has been linked to the onset of hypoparathyroidism as has the surgical removal or compromise of the vascular supply to the parathyroid glands. Autoimmune destruction of the parathyroid gland can be an isolated process or as part of a polyglandular autoimmune disease type 1, an autosomal recessive disorder also associated with hypoadrenocorticism, hypogonadism, thyroid disease, type I diabetes mellitus, pernicious anemia, chronic active hepatitis, malabsorption, and manifestations of ectodermal dysplasia such as alopecia, vitiligo, mucocutaneous candidiasis, keratopathy, and enamel hypoplasia [19]. In this disorder, chronic oral candidiasis is the first manifestation usually in early infancy. The average age of onset for mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency is 5 years, 9 years, and 14 years of age, respectively. About half of affected children end up having at least these three manifestations. The presence of intestinal malabsorption complicates the treatment of

hypocalcemia as calcium and vitamin D absorption is often impaired.

Several conditions are characterized by impaired PTH secretion despite the presence of viable parathyroid tissue and PTH synthesis. PTH secretion can be impaired in the presence of severe hypomagnesemia. The etiology of hypomagnesemia can be secondary to intestinal malabsorption or excessive renal wasting as seen in Bartter syndrome and renal tubular acidosis [20]. In autosomal dominant hypocalcemia, activating mutations of the CaR shift the curve of inhibition of PTH secretion to change the set point of serum Ca^{2+} to a concentration that can be sufficiently low to elicit adverse effects. Correction of hypocalcemia causes significant hypercalciuria as the ability of CaR to decrease tubular absorption of calcium also increases, augmenting the risk to develop urinary stones when compared to other forms of hypoparathyroidism. Finally, PTH secretion has been shown to be impaired in critical illness, perhaps mediated by an interleukin-mediated overexpression of CaR [21].

Tissue insensitivity to PTH has a clinical presentation very similar to hypoparathyroidism. Pseudohypoparathyroidism (PHP) describes various familial disorders, often inherited as autosomal dominant trait, that are characterized by the peripheral resistance to PTH [22]. Hypocalcemia occurs despite very elevated PTH levels, but without a concomitant elevation of $1,25(OH)_2D$ levels or increased renal phosphaturia. In patients with type 1a PHP or Albright hereditary osteodystrophy, the characteristic phenotype is short stature, stocky habitus, developmental delay, round face, short distal phalanx of the thumb, brachymetatarsias and brachymetacarpals, dental hypoplasia, and subcutaneous calcifications. Hypocalcemia is often not diagnosed until the mid-childhood years. PTH resistance has been characterized by the absence of urinary cAMP after administration of PTH, normally elevated when the kidney is responsive to PTH. Inactivating mutations in the α subunit of the stimulatory protein G_s are responsible for PTH resistance in this condition by presumably preventing the activation of adenylyl cyclase by the PTH receptor. These patients can show additional deficiencies due to the defective action of other peptide hormones that use the same stimulatory G_s to enhance cAMP production. In particular, thyrotropin action is often affected and occasionally hypothyroidism is diagnosed before the hypocalcemia is noted. The action of corticotropin, gonadotropin, glucagon, and GH-releasing hormone, among other hormones, have been shown to be affected. Pseudopseudohypoparathyroidism is used to describe patients with the Albright osteodystrophy phenotype without the biochemical abnormalities and may represent the inheritance of the paternal defective gene, suggesting the presence of imprinting in the inheritance of this disorder. Type 1b PHP resembles type 1a except that the $G_{s\alpha}$ subunit is normal, pointing to a defect in another step of the pathway that stimulates cAMP. Type II PHP is another variant where the phenotypic features are absent and infusion of PTH induces the normal elevation of urinary cAMP but without the expected phosphaturia, suggesting a defect distal to cAMP production.

Vitamin D Deficiency or Resistance

If vitamin D stores are depleted, intestinal calcium absorption can decrease sufficiently to cause hypocalcemia. In growing children, the negative calcium balance affects bone deposition and results in rickets. The parathyroid response to hypocalcemia is intact, but the elevated levels of PTH cannot compensate for the absence of substrate necessary to produce $1,25(OH)_2D$. Inadequate sun exposure or lack of Vitamin D intake can cause a decrease in vitamin D levels. Children with liver disease or taking drugs that enhance the activation of liver hydroxylating enzymes (i.e., phenobarbital) may have impaired 25OHD production or increased turnover to inactive metabolites of 25OHD, respectively. In rare occasions, a deficiency in 1-α-hydroxylase activity in the kidney or the presence of abnormal receptors for $1,25(OH)_2D$, conventionally classified as vitamin D-dependent rickets (VDDR) I and II, respectively, can have the same biochemical consequences and clinical presentation as vitamin D deficiency, including hypocalcemia [23]. Patients with VDDR-I do not respond to massive doses of vitamin D or 25OHD. Interestingly, alopecia is often seen in VDDR-II,

suggesting a role of vitamin D receptors in hair development and growth.

Other Causes of Hypocalcemia

When calcium handling by the gastrointestinal tract, bone, or kidney is abnormal or not responsive to calciotropic hormones, hypocalcemia can persist despite an appropriate hormonal response (i.e., increased PTH secretion and calcitriol production). The hyperphosphatemia that ensues with renal failure causes hypocalcemia, as excess phosphate complexes with Ca^{2+}, reducing its serum concentration. The lack of calcitriol production in advanced renal failure further aggravates the risk for hypocalcemia by decreasing intestinal calcium absorption. In disorders that have intestinal malabsorption as one of their manifestations or in cases of short gut syndrome calcium absorption can diminish sufficiently to cause hypocalcemia. In conditions where calcium deposition in bone exceeds nutritional intake (i.e., hungry bone syndrome), as occasionally seen during the treatment phase of severe rickets or following parathyroid surgery for hyperparathyroidism, acute onset of hypocalcemia is not uncommon.

Hypocalcemia can occur in settings where there is a high influx of phosphate or another anion into the extracellular space to complex with Ca^{2+}. The release of high loads of phosphate in tumor lysis syndrome and rhabdomyolysis can cause severe hypocalcemia with deposition of calcium phosphate salts in various tissues. Likewise, an exogenous source of phosphate as in high phosphate content formula can have a similar effect in small infants. In acute pancreatitis, calcium is sequestered by free fatty acid complexes decreasing its effective concentration in serum, while the presence of citrate in exchange blood transfusions or alkalosis can decrease serum Ca^{2+} acutely.

Classification of Neonatal Hypocalcemia

Neonatal hypocalcemia has been traditionally described as "early" when it occurs in the first 72 hours of life or "late" when it occurs beyond that period of time [14] (Table 20.2). Infants that are born prematurely or experience asphyxia are particularly prone to experience a period of hypocalcemia in the early neonatal period. Preterm infants may have a deficient increase in PTH secretion to counteract the normal drop in serum Ca^{2+} after birth. In addition, calcium intake is often suboptimal, increasing the risk for hypocalcemia. The role of asphyxia in causing hypocalcemia is poorly defined but may be similar to the hypocalcemia seen in acute illness. Infants of diabetic mothers are also prone to develop hypocalcemia early in the neonatal period. Although both a history of prematurity and asphyxia are usually present in these babies, magnesium deficiency has also been invoked as a likely cause of hypocalcemia since maternal glycosuria is accompanied by significant magnesium losses predisposing the fetus to total body magnesium deficiency.

Table 20.2 Common causes of neonatal hypocalcemia

Early
Asphyxia
Prematurity
Maternal gestational diabetes
Hypomagnesemia
Late
Maternal hyperparathyroidism
Hyperphosphatemia
Transient hypoparathyroidism
Congenital forms of hypoparathyroidism

Late neonatal hypocalcemia encompasses most of the etiologies described earlier that are commonly seen in childhood. A common cause of hypocalcemia is a transient form of hypoparathyroidism that lasts from a few days to several weeks. These infants appear to have a deficient PTH response to hypocalcemia that improves slowly with time. In some instances, this transient deficiency is due to exposure to maternal hypercalcemia in utero. Maternal serum Ca^{2+} should be measured to rule out this possibility. Infants with transient hypoparathyroidism have been shown to have a higher risk to develop hypocalcemia later in life, suggesting that a mild abnormality in parathyroid function may be present.

Diagnosis and Evaluation of Hypocalcemia

Hypocalcemia can be asymptomatic in children and adolescents, especially when it is longstanding, and is often diagnosed in the setting of a routine biochemical screen. Abrupt decreases in serum Ca^{2+} predispose children to more severe symptoms, mostly neurological in nature, that require prompt medical attention. Early neuromuscular symptoms include numbness around the mouth, tingling, paresthesias, muscular cramping (especially after vigorous exercise), and carpopedal spasm. More severe symptoms include seizures, tetany, laryngospasm, and mental status changes. In neonates, symptoms can be more subtle and the only manifestation may be poor feeding and vomiting; however, acute presentations are usually characterized by a history of recurrent seizures, twitching of the extremities, agitation, high-pitched voice, tachypnea, or apnea. In some instances, neonates with acute hypocalcemia may present in cardiac failure.

Infants with acute symptomatic hypocalcemia frequently show hypotonia, tachycardia, and a bulging fontanelle on physical examination. In older asymptomatic children, the physical exam usually reveals no striking abnormality other than hyperreflexia, a positive Chvostek sign (twitching of facial muscles after tapping the facial nerve just in front of the ear) and/or a Trousseau sign (carpopedal spasm with hypoxia after maintaining a blood pressure cuff above the systolic blood pressure for 3–5 min). These findings are not exclusively present in hypocalcemic states; the Chvostek sign can be present in normal adolescents and other ionic abnormalities such as hypokalemia, hyperkalemia, hypomagnesemia, and severe hypo- or hypernatremia can also cause tetany. Hypocalcemia affects cardiac function by impairing myocardial contractility and prolonging the QTc interval, increasing the predisposition to cardiac arrythmias. Ophthalmologic findings can include papilledema, optic neuritis, and subcapsular cataract formation. Calcium deposition in intracranial locations with a preference for basal ganglia is not uncommon in chronic hypocalcemia. Other physical findings in chronic hypocalcemia include coarse hair, dry skin, brittle nails, and defective dentition, all the consequence of inadequate serum Ca^{2+}. When hypocalcemia is accompanied by vitamin D deficiency and decreased intestinal calcium absorption, the bone abnormalities commonly seen in rickets are a prominent feature of the physical presentation.

Other findings in the history and physical exam frequently prove useful in the determination of the etiology of hypocalcemia. If the phenotypic features of type 1 PHP are present, PTH resistance should be suspected, whereas the presence of facial anomalies (i.e., mandibular hypoplasia, hypertelorism, short philtrum, and low set ears), a heart murmur, or a history of recurrent infections suggests DiGeorge syndrome. The absence of a thymus shadow on a chest X-ray in a neonate with hypocalcemia should point to this syndrome. A history of mucocutaneous candidiasis, vitiligo, or alopecia may suggest the presence of autoimmune polyendocrinopathy type 1.

Serum calcium concentration should always be obtained and compared to normal values to confirm hypocalcemia. Since calcium is found in both protein-bound and ionized forms in serum, conditions that alter protein content and binding affinity affect the Ca^{2+} concentration in serum. In acidic states, calcium is dissociated from albumin and the concentration of serum Ca^{2+} increases, while the reverse occurs in alkaline conditions. An ionized measurement is the more accurate assessment of serum Ca^{2+} concentration and has currently become more routinely available, especially in the hospital setting. Normal values often range 1.12–1.23 mmol/L in most laboratories. Adequate sampling is imperative to prevent excessive exposure to air or to high amounts of heparin since, in both circumstances, readings are artificially lower.

As part of a complete evaluation of mineral ion homeostasis, both serum phosphate and magnesium levels should be obtained. Phosphate levels should be compared to normal values adjusted for age. Vitamin D stores can be measured by obtaining 25OHD levels, while $1,25(OH)_2D$ levels provide a good measure of PTH activity. The bone-derived serum alkaline phosphatase level is

a measure of osteoblast activity and bone turnover. It is usually elevated in states of high bone turnover as seen in hyperparathyroidism and rickets. Renal function can be adequately screened by measurement of total protein, electrolytes, bicarbonate, BUN, and creatinine. In addition, urine calcium, phosphate, and creatinine levels provide a measure of mineral ion handling by the kidney, especially when done in conjunction with serum measurements.

Several useful calculations provide a measure of calcium handling before and during therapy:

Ca × Phosphate, if >60 there is a high predisposition to insoluble mineral deposition in joints and tissues.

Urine Ca/urine creatinine, if >0.2 the predisposition to calcium deposition in the urinary tract and nephrocalcinosis increases. In healthy neonates and infants, this ratio can be more elevated. Spot measurements are usually adequate, especially if obtained early in the morning and fasting.

TRP (tubular reabsorption of phosphate) = 1 − (urine phosphate × serum creatinine/serum phosphate × urine creatinine). This measure provides a measure of phosphate retention by the kidney. TmP/GFR = TRP × serum phosphate (normal range 2.5–4.2 mg/dL), TRP adjusted for glomerular filtration rate.

In most instances, when hypocalcemia has been confirmed, a concomitant measure of serum Ca^{2+} and intact PTH provides an adequate assessment of parathyroid function. In hypocalcemic states, PTH levels should be elevated when parathyroid function is normal. In most laboratories, the normal range of serum intact PTH values falls between 10 and 65 pg/mL. If PTH values are below detection level or inappropriately normal for the degree of hypocalcemia, a form of primary hypoparathyroidism is the likely diagnosis. Elevations in serum phosphate would also support this diagnosis. If serum magnesium levels are low, usually below 1.5 mg/dL, hypocalcemia may be due to impaired PTH secretion and action; restoration of normal serum magnesium levels and monitoring of serum Ca^{2+} should be considered before diagnosing an intrinsic abnormality in parathyroid function.

When the PTH level is appropriately elevated in the presence of hypocalcemia, a form of PTH resistance or PHP is the likely diagnosis. In PHP, PTH levels are frequently very elevated while calcitriol levels are generally in the normal range or even low despite normal vitamin D stores. To distinguish between different types of PHP, in addition to careful description of the physical phenotype, a PTH infusion with concomitant measurement of urinary cAMP would be required; a test that is seldom performed since PTH is not readily available in most clinical centers. Fortunately, the treatment is currently similar for all forms of PHP and their clinical classification is less critical for adequate management.

If hypocalcemia is accompanied with normal or low serum phosphate levels, a form of vitamin D deficiency should be suspected, a diagnosis that would be supported by physical findings of rickets and an elevated alkaline phosphatase level. Low 25OHD levels would suggest a dietary deficiency, an intestinal malabsorptive process or improper processing by the liver. Normal 25OHD levels would point to a defect in calcitriol production or action. It is not unusual to see very high levels of $1,25(OH)_2D$ in patients with vitamin D receptor defects or VDDR-II disorders.

Management of Hypocalcemia

Acute Hypocalcemia

In a symptomatic patient, the initial goal is to take the appropriate steps to eliminate symptoms associated with hypocalcemia. In patients whose acid–base status or the infusion of agents that may complex with calcium is responsible for the hypocalcemia, adequate steps to ameliorate these causes should be taken. In acute symptomatic cases or in neonatal hypocalcemia, an intravenous infusion of calcium is the most effective intervention. Calcium gluconate (10% calcium gluconate = 9.3 mg Ca/mL), 2 mL/kg can be administered slowly, over a 10-min period to avoid cardiac conduction problems while monitoring the ECG. The dose can be repeated every 6–8 h.

To maintain normocalcemia, it is occasionally necessary to start a continuous intravenous

infusion of calcium (20–80 mg Ca/kg/24 h). The infusion rate should be titrated to achieve a low normal serum Ca^{2+} level. Hypomagnesemia should be corrected when present. $MgSO_4$ (50% solution) 25–50 mg Mg^{2+}/kg in intravenous or intramuscular form every 4–6 h, 10–20 mg Mg^{2+}/kg for the neonate. A maintenance dose of 30–60 mg Mg^{2+}/kg/day as an oral or continuous intravenous infusion could also be given if necessary.

It is preferable to transition patients to oral therapy as soon as possible. In asymptomatic patients, it is likely that the hypocalcemia, even when very severe, has been longstanding and oral therapy should be the first line of therapy. Several forms of calcium supplements [calcium salts of carbonate (40% Ca), citrate (21% Ca), lactate (13% Ca), gluconate (9.4% Ca), glubionate (6.6% Ca)] are available to be used for this purpose. The dose of oral calcium should provide 25–100 mg Ca/kg/day divided every 4–6 h. Milk is also good source of calcium (119 mg Ca/100 mL), but not necessarily appropriate in hyperphosphatemic states since its phosphate content is high (93 mg/100 mL). Both forms of therapy should be adjusted as needed with monitoring, paying attention to serum Ca^{2+} levels, Ca × Phosphate, and Urine Ca/Urine creatinine to avoid the deposition of calcium salts in peripheral tissues and kidney.

Chronic Hypocalcemia

The overall goal in management of chronic hypocalcemia is to achieve a serum Ca^{2+} level that does not cause symptoms while avoiding hypercalcemia or excessive hypercalciuria (i.e., Urine Ca/Urine creatinine >0.2), the latter being particularly difficult to achieve in hypoparathyroidism as the absence of PTH limits calcium absorption in the renal distal tubule. In hypoparathyroidism, serum Ca levels <9 mg/dL limit the degree of hypercalciuria. In some patients that normocalcemia has been difficult to achieve without significant hypercalciuria, the addition of a thiazide diuretics has been shown to limit hypercalciuria while increasing serum Ca^{2+} significantly. Correction of hypocalcemia does not need to be so stringent in most forms of PHP since hypercalciuria is rarely seen even when calcium levels reach high normal values. It is not unusual to require relatively high doses of calcium to overcome longstanding hypocalcemia, especially in PHP; however, calcium requirements are frequently reduced once normocalcemia has been achieved and the degree of hyperphosphatemia has been reduced.

In all forms of hypoparathyroidism, vitamin D administration is an integral part of the therapy once oral supplementation of calcium is initiated. Calcitriol is, in most instances, the adequate choice due to its short half-life and high activity, which limits its toxicity and increases efficacy, respectively. The standard dose of 10–50 ng/kg/day is usually sufficient to promote adequate calcium absorption, but the dose is often increased further if the hypocalcemia remains recalcitrant to oral therapy. Calcitriol is also the adequate choice in the treatment of hypocalcemia secondary to renal failure, liver disease, or defects in 1-α-hydroxylase function. In intestinal malabsorption syndromes where there is a deficiency in fat absorption, calcidiol (1–3 mcg/kg/day), the more polar vitamin D metabolite can be used. When hypocalcemia is caused by poor vitamin D stores, vitamin D, 1,200–1,600 U/day, or 50,000 U IM should be quite adequate since calcitriol production and action is not defective. Finally, patients with 1-α-hydroxylase deficiency or VDDR-I respond well to calcitriol therapy, while VDDR-II patients with an abnormal vitamin D receptor usually require an exceedingly high dose of calcitriol (up to 1,000 mcg/day) or chronic parenteral calcium to maintain normal serum Ca^{2+}.

In general, phosphate binders are not required to manage hyperphosphatemia in all forms of hypoparathyroidism; moreover, the use of calcium alone limits intestinal phosphate absorption. The intake of phosphate-rich foods (i.e., dairy products) should not be encouraged. The use of a nonabsorbable antacid when serum phosphate levels remains greater than 6 mg/dL in the older child may be useful to prevent metastatic calcifications.

In chronic forms of hypoparathyroidism, frequent follow up (i.e., every 3–4 months) to ensure adequate calcium balance may be adequate as is periodical screening of kidney function by urine analysis and ultrasound to rule out the presence of hematuria, kidney stones, and nephrocalcinosis.

Neonatal Hypocalcemia

The initial treatment of hypocalcemia in neonates with hypothyroidism should be approached as described for all children. As a large proportion of these infants ultimately have a form of transient hypoparathyroidism, initial treatment should be limited to calcium supplementation alone without addition of calcitriol. Since infants depend on maternal or formula milk for their nutrition, a useful approach has been to supplement their milk with calcium. When hyperphosphatemia is significant, the use of a low phosphate content formula (i.e., PM60/40) supplemented with calcium to bring the calcium/phosphate ratio to 4:1 is often sufficient to limit phosphate absorption while supplying sufficient calcium to achieve normocalcemia. The amount of calcium can be slowly tapered as long as the infant remains normocalcemic, with serum Ca^{2+} measured following each decrease in dose. When a permanent form of hypoparathyroidism has been confirmed (i.e., clear features of DiGeorge syndrome are present or PTH measurements are persistently low) or the hypocalcemia is resistant to oral calcium treatment, calcitriol could be administered to enhance calcium absorption.

Hypercalcemia

Hypercalcemia develops when either there is an increased influx of calcium from the gastrointestinal tract or bone into the extracellular space that exceeds the renal excretory capacity or when there is enhanced renal tubule absorption of calcium. Causes of hypercalcemia can also be divided into etiologies that involve abnormalities in calciotropic hormones or defects in calcium handling by organs targeted by these hormones (Table 20.3).

Table 20.3 Differential diagnosis of hypercalcemia

Alterations in hormonal response
Hyperparathyroidism
Excessive PTH production
Primary Hyperparathyroidism
MEN (type I, IIa)
Sporadic forms
Secondary/tertiary hyperparathyroidism
Renal failure
Renal tubular acidosis
Treatment of hypophosphatemic rickets
Transient hyperparathyroidism
Neonatal hyperparathyroidism (secondary to maternal hypoparathyroidism)
Excessive PTH secretion
Lithium toxicity
Calcium-sensing receptor inactivating mutations
Familial hypocalciuric hypercalcemia (FHH)
Neonatal severe hyperparathyroidism
Excessive PTH receptor activity
Jansen syndrome
Vitamin D excess
Nutritional
Granulomatous disorders
Neoplasms and lymphomas
Alterations of organs involved in calcium homeostasis
Skeleton
Immobilization
Hyperthyroidism
Neoplastic bone metastasis
Other causes of hypercalcemia
Hypercalcemia of malignancy
PTHrP excess
Excess cytokine and osteoclast activating factors
Hypophosphatemia
High calcium Load (Milk alkali syndrome)
Vitamin A intoxication
Drugs (e.g., thiazides)
William's syndrome
Hypophosphatasia
Subcutaneous fat necrosis
Adrenal insufficiency
Pheochromocytoma
Vasoactive intestinal peptide-secreting tumor

Alterations in Calciotropic Hormones Causing Hypercalcemia

Hyperparathyroidism

Hyperparathyroidism (HPT) is diagnosed when hypercalcemia is accompanied by elevated PTH levels. HPT is one of the most common causes of hypercalcemia in adults, but it is a relatively uncommon disorder in children and neonates. Less than 20% of pediatric cases are diagnosed in children younger than 10 years. Most cases of HPT (80%) represent a sporadic adenomatous change in one of the parathyroid glands, but a subset of patients show generalized hyperplasia of all glands that can occur sporadically or as part of the multiple endocrine neoplasia (MEN) type 1 and 2A. Parathyroid carcinoma is an even less common but more indolent form of parathyroid cell neoplasia. Parathyroid adenomas show a marked decrease in sensitivity to elevations of serum Ca^{2+}, while hyperplastic glands remain sensitive to Ca^{2+} but secrete more PTH by virtue of the increased cell number.

The underlying cause for sporadic primary HPT is not known, but most tumors are monoclonal in origin; the genetic defect in some of them has been allocated to translocation of cyclin D1 to the proximity of the PTH gene promoter inducing its overexpression [24]. Familial forms of HPT, accounting for about 10% of all cases and comprising most cases of hyperplasia, are usually transmitted in autosomal dominant fashion. In type 1 MEN, the affected gene, menin, has been mapped to chromosome 11q13 [25]. HPT is associated with almost all affected members and is often the first manifestation of the disorder; pancreatic tumors, pituitary adenomas, and neuroendocrine tumors of the gastrointestinal tract are other common manifestations. MEN type 2A is also an autosomal dominant disorder in which HPT occurs in association with medullary carcinoma of the thyroid and pheochromocytoma. The incidence of HPT is only 10–30% and is rarely the first manifestation of the syndrome. The typical presentation is hyperplasia of all glands, but adenomatous changes are not uncommon, especially in type 2A. The affected gene is the RET proto-oncogene in chromosome 10q11.2 [26].

In conditions where a normal parathyroid is exposed to chronic hypocalcemia (e.g., renal failure, renal tubular acidosis, therapy for hypophosphatemic rickets), the gland can undergo hyperplastic changes with concomitant increases in PTH secretion that cause hypercalcemia and secondary HPT. In severe cases, often in the setting of renal failure, adenomatous changes can also occur (tertiary HPT). A similar but usually less severe and transient form of HPT has been observed in neonates born to mothers with hypoparathyroidism and exposed to low serum Ca^{2+} in utero.

Hypercalcemia has been observed in patients treated with lithium [27]. PTH levels are elevated, suggesting a form of HPT. Lithium has been shown to decrease the sensitivity of the parathyroid cell to serum Ca^{2+}, by interfering with the signaling mechanisms utilized by the CaR.

In Jansen syndrome, children present with hypercalcemia, a metaphyseal dysplasia and other skeletal findings consistent with HPT. Recently, the genetic defect has been identified as a mutation of the PTH receptor that renders it constitutively active [28]. These children have undetectable PTH levels as their parathyroids respond appropriately to hypercalcemia.

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disorder characterized by mild, asymptomatic hypercalcemia, increased tubular reabsorption of calcium, and inappropriately normal PTH values, both caused by the presence of an inactivation mutations in one of the alleles coding for the CaR [29]. Affected individuals often go undiagnosed until a laboratory screen reveals the hypercalcemia. They do not have the common skeletal and gastrointestinal manifestations seen in primary hyperparathyroidism and are not at risk to develop urinary calcium stones or pancreatitis. The parathyroid glands are normal in appearance and do not show significant hyperplasia in mild forms of the disorder. There is, nevertheless, a broad spectrum of the disorder ranging from mild hypercalcemia to severe, life-threatening hypercalcemia that typically presents in the neonatal period. This severe form, classically described as neonatal

severe hyperparathyroidism, are either homozygous for inactivation mutations of the CaR, or heterozygous for a very severe inactivation mutation aggravated by exposure to low Ca^{2+} in fetal development. These infants have very elevated PTH levels and all the manifestations of HPT including hyperplasia of the parathyroid glands. Removal of most parathyroid tissue is often necessary.

Vitamin D Excess

Excessive exposure to vitamin D in the diet or for therapeutic reasons will cause an increase in intestinal calcium absorption and hypercalcemia. In this setting, phosphate absorption also is increased, and PTH levels are appropriately suppressed. Hypercalcemia is similarly present in a number of granulomatous disorders (i.e., sarcoidosis, tuberculosis, leprosy), chronic collagen vascular inflammatory disorders, and some neoplastic diseases (Hodgkin B cell lymphoma), where there is proliferation and activation of monocytic cells, production of $1,25(OH)_2D$ is increased due to the unregulated expression of 1-α-hydroxylase in these cells [30].

Other Causes of Hypercalcemia

As bone is the repository of greater than 98% of the body's calcium, increased or unregulated bone turnover can easily overcome the renal excretion capacity for calcium. Excess thyroid hormone can promote a disproportional stimulation of osteoclast function causing increased bone resorption and hypercalcemia [31, 32]. Immobilization, particularly in adolescents and when prolonged for more than 2 weeks, results in decreased bone accretion and increased bone resorption that is initially noted as hypercalciuria, but when persistent, frank symptomatic hypercalcemia can occur requiring immediate treatment [33]. Increased prostaglandin E secretion by renal tubular cells in Bartter syndrome has been suggested to promote bone resorption [11]. Vitamin A excess has been shown to cause hypercalcemia likely mediated by the activation of osteoclast-mediated bone resorption [34].

Malignancy is a rare cause of hypercalcemia in children. When it occurs, it can be the result of metastases to bone with concomitant dissolution of mineral content or the production of lytic factors by the original tumor that promote the mobilization of calcium (i.e., PTHrP, IL-1, IL6, TNF, prostaglandins).

Excessive intake of calcium in milk, calcium containing antacids and alkali can result in absorptive hypercalcemia. Conversely, severe hypophosphatemia associated with parenteral nutrition and prematurity is associated with a reciprocal increase in serum Ca^{2+} concentration, partly due to increased calcitriol levels and intestinal calcium absorption. Hypercalcemia has also been observed in adrenal insufficiency, pheochromocytoma, and vasoactive polypeptide secreting tumors by mechanism(s) that have not been well defined.

Hypercalcemia is present transiently during infancy in 15% of children with Williams syndrome, a sporadic disorder linked to the loss of the elastin gene in chromosome 7 characterized by a defined facial features (e.g., dolichocephaly, periorbital prominence, bitemporal depression, long philtrum with prominent lips and nasal tip, full cheeks, epicanthal folds, and periorbital prominence) among other physical features. More prominently up to 30% of affected children have supravalvular aortic stenosis. The etiology of hypercalcemia is unknown; however, mildly elevated calcitriol and calcidiol levels have been reported [35, 36]. The hypercalcemia often resolves before the first year of life; however, hypercalciuria often persists.

Hypercalcemia, sometimes very severe and life-threatening, has been seen in infants with subcutaneous fat necrosis, a condition seen in neonates, often premature, that have had traumatic births or a history of critical illness with significant poor peripheral perfusion. Subcutaneous fat undergoes necrosis, showing a significant infiltration by mononuclear cells. Although the etiology of hypercalcemia is not known, excessive prostaglandin E production and mononuclear-derived calcitriol, which in some cases have been mildly elevated, have been invoked as causes [37, 38].

Diagnosis and Evaluation of Hypercalcemia

Children with mild (total calcium <12 mg/dL) or chronic hypercalcemia frequently go undiagnosed unless a routine biochemical screen reveals the elevation of serum calcium. The predominant manifestation may be failure to thrive with arrest of weight gain and linear growth. In mild hypercalcemia (total calcium 12–13.5 mg/dL) generalized weakness, anorexia, constipation, and polyuria are usually present. In severe hypercalcemia (total calcium >13.5 mg/dL), nausea, vomiting, dehydration, and encephalopathic features including coma and seizures may occur. Neonates with severe hypercalcemia often present in respiratory distress and have hypotonia and apnea. It is not uncommon for relatives and patients to note significant psychological changes ranging from depression to paranoia and obsessive-compulsive behavior.

The physical examination is usually normal in hypercalcemic patients. In patients with MEN 2B, a Marfanoid habitus is often present. A parathyroid mass is rarely palpable. When not dehydrated, hypertension may be noted, and a cardiac evaluation may show shortened QTc intervals in ECG tracings. In chronic hypercalcemia, a survey of soft tissues may reveal calcifications in kidney, skin, SQ tissues, cardiac arteries, and gastric mucosa. In untreated patients with prolonged HPT, and occasionally reported in untreated children where the diagnosis was never suspected, distinctive skeletal findings showing subperiosteal resorption of the distal phalanges, tapering of the distal clavicles, salt and pepper appearance of the skull, bone cysts, and brown tumors (liquefied bone) are the constellation of findings that describe osteitis fibrosa cystica. These findings are readily visible by conventional radiography.

The evaluation of hypercalcemia should include a thorough medical history searching for exposure to drugs, agents, and conditions that can cause hypercalcemia and a family history of hypercalcemia or other associated medical conditions. The approach to the biochemical evaluation is similar to the evaluation described for hypocalcemia and should initially include the measurement of serum intact PTH levels, phosphate, and magnesium together with measurements of urine calcium excretion. Renal function should also be assessed to rule out renal insufficiency, and a urine analysis is useful to look for the presence of hematuria or calcium salt residue.

HPT is diagnosed when hypercalcemia is noted in conjunction with elevated PTH levels. In the absence of secondary causes of HPT, the presence of hypercalciuria is consistent with primary HPT. Hypercalciuria is usually present in HPT since the PTH-mediated increase in tubular calcium resorption does not fully compensate for the increase in calcium concentration in the glomerular filtrate. The degree of hypercalciuria has significant diagnostic value, especially when trying to distinguish mild HPT from FHH, since mild elevations of PTH are often seen in both cases [29]. The calculation of 24 h urinary calcium clearance provides a measure of calcium handling by the kidney. Decreased urinary calcium excretion in the presence of mild hypercalcemia should raise the possibility of inactivating mutation of the CaR and FHH. A better measure of hypercalciuria that takes into account changes in glomerular filtration is the calcium clearance ratio ([Urine Ca × Serum creatinine]/[Urine creatinine × Serum Ca]). The clearance ratio in FHH is one third of that in typical primary HPT, and a value less than 0.01 is virtually diagnostic of FHH. Unfortunately, FHH patients do not always show significant hypocalciuria. Mild elevations of magnesium can sometime distinguish FHH from HPT, since serum magnesium is usually in the low normal range in HPT. A family history of asymptomatic hypercalcemia would provide further support for a diagnosis of FHH. Both parents should be evaluated when the diagnosis is suspected in a child. Adequate distinction between HPT and FHH is not trivial since hypercalcemia in FHH has not been associated with any long term adverse outcome and requires no treatment. Furthermore, the surgical removal of parathyroid tissue in FHH, in cases that were thought to represent HPT, does not correct the hypercalcemia.

When PTH levels are adequately suppressed in the presence of hypercalcemia, elevated 25OHD levels would suggest vitamin D intoxication. Elevated $1,25(OH)_2D$ without a concomitant elevation of 25OHD points to an ectopic source of 1-α-hydroxylase. In both settings, hyperphosphatemia and marked hypercalciuria are usually present greatly increasing the predisposition to calcium toxicity. In the absence of elevated PTH and vitamin D metabolites, hypercalcemic patients that have not been exposed to high calcium ingestion or prolonged immobilization should be screened for the secretion of other hypercalcemic factors (i.e., PTHrP, prostaglandin E).

Management of Hypercalcemia

The management of hypercalcemia depends on the severity and cause of the elevation of serum Ca^{2+}. When hypercalcemia is mild and the patient is asymptomatic, no initial treatment may be necessary and medical efforts to reach a diagnosis should be given preference.

When hypercalcemia is severe (total serum calcium >14 mg/dL) or when there are symptoms and signs of cardiac, gastrointestinal, and central nervous system dysfunction, prompt intervention is appropriate. Since patients are usually dehydrated because of the polyuria and anorexia associated with severe hypercalcemia, the initial step is to provide adequate hydration, preferably in the form of isotonic saline at 3,000 cm^3/M^2 for the first 24–48 h, to restore vascular volume, increase glomerular filtration rate, and dilute serum Ca^{2+}. After hydration, the loop diuretic furosemide (1 mg/kg every 6 h) can further inhibit the reabsorption of calcium, especially in the presence of sodium, further promoting calciuresis. In comatose patients, hemodialysis should be considered as a means to decrease serum Ca^{2+} more aggressively.

If hypercalcemia does not respond to these initial measures, agents that block bone resorption may be useful as adjuvant therapy. Calcitonin 4 U/Kg SQ q 12 h is commonly used for this purpose; however, its efficacy diminishes with continuous administration due to tachyphylaxis. Bisphosphonates, analogues of pyrophosphate that inhibit osteoclast action, have been used, especially when hypercalcemia is primarily driven by the mobilization of calcium from bone as in cases of tumor induced hypercalcemia, severe HPT, or immobilization. Both etidronate and pamidronate could be used, the latter given as a single dose intravenous infusion.

When hypercalcemia is due to excess vitamin D ingestion or activity, glucocorticoids (prednisone 1 mg/kg/day) can be very effective since they inhibit both 1-α-hydroxylase activity and intestinal calcium absorption. Ketoconazole (3 mg/kg/day divided in three doses) is also a very effective inhibitor of 1-α-hydroxylase activity, but its use is associated with significant gastrointestinal side effects and can cause adrenal insufficiency.

Pharmacological agents may become available in the near future that can activate the CaR and suppress PTH secretion in affected glands. Pharmacological agents, i.e., calcimimetics, that can activate de CaR and suppress the secretion of PTH are now available. However, in young patients with well-described HPT, preferably confirmed by several measurements of serum calcium and PTH, the surgical removal of the affected gland is ultimately required to control hypercalcemia. A number of imaging techniques (i.e., neck ultrasound, computed tomography, magnetic resonance imaging, and radionuclide scanning) have been used to detect a hyperfunctioning gland; however, the reported sensitivities have ranged between 40 and 90% and may be more informative when used in combination. More recently, ^{99m}Tc-sestamibi scanning has shown some promise, especially in the visualization of adenomas [39]. Intraoperative measurements of PTH are now feasible, aiding the surgeon in his search for hyperplastic or adenomatous tissue since successful removal would be reflected by an adequate rapid drop of PTH levels [40]. In cases of an isolated adenoma, its resection is usually curative. In cases of isolated hyperplasia or secondary HPT, removal of three and one-half glands is recommended. Total parathyroidectomy is recommended with autotransplantation of

minced parathyroid tissue in the forearm for patients with MEN, where it could easily be removed in cases of recurring hypercalcemia. Post surgical hypocalcemia is common and easily treated with calcium supplements. In cases of severe HPT, hypocalcemia can be more severe and prolonged due to hungry bone syndrome. These patients have severe phosphate and calcium deficits as mineral bone deposition takes place. The use of both calcium and phosphate supplements together with calcitriol is recommended. In some instances, permanent hypoparathyroidism ensues, requiring lifelong therapy.

References

1. Diaz R, Fuleihan GE, Brown EM. Parathyroid hormone and polyhormones: production and export. In: Fray JCS, editor. Handbook of physiology. New York: Oxford University Press; 2000. p. 607–62.
2. Juppner H, Potts JT. The roles of parathyroid hormone and parathyroid hormone-related peptide in calcium metabolism and bone biology: their biological actions and receptors. In: Fray JCS, editor. Handbook of physiology. New York: Oxford University Press; 2000. p. 663–98.
3. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev. 2001;81(1):239–97.
4. Slatopolsky E, Dusso A, Brown AJ. The role of phosphorus in the development of secondary hyperparathyroidism and parathyroid cell proliferation in chronic renal failure. Am J Med Sci. 1999;317(6):370–6.
5. Rubin DA, et al. A G protein-coupled receptor from zebrafish is activated by human parathyroid hormone and not by human or teleost parathyroid hormone-related peptide. Implications for the evolutionary conservation of calcium-regulating peptide hormones. J Biol Chem. 1999;274(33):23035–42.
6. Suva W, Winslow GA, Wettenhall RE, et al. A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. Science. 1987;237(4817):893–6.
7. Kronenberg HM, Karaplis AC, Lanske B. Role of parathyroid hormone-related protein in skeletal development. Ann N Y Acad Sci. 1996;785:119–23.
8. Kovacs CS, et al. Parathyroid hormone-related peptide (PTHrP) regulates fetal-placental calcium transport through a receptor distinct from the PTH/PTHrP receptor. Proc Natl Acad Sci USA. 1996;93(26):15233–8.
9. Bikle D, Adams J, Christakos S. Vitamin D: production, metabolism, mechanism of action, and clinical requirements. In: Rosen C, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Hoboken, NJ: Wiley; 2008. p. 141–9.
10. Fuss M, et al. Calcium and vitamin D metabolism in granulomatous diseases. Clin Rheumatol. 1992;11(1):28–36.
11. Friedman PA. Calcium transport in the kidney. Curr Opin Nephrol Hypertens. 1999;8(5):589–95.
12. Martin TJ, Moseley JM. Calcitonin. In: DeGroot LJ, Jameson JL, editors. Endocrinology. Philadelphia, PA: WB Saunders; 2001. p. 999–1008.
13. Kovacs CS, Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, pueperium and lactation. Endocr Rev. 1997;18:832–72.
14. Carpenter TO. Disorders in mineral metabolism in childhood. In: Rosen C, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Hoboken, NJ: Wiley; 2008. p. 349–53.
15. Thakker RV. The molecular genetics of hypoparathyroidism. In: Bilezekian JP, Levine MA, Marcus R, editors. The parathyroids. San Diego, CA: Academic; 2001. p. 779–90.
16. Tomar N, Bora H, Singh R, et al. Presence and significance of a R110W mutation in the DNA-binding domain of GCM2 gene in patients with isolated hypoparathyroidism and their family members. Eur J Endocrinol. 2010;162(2):407–21.
17. Carey AH, et al. Molecular genetic study of the frequency of monosomy 22q11 in DiGeorge syndrome. Am J Hum Genet. 1992;51(5):964–70.
18. Thakker RV. Molecular genetics of mineral metabolic disorders. J Inherit Metab Dis. 1992;15(4):592–609.
19. Whyte MP. Autoimmune hypoparathyroidism. In: Bilezekian JP, Levine MA, Marcus R, editors. The parathyroids. San Diego, CA: Academic; 2001. p. 791–806.
20. Bettinelli A, et al. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. J Pediatr. 1992;120(1):38–43.
21. Cardenas-Rivero N, et al. Hypocalcemia in critically ill children. J Pediatr. 1989;114(6):946–51.
22. Rubin MR, Levin MA. Hypoparathyroidism and pseudohypoparathyroidism. In: Rosen C, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Hoboken, NJ: Wiley; 2008. p. 354–61.
23. Lips P, van Schoor NM, Bravenboer N. Vitamin D-related disorders. In: Rosen C, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Hoboken, NJ: Wiley; 2008. p. 329–35.
24. Arnold A. Genetic basis of endocrine disease 5. Molecular genetics of parathyroid gland neoplasia. J Clin Endocrinol Metab. 1993;77(5):1108–12.
25. Chandrasekharappa SC, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science. 1997;276(5311):404–7.
26. Mulligan LM, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature. 1993;363(6428):458–60.
27. Haden ST, et al. The effect of lithium on calcium-induced changes in adrenocorticotrophin levels. J Clin Endocrinol Metab. 1999;84(1):198–200.

28. Schipani E, Kruse K, Juppner H. A constitutively active mutant PTH-PTHrP receptor in Jansen-type metaphyseal chondrodysplasia. Science. 1995; 268(5207):98–100.
29. Diaz R, Brown EM. Familial hypocalciuric hypercalcemia and other disorders due to calcium-sensing receptor mutations. In: DeGroot LJ, Jameson JL, editors. Endocrinology. Philadelphia, PA: WB Saunders; 2001. p. 1121–32.
30. Rigby WF. The immunobiology of vitamin D. Immunol Today. 1988;9(2):54–8.
31. Burman KD, et al. Ionized and total serum calcium and parathyroid hormone in hyperthyroidism. Ann Intern Med. 1976;84:668–71.
32. Britto JM, et al. Osteoblasts mediate thyroid hormone stimulation of osteoclastic bone resorption. Endocrinology. 1994;134(1):169–76.
33. Bergstrom WH. Hypercalciuria and hypercalcemia complicating immobilization. Am J Dis Child. 1978;132(6):553–4.
34. Valentic JP, Elias AN, Weinstein GD. Hypercalcemia associated with oral isotretinoin in the treatment of severe acne. JAMA. 1983;250(14):1899–900.
35. Garabedian M, et al. Elevated plasma 1,25-dihydroxyvitamin D concentrations in infants with hypercalcemia and an elfin facies. N Engl J Med. 1985;312(15):948–52.
36. Taylor AB, Stern PH, Bell NH. Abnormal regulation of circulating 25-hydroxyvitamin D in the Williams syndrome. N Engl J Med. 1982;306(16): 972–5.
37. Sharata H, Postellon DC, Hashimoto K. Subcutaneous fat necrosis, hypercalcemia, and prostaglandin E. Pediatr Dermatol. 1995;12(1):43–7.
38. Kruse K, Irle U, Uhlig R. Elevated 1,25-dihydroxyvitamin D serum concentrations in infants with subcutaneous fat necrosis. J Pediatr. 1993;122(3):460–3.
39. Chen CC, et al. Comparison of parathyroid imaging with technetium-99 m- pertechnetate/sestamibi subtraction, double-phase technetium-99 m- sestamibi and technetium-99 m-sestamibi SPECT. J Nucl Med. 1997;38(6):834–9.
40. Boggs JE, et al. Intraoperative parathyroid hormone monitoring as an adjunct to parathyroidectomy. Surgery. 1996;120(6):954–8.