4 Disorders of Calcium Metabolism

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Key Points

1. Three organ systems are involved in the transport of calcium into the extracellular fluid: gastrointestinal, renal, and bone.
2. Two interdependent endocrine systems are responsible for the control of the concentration of extracellular calcium: parathyroid and vitamin D axis.
3. For disorders of extracellular calcium concentrations in complicated patients, measure ionized calcium rather than relying on "corrected" calcium measurements.
4. 25(OH)vitamin D and not $1,25(OH)_2$vitamin D concentration is the best measure of vitamin D deficiency.
5. In refractory hypocalcemia, especially in infants, hypomagnesemia should be considered as a possible cause.
6. Hypercalcemia generally results from increased absorption from the gastrointestinal tract, decreased excretion by the kidneys, or an imbalance of bone mineralization and resorption.
7. In contrast to adults where primary hyperparathyroidism and hypercalcemia of malignancy account for the vast majority of cases of hypercalcemia, these conditions are relatively rare in childhood.

Key Words: Calcium; hypercalcemia; hypocalcemia; parathyroid hormone; bisphosphonates; vitamin D

1. INTRODUCTION

Calcium plays several very diverse roles in the body. In the skeleton where 99% of the calcium lies, calcium crystals provides structural integrity, in the extracellular fluid ionized calcium modulates enzymatic processes and acts as an important intracellular second messenger. To provide these functions, its concentration in the extracellular and intracellular fluids must be tightly regulated and calcium balance must be maintained to assure skeletal integrity. Calcium balance is achieved by transport across three organ systems: the intestine, the kidney, and bone. Two hormones are primarily responsible for regulation of the control of the calcium fluxes across the membranes of these organs: parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).

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2. DISTRIBUTION OF CALCIUM IN THE BODY

The total amount of calcium in the body increases from 30 g at birth to about 1300 g in adulthood *(1)*. It is the most abundant electrolyte in the body but 99% is in the mineral phase of bone where the majority exists in crystalline form as hydroxyapatite [$Ca_{10}(PO4)_6(OH)_2$]. The other 1% is in the teeth, soft tissues and extracellular space. It is the 1 g of calcium in the plasma and extravascular space that is responsible for the control of multiple biologic systems and is regulated by PTH and vitamin D *(2, 3)*.

2.1. Serum Calcium

Normal serum calcium concentrations range from 9.0 to 10.5 mg/dL, although normal values vary by age and from laboratory to laboratory *(4, 5)*. About 50% of the total calcium exists in the ionized form (Ca^{2+}), 40% is bound to protein, and 10% complexed with phosphate, citrate, bicarbonate, and lactate. The ionized and complexed fractions together make up the ultrafilterable calcium, which can cross membranes such as the glomerular basement membrane. Ionized calcium is the physiologically important moiety. It can freely exchangeable across membranes, is responsible for regulation of cellular processes, and is highly regulated by PTH and vitamin D.

The percentage of Ca^{2+} can be altered by a number of factors including the concentration of albumin, the complexing anions, and blood pH. The most important variation in the fraction of ionized calcium occurs with changes in the concentration of albumin, which accounts for 75–90% of the protein bound calcium. Protein bound calcium acts as a rapidly available reserve pool during periods of rapid change in total calcium. Each gram of albumin binds approximately 0.8 mg of calcium. In hypoproteinemic states such as nephrotic syndrome, total calcium may be low but the concentration of Ca^{2+} remains in the normal range. Since calcium binding to albumin is pH dependent, changes in serum pH will affect the concentration of ionized calcium without altering the level of total calcium. During alkalosis, binding to albumin increases so the concentration of ionized calcium can drop resulting in physiologic changes such as tetany while measurements of total calcium remain in the normal range. The levels of the complexing anions are less commonly associated with physiologically important changes in the ionized calcium but there are rare circumstances such as with "citrate lock" where very high levels of citrate are associated with high total serum calcium but low ionized calcium. In general changes in total calcium are equally distributed across all three fractions. Since only about 10–15% of the albumin binding sites for calcium are occupied, albumin has the capacity to bind extra calcium in hypercalcemic states.

2.2. Distribution Across Cellular Membranes

In contrast to extracellular fluids where Ca^{2+} is 10^{-3} M, the concentration of cytosolic calcium is 10^{-6} M *(2)*. The level of Ca^{2+} is maintained by a series of pumps and transporters that extrude calcium from the cell, intracellular organelles which sequester calcium and by the binding of calcium to organic and inorganic compounds in the cytosol. The two major mechanisms responsible for the transport across the cell membrane or into the organelles are the Na^{+}–Ca^{2+} exchanger (NCX) and Ca^{2+}-ATPase (PMCA).

These cellular processes must protect the level of intracellular Ca^{2+} despite a 1000-fold gradient of calcium across the plasma membrane and a 50-mV electrical gradient that also favors entry of calcium into the cell. The mitochondria and the endoplasmic reticulum can also sequester calcium. There is a Ca-uniporter in mitochondria that can trap calcium in the form of amorphous tricalcium phosphate and help maintain cytosolic Ca^{2+}. Without proper functioning of these processes, toxic levels of calcium would enter the cell and lead to cell death. Inside the cell, calcium also performs important intracellular signaling function by the opening of Ca^{2+} channels by the second messenger IP_3.

2.3. Calcium Distribution During Neonatal Period

The fetus accumulates 120–150 mg of calcium per kilogram body weight from across the placenta during the third trimester resulting in approximately a whole body calcium content of 30 g in the normal full term infant *(1, 6)*. The concentration of serum total and ionized calcium falls after birth. The normal total calcium in cord blood from term infants starts above 10 mg/dL and falls to a nadir at 24 h whereas in preterm infants the concentration starts slightly lower but falls to a much lower nadir at 48 h of life and may not return to the baseline concentration until the 5th day of life (Table 1). A rise in the concentration of phosphorus and bicarbonate also may cause a physiologically significant fall in ionized calcium as the proportion of complexed calcium increases.

Table 1
Mean Serum Calcium Concentrations (mg/dL) in Term and Preterm Infants Over First 5 Days of Life

Age	*Term*	*Preterm*
Birth (Cord Blood)	10.2	8.96
Day 1	9.0	7.76
Day 2	9.56	7.4
Day 5	9.84	8.88

3. HOMEOSTASIS

After birth, calcium enters the body from absorption of dietary calcium in the intestine *(7)*. The calcium can be excreted by the kidneys through the processes of filtration and reabsorption or it can enter the skeleton, which is the largest repository of calcium. Calcium fluxes in and out of bone through the processes of bone mineralization and bone resorption but there is also a significant rapidly exchangeable calcium pool. During development, the body must protect the concentration of calcium in the serum and extracellular fluid while maintaining sufficient calcium intestinal absorption and retention by the kidneys to allow skeletal growth. The body must adjust for variability of dietary calcium and factors that affect renal calcium handling. The adaptations to these challenges are mediated largely by PTH and $1,25(OH)_2D$ although there is also a role for growth hormone and the sex steroids.

3.1. Systemic Transport of Calcium

3.1.1. Intestine

The intestine is the only organ system by which calcium enters the body *(7)*. The net amount of calcium absorbed normally equals the amount deposited in bone and lost in the urine and sweat. The net absorption of calcium is approximately 30% of the normal dietary intake with variation from 20 to 60% depending on the intake and the age of the individual with net absorption in the normal newborn approaching the upper range. The balance of calcium must also account for the 100–200 mg/day of calcium secreted from pancreatic and biliary juices and mucosal secretion. Intestinal absorption occurs by both passive and active transport and at low intakes the active transport is stimulated by $1,25(OH)_2D$ increasing net absorption.

Active transport across the intestinal mucosa is transcellular and occurs in the duodenum and upper jejunum, which are normally responsible for 90% of the calcium absorption *(8)*. The duodenum is the segment most responsive to stimulation of active transport by $1,25(OH)_2D$. The cellular processes of active transport involve transport of calcium across the apical membrane, movement across the cytoplasm and then extrusion across the basolateral membrane into the interstitial fluid. Influx of calcium into the cell is mediated by the calcium transport protein 1 (TRPV6). Calcium then is transported along the microvillar stalk by calmodulin/myosin to the glycocalyx where it is then bound to vesicles containing the calcium binding protein calbindin 9K. This compound is involved in the transport of calcium across the cytosol while protecting the cell from potential toxic effects of concentrations of calcium. On the basolateral surface, calcium is extruded from the cell by low-affinity, high capacity Na^+–Ca^{2+} exchanger and energy-dependent, high affinity, limited capacity Ca^{2+}-ATPase. To move calcium across the intestinal cell requires a "pump" action that is provided by Ca^{2+}-ATPase.

In contrast to the active transport, passive absorption occurs by diffusion from the lumen to the blood by diffusion via a paracellular pathway. This pathway becomes more significant as calcium intakes increase in part due to inhibition of $1,25(OH)_2D$ levels. Factors that increase calcium absorption include the young age, low calcium and phosphorus intake, vitamin D, and PTH through activation of $1,25(OH)_2D$ formation. Glucocorticoids can also decrease calcium absorption.

Calcium absorption in preterm infants fed human milk has been measured to be as high as 60–70% with formula fed infants absorbing 35–60% *(1, 6, 9)*. Net retention of calcium though is limited by phosphorus content and other mediators of solubility. In preterm infants the fatty acid content of most preterm formulas may limit calcium absorption, a problem that is ameliorated with fat blends that do not result in calcium soap formation. Even with optimal feeding, the preterm infant cannot match the accretion of calcium achieved during the last trimester of pregnancy with calcium transport across the placenta.

3.1.2. Kidney

Renal calcium handling is the product of filtration at the glomerulus and reabsorption by the renal tubule *(2, 3)*. The ionized and complexed fractions of calcium combined make up the "ultrafilterable" portion and this fraction that is equal to about 60% of the

total calcium, which is freely filtered. Approximately 8 g of calcium are filtered daily in the adult, which exceeds by about 10-fold the calcium content of the non-skeletal calcium. After filtration, about 98% of the filtered load is normally reabsorbed resulting in the adult of 150–200 mg of calcium appearing in the urine. By matching the amount of calcium absorbed by the intestine, renal excretion in the adult keeps calcium in balance. In contrast, in the growing child, calcium excretion is less than net intestinal absorption, which results in net retention of calcium and accretion by the skeleton.

Calcium is reabsorbed by the different segments in the renal tubule in the following proportions: 65% proximal tubule, 20% thick ascending limb, 10% distal tubule, and 2% collecting duct. The proximal convoluted tubule (PCT) is responsible for the majority of the reabsorption of calcium. The mechanisms responsible include solvent drag, increased tubular concentration of calcium as result of sodium and water reabsorption and as result of the transepithelial potential difference. Whereas the majority of the reabsorption is passive and paracellular, there is also evidence of an active transcellular component as well. In the proximal straight tubule, which includes the parts of the S_2 and S_3 segments, the reabsorption is passive in S_2 and active in S_3. Ca^{2+}-ATPase (PMCA) appears to play the predominant role in straight portion of the proximal tubule with there being involvement of the Na^{+}–Ca^{2+} exchanger (NCX).

The thick ascending limb of the loop of Henle is very important for calcium reabsorption and its control *(10)*. This segment, which accounts for about 20% of calcium reabsorption, is the site of regulation of calcium excretion by PTH and calcitonin. There appears to be both active transcellular and passive paracellular mechanisms. The reabsorption is coupled to sodium reabsorption and is inhibited by the loop diuretics: furosemide, bumetanide, and ethacrynic acid. The calcium sensing receptor, CaSR, has also been linked to the control of calcium as well as sodium and magnesium reabsorption in this segment of the renal tubule. Finally, recent studies have shown that the epithelial tight junction protein paracellin-1 (PCLN1) also plays an important role in both calcium and magnesium reabsorption. Under resting conditions, calcium transport across the thick ascending limb is driven by the transepithelial potential difference with the lumen being positive as generated by sodium reabsorption by the Na–K–2Cl transporter. Decreased activity of this transporter by the loop diuretics lowers the potential difference and calcium reabsorption. Paracellin-1 allows selective permeability for calcium and magnesium while otherwise establishing a tight junction for the passage of other ions.

Calcium reabsorption in the distal convoluted tubule is interesting for a number of reasons including its disassociation from sodium reabsorption in certain circumstances. The epithelial transport is all transcellular and is against the electrochemical gradient. Entry of calcium into the cells from the apical membrane involves the calcium channel (TRPV6) and has been suggested to be the rate-limiting step for calcium transport in this segment. The insertion of these calcium channels into the membrane is increased by agents such as PTH and calcitonin that stimulate calcium reabsorption. Calcium diffuses across the cytosol while being bound by the vitamin D stimulated calcium binding protein, calbindin D_{28K}. At the basolateral surface, calcium is extruded from the cell by PMCA, possibly with the involvement of the calcium binding protein, calbindin D_{9K}. The presence of the CaSR in the basolateral membrane of the DCT cells suggests a

possible role in this segment as well. One of the interesting features of calcium transport across the distal tubule is the stimulation by thiazide diuretics. These agents, which inhibit the entry of sodium across the apical membrane by the Na^+–Cl^- cotransporter, have been shown to activate apical calcium entry through calcium channels and extrusion of calcium across the basolateral surface by a Na^+–Ca^{2+} exchange.

There is further transport in the connecting tubule and collecting duct accounting for about 1–2% of total calcium reabsorption. This transport is stimulated by amiloride, which inhibits the apical sodium channel suggesting a mechanism involving a sodium calcium exchange that drives calcium exit across the basolateral membrane. Other mechanisms described in the distal nephron include active transport involving either the Na^+–Ca^{2+} exchanger (NCX) or Ca^{2+}-ATPase (PMCA).

3.1.3. Bone

Bone is the repository of more than 99% of the total body calcium *(7)*. Skeletal calcium exists in both a rapidly exchangeable pool as well as a much more slowly exchangeable pool. The latter refers to calcium in the form of hydroxyapatite that is deposited with collagen fibers whereas the rapidly exchangeable pool is much more poorly characterized but includes calcium at the site of active bone formation. The processes of bone formation and bone resorption are generally well coordinated or "coupled." Due to the large amount of calcium constantly entering and leaving bone, disease states that disturb the coupling of bone resorption and mineralization can overwhelm other physiologic systems in the body to maintain calcium homeostasis.

Osteoblasts, the cells responsible for bone mineralization, arise from bone marrow derived osteoprogenitor cells and are also responsible for activation of osteoclasts *(11)*. Osteoblasts activated by PTH (Section 3.2.1) express the ligand (RANKL) for a receptor on osteoclasts and their precursors termed "receptor for activation of nuclear factor kappa B" or RANK *(12)*. PTH also increases the production of macrophage-colony stimulating factor (M-CSF), which is also required for osteoclastic differentiation. The activity of RANK is also normally suppressed by a decoy receptor for RANKL called osteoprotegerin (OPG), which is formed by osteoblasts and whose secretion is also decreased by PTH. Osteoblasts therefore in response to PTH stimulate osteoclasts to differentiate and to resorb bone by expressing RANKL, secreting M-CSF, and decreasing levels of the inhibitor OPG. This coupling between osteoblasts and osteoclasts is responsible for the increases and decreases in mineralization and bone resorption that occurs during skeletal remodeling.

3.1.4. Placenta

Transport of calcium across the placenta is an active process for transfer of calcium from the mother to the fetus *(6, 13)*. The mechanism is active transport by a calcium pump in the basal membrane of the placental cells that normally maintains a positive fetal–maternal gradient. This process is regulated by parathyroid hormone related protein (PTHrP), which appears to be produced in the placenta as well as the fetal parathyroid glands. Fetal PTH otherwise controls the level of serum calcium in the fetus

and is involved in bone mineralization. During the third trimester of pregnancy, 120–150 mg calcium/kg fetal weight is transported daily across the placenta. This movement of calcium is critical for normal fetal bone accretion and cannot be matched in the extremely preterm infant through other routes. This very large influx of calcium into the exchangeable pool of calcium is lost at the time of birth and homeostatic mechanisms must be in play to avoid the development of severe hypocalcemia.

3.2. Regulation of Calcium Metabolism

3.2.1. Parathyroid

The parathyroid gland plays the central role in the control of calcium metabolism through the secretion of parathyroid hormone (PTH) *(14)*. The primary regulator of serum PTH levels is serum calcium, which inhibits PTH secretion through activation of the calcium-sensing receptor (CaSR). CaSR is a G-protein coupled receptor on the surface of parathyroid cells that responds to changes in extracellular calcium by actions on a series of effects depending on duration of effect *(15)*. There is an increase in the secretion of preformed PTH in seconds to minutes, an increase PTH gene expression over several hours to a few days then finally an increase in the number of parathyroid cells through cell proliferation in a time period taking days or longer. There have been described activating and inactivating defects of the CaSR gene, which lead to states of hypo- and hyperparathyroidism. The CaSR is also the target of a class of medications called "calcimimetics" or "calcilytics," which suppress or activate PTH secretion, respectively.

Other regulators of PTH secretion include $1,25(OH)_2D$ and extracellular phosphate, both of which inhibit secretion. The mechanism for suppression of PTH by vitamin D is through the vitamin D receptor, which acts as a nuclear transcription factor. The effects of vitamin D and phosphate on PTH secretion are more long-term than calcium and predominantly affect PTH gene expression and cell proliferation.

The actions of PTH in the body are mediated by through the PTH/PTHrP receptor (PTH1R), which is a G-protein coupled receptor that then activates adenylate cyclase or phospholipase C *(3)*. Many tissues express PTH1R but the kidney and bone have the greatest physiologic relevance for mineral homeostasis. Defects in the $G\alpha_s$ peptide as found in pseudohypoparathyroidism type 1, result in hypocalcemia, hyperphosphatemia, and a variety of bone defects. In bone, osteoblasts and their precursors are directly activated by PTH where they stimulate the differentiation and activation of osteoclasts through activation of RANK (Section 3.1.3). In response to PTH, there is release of calcium from the rapidly exchangeable pool at the surface of bone in minutes and from a more slowly exchangeable pool within hours. As osteoclasts are stimulated to resorb bone, phosphate and collagen degradation products are released into bloodstream.

In the kidney, PTH receptors are found along the renal tubule where it activates PTH1R leading to a variety of actions. PTH regulates mineral metabolism in the kidney by stimulating calcium reabsorption, phosphate excretion, and $1,25(OH)_2D$ formation. PTH stimulates calcium reabsorption by activating paracellular mechanisms in the thick ascending limb and transcellular processes in the distal convoluted tubule (Section 3.1.2). Despite the fact that PTH stimulates calcium reabsorption, in

hyperparathyroid states with hypercalcemia, calcium excretion is elevated as result of the increased filtered load resulting from calcium released from bone and absorbed from the intestine.

In response to hypocalcemic stresses, PTH stimulates both calcium and phosphorus release from bone (directly) and absorption from the intestine (indirectly through $1,25(OH)_2D$ formation *(3)*. To maintain serum calcium, the excess phosphate must be excreted and PTH stimulates phosphaturia by blocking the sodium-dependent phosphate in the proximal renal tubule through inhibition of expression of the phosphate transporter NPT-2a. In hyperparathyroid states, hypophosphatemia is the result. PTH increases calcium by stimulating the synthesis of 25-hydroxyvitamin D_3-1-α-hydroxylase found in mitochondria of the proximal renal tubule. This process over hours increases the formation of $1,25(OH)_2D$ that stimulates calcium absorption in the intestine and calcium release from bone.

3.2.2. Vitamin D Axis

Vitamin D through its biologically active form $1,25(OH)_2D$ plays a central role in calcium homeostasis *(14)*. $1,25(OH)_2D$ stimulates absorption of dietary calcium and recruits stem cells in bone to form osteoclasts, which can then release calcium from the skeleton. $1,25(OH)_2D$ acts as a hormone in the body whose formation in the kidney is highly regulated by PTH, calcium, phosphate and other factors. There are now well-described non-calcemic functions for vitamin D where local formation of $1,25(OH)_2D$ leads to autocrine and paracrine effects.

Vitamin D can either be formed in the skin or be absorbed in the diet but the latter pathway usually requires supplementation because of the paucity of natural sources. Formation in the skin involves the transformation of 7-dehydroxycholesterol (provitamin D_3) by sunlight to previtamin D_3, which is rapidly isomerized to vitamin D_3 (cholecalciferol). Continued or excessive sunlight leads to the conversion of vitamin D_3 to inert products, which prevents toxic amounts of vitamin D from resulting from sun exposure. Many factors can modulate the cutaneous formation of vitamin D_3 including the amount of melanin in the skin, the intensity of the suns rays, the age of the patient, and the use of sunscreens. The vitamin D_3 that is formed is then bound to vitamin D-binding protein in the blood. Dietary vitamin D usually comes from certain foods such as oily fish but more commonly comes from either supplements or fortified foods. Fortified foods such as milk usually contain vitamin D_2 (ergocalciferol) but supplements can contain either vitamin D_3 or vitamin D_2. Whereas in the past, these two forms were thought to be biologically equal, more recent evidence suggests that vitamin D_3 may be 2–3 times more potent.

To become biologically active, vitamin D must undergo two hydroxylation steps *(16)*. The first occurs in the liver where one of several cytochrome P_{450}-vitamin D-25-hydroxylases converts vitamin D to 25(OH)D in substrate dependent, non-regulated process. This compound is then transported in the blood to the kidney and other tissues where it can undergo further metabolism. In the proximal renal tubule, where it is bound to 25(OH)D-DBP and taken in to the cell where the cytochrome P_{450}-mono-oxygenase, 25(OH)-1-α-hydroxylase (CYP27B1) converts it to $1,25(OH)_2D$.

The conversion from 25(OH)- to $1,25(OH)_2D$ is stimulated by PTH, low serum phosphate and low calcium. Other regulators include fibroblast growth factor-23 (FGF-23) that lowers $1,25(OH)_2D$ formation and IGF-1 that increases it. Another important determinant of $1,25(OH)_2D$ concentration is metabolism by the renal 24-hydroxylase (CYP24), which can act on both 25(OH)D and $1,25(OH)_2D$ to form $24,25(OH)_2D$ and $1,24,25(OH)_3D$, respectively.

$1,25(OH)_2D$ works to maintain serum calcium by its affects on the intestine and bone. This steroid hormone binds to the vitamin D receptor (VDR) in the cytoplasm in its target tissues after it translocates to the nucleus and forms a heterodimeric complex with RXR. This complex then is able to bind to chromosomal VDR response element (VDRE) where after binding other initiation factors, and the transcription of vitamin D responsive genes are either enhanced or inhibited. In the intestine, such genes as the TRPV6, calbindin 9 K, and other proteins promote calcium transport across the intestinal epithelial cell. In bone, the proteins induced by activation of VDR by $1,25(OH)_2D$ in osteoblasts include RANKL, alkaline phosphatase, osteocalcin, and osteoprotegerin. The stimulation of bone mineralization by vitamin D is through its ability to maintain adequate levels of calcium and phosphorus rather than by direct effects on bone.

3.2.3. Other

Calcitonin is a peptide hormone secreted by the C cells in the thyroid in response to elevated levels of serum calcium *(17)*. It can inhibit osteoclasts although the exact physiologic significance in human mineral metabolism is unclear. There are reports of elevated calcitonin in certain hypocalcemic conditions. Parathyroid hormone-related protein (PTHrP), which is part of the PTH gene family and can activate a common receptor (PTH1R), functions primarily in the fetus where formation of the cartilaginous growth plate, transport of calcium across the placenta, and development of the teeth. Postnatally, the most important function for PTHrP appears to be the development of the mammary gland and transport of calcium into breast milk. Clinically though, PTHrP is important as the most common mediator of hypercalcemia of malignancy.

4. CLINICAL ASSESSMENT OF CALCIUM DISORDERS – INTRODUCTION

Evaluation of calcium disorders requires proper measurement and interpretation of the divalent ions, calcium, phosphorus, and magnesium. Secondly the evaluation of the calcium regulating hormones, parathyroid hormone (PTH), vitamin D metabolites and in hypercalcemia, parathyroid hormone-related protein (PTHrP) is essential to evaluate their role in or response to changes in serum calcium. Studies of renal calcium handling may be helpful but is a less useful tool than the previous mentioned studies. Finally radiologic studies of the skeleton may help pinpoint certain diagnoses. Markers of bone turnover, bone density measurements, and bone biopsy are important in the evaluation of skeletal health but do not add significantly to the evaluation of disorders of calcium metabolism.

5. MEASUREMENT OF DIVALENT IONS

5.1. Serum Calcium

Serum calcium is made up by three fractions: protein-bound, complexed, and ionized. The ionized portion, representing about 50% of the total, is the only one that is physiologically important *(7)*. Ionized calcium helps maintain normal blood coagulation, membrane stability, bone mineralization, and other process and is the only portion that is regulated by PTH and 1,25-dihydroxyvitamin D ($1,25(OH_2)D$). Disorders of serum calcium are often expressed by deviation of total calcium from normal although it is the level of ionized calcium that is clinically relevant. Therefore changes in ionized calcium are the product of the total serum calcium and relative distribution between the three fractions.

Total serum calcium is measured by most laboratories using automated spectrophotometric analysis using dyes such as o-cresolphthalein as an indicator *(4)*. In most clinical use in the United States, the calcium concentration is expressed as mg/dL. With an atomic weight of 40.08 and valence of 2, this value can be easily converted to mmol/L (mM) and mEq/L by dividing by 4 and 2, respectively. The normal value for total calcium ranges from about 9–10.4 but can vary by age with greater values in infants and young children (Table 2). Total calcium should be measured either in serum or heparinized plasma whereas plasma from samples using citrate, oxalate, or EDTA that form complexes with calcium should be avoided. Hemolysis, icterus, and lipemic samples can also interfere with the normal spectrophotometric analysis.

Table 2
Total (mg/dL) and Ionized (mM) Calcium Serum Concentrations in Childhood

Age (years)	*Total calcium*	*Ionized calcium*
Infants 0.25–1	8.8–11.3	1.22–1.4
Young child 1–5	9.4–10.8	1.22–1.32
Older child 6–12	9.4–10.3	1.15–1.32
Adolescents	9–10.2	1.12–1.3

Total calcium measurements also display both postural and circadian increases of up to 0.5 mg/dL during midday when an upright position leads to increased albumin concentrations, which accounts for up to 90% of protein bound calcium *(18)*. Improper tourniquet technique causing venous stasis can also increase albumin and total calcium *(19)*. The proportion of total calcium that is protein-bound to albumin is also altered by changes in pH that changes the conformation of albumin. An increase in pH of 0.1 will increase the protein-bound form of calcium by about 1.2 mg/dL resulting in the lowering of the physiologically and clinically relevant ionized portion of 0.05 mM *(20)*. The shifting of calcium to the protein-bound fraction with alkalosis is a common cause of hypocalcemia and tetany in the patent with a borderline ionized calcium level. Disease states that are associated with low levels of serum albumin such as nephrotic syndrome

or liver cirrhosis characteristically have low total calcium but normal ionized calcium levels.

To better evaluate the clinically relevant ionized portion of the total serum calcium a number of formulas have been suggested to "correct" the serum calcium for changes in albumin including: corrected serum calcium (mg/dL) = total calcium (mg/dL) + 0.8 (4) – serum albumin (g/dL) *(2)*. It has been found that these "corrected" values poorly predict the changes in ionized calcium in many individuals. Changes in pH, the complexing anions citrate, and phosphate, and other factors can all alter ionized calcium in ways not appreciated with "corrected" values. With the availability of semi-automated instruments using ion-specific electrodes to measure ionized calcium, it is now recommended to directly measure ionized calcium in the sick and hospitalized patients *(21)*. Routine use of total calcium measurements in relatively well outpatients is usually adequate. The normal levels of ionized calcium do vary by age but not to the extent as total calcium (Table 2). There are minor circadian effects on ionized calcium and samples should be collected anaerobically to avoid pH effects. Heparinized plasma samples for rapid analysis are best collected with either 50 IU/ml of calcium-titrated heparin or 15 U/ml of lithium heparin and the tubes completely filled to avoid dilutional and heparin effects.

5.2. Serum Phosphate

The measurement of serum phosphate is covered more comprehensively in later chapters but is considered briefly here because of its importance in evaluation of calcium disorders. It is the inorganic phosphorus in the form of phosphate in blood that is measured and is expressed as phosphate *(4, 18)*. Again serum is preferred but heparinized samples can be used but the values are 0.2–0.3 mg/dL lower. Citrate, oxalate, and EDTA that interfere with the analysis method should be avoided. Serum or plasma should be rapidly separated from red blood cells that contain greater amounts of phosphorus and can artifactual increases. Phosphorus levels are usually expressed in mg/dL or with its atomic weight of 30.98, in mM by dividing by 3.1. To express in mEq/L, the value is pH dependent since there is a mixture of monovalent and divalent ions with a composite valence of 1.8 at pH 7.4. Therefore at normal pH, the mEq of phosphorus can be calculated by multiplying the mM by 1.8.

There is both a significant circadian rhythm to serum phosphate levels as well as a dietary effect that can increase phosphorus levels by 1.2 mg/dL. The optimal time to measure phosphate is a morning, fasting sample. Factors that can redistribute phosphorus into cells such as insulin, glucose, and other carbohydrate loads, respiratory alkalosis and epinephrine, all can acutely lower phosphorus levels as much as 2 mg/dL. Much more than calcium, there is strong role of age in phosphorus levels. Normal phosphorus levels fall from a normal range of 4.8–7.4 mg/dL in infants to 4.5–6.2 mg/dL young children to a range of 3.5–5.5 mg/dL in older children till late adolescence.

5.3. Serum Magnesium

Serum magnesium has three fractions as calcium but in different proportions (see also Section 5, Chapter 8, Clinical Assessment of Magnesium Metabolism in Infants

and Children). The protein-bound portion of magnesium is only 30%, complexed portion makes up 15%, and the ionized portion represents 55% of total serum magnesium *(4)*. Like calcium, it is the ionized portion that is physiologically and clinically important since it involved in neuromuscular and cardiovascular function. Unlike calcium, the measurement of ionized magnesium is not measured in clinical situations. The normal serum concentration of magnesium is 1.6–2.4 mg/dL and does not vary significantly with age. With a molecular weight of 24.31 and valence of 2, to convert the concentration of magnesium from mg/dL to mM, the value is divided by 2.4 and by 1.2 to derive the concentration in mEq/L *(19)*.

6. MEASUREMENT OF CALCIOTROPIC HORMONES

6.1. Parathyroid Hormone

The normal inverse relationship between serum calcium and PTH secretion makes measurement of PTH an invaluable tool in the evaluation of disorders of serum calcium. If control of PTH secretion is intact and not part of the primary cause of the disturbance in serum calcium, PTH levels should be suppressed in hypercalcemia and elevated in hypercalcemia. PTH is now routinely measured by 2-site assays that recognize the "intact" PTH molecules and not fragments as were recognized by older "mid-region" and "carboxy-terminal" assays *(21)*. There are both immunoradiometric assays (IRMA) that use radioactive tracers and immunochemiluminometric assays (ICMA) that have the advantage of not needing radioactivity. The normal ranges for each assay are laboratory specific but the normal adult range are usually about 10–65 pg/ml. Over the last few years, "third generation" PTH assays that measure "whole molecule" has been promoted for use with renal failure, but there is no current indication for their use with hypo- and hypercalcemic disorders.

PTH as measured by the intact PTH assays has a very short half-life (2–4 min) and has been shown to demonstrate pulsatile secretion *(22)*. Because of the inverse relationship between calcium and PTH secretion, PTH levels should be performed with simultaneous calcium levels. In the presence of non-parathyroid hypercalcemia, PTH values are below the normal range in 70–80% of patients and below 25 pg/ml in the rest. In patients with primary hyperparathyroidism, 90% will have elevated PTH levels by the intact assay with the rest having PTH levels inappropriately elevated for the degree of hypercalcemia. In patients with hypocalcemia and hypoparathyroidism, PTH levels are usually below the normal range or inappropriately low for the level of calcium in contrast to non-parathyroid causes of hypocalcemia where secondary hyperparathyroidism with high PTH levels are expected.

6.2. Vitamin D

The two vitamin D metabolites with assays available for measurement are 25-hydroxyvitamin D (25(OH)D) and 1,25(OH_2)D. 25(OH)D is the major circulating form of vitamin D and reflects vitamin D nutrition including cutaneous formation *(16)*. In contrast, the levels of biologically active 1,25(OH_2)D normally reflect the highly regulated renal formation that is stimulated by high PTH and low phosphorus and calcium

levels. 25(OH)D is measured most often by a competitive protein-binding assay after chromatography over a C-18 silica column *(23)*. The normal values are 10–80 ng/ml (25–200 nmol/L) but can vary seasonally with higher levels in summer and fall after sun exposure *(20)*. Lower levels are often seen in people with greater skin pigmentation or who live at higher latitudes. 1,25(OH_2)D normally circulates in concentrations of 20–60 pg/ml (50–150 pmol/l) and where it is not affected by season, there are higher levels recorded in infants and children. Vitamin D exists in two forms: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is naturally formed in the skin whereas ergocalciferol is artificially derived from yeast. Despite the ability of certain assays to differentiate between vitamin D_2 and D_3, in general for both 25(OH)D and 1,25(OH_2)D, both D_2 and D_3 are measured because the total is most clinically relevant.

Measurement of 25(OH)D is useful in determining the presence of vitamin D deficiency or excess in hypocalcemia and hypercalcemia, respectively *(20, 23)*. In vitamin D deficiency, serum 25(OH)D levels are less than 8 ng/ml whereas in hypercalcemia due to vitamin D intoxication, levels greater than 200 ng/ml are required. In contrast to 25(OH)D, 1,25(OH_2)D is usually normal in vitamin D deficiency and its measurement is only useful in selective clinical situations. Levels can be high in the presence of hypercalcemia due to extrarenal production of 1,25(OH_2)D by certain lymphomas and granulomatous disorders such as sarcoidosis. Levels are characteristically low in patients with vitamin D dependent rickets type 1 who lack the renal 25(OH)-1-α-hydroxylase and very high in vitamin D dependent rickets type 2 in which there is the lack of the vitamin D receptor leading to hypocalcemia, secondary hyperparathyroidism, and stimulation of 1,25(OH_2)D formation. For the most part, measurement of 1,25(OH_2)D in disorders of serum calcium is inappropriate and not cost-effective.

6.3. Parathyroid Hormone-Related Protein

Parathyroid hormone-related protein (PTHrP) plays a number of important roles in the fetus and in the postnatal period, but after birth it is measurable only in certain rare disease states *(24)*. It is most associated with certain cancers and the syndrome of humoral hypercalcemia of malignancy, which is characterized, by severe hypercalcemia, low serum phosphate, suppressed PTH, and elevated PTHrP. The most common assay is an immunoradiometric assay (IRMA) with an antibody directed against the N-terminal, which shares homology with PTH as well as mid-region that recognizes an area distinct from PTH so the assay can distinguish between PTH and PTHrP *(25)*. Whereas normal individual have levels of <1 pmol/L but most humoral hypercalcemia of malignancy (HHM) patients have levels >5 pmol/L. PTHrP is a very labile molecule and proper handling of the sample is required.

7. CLINICAL EVALUATION OF RENAL DIVALENT HANDLING

The assessment of renal function in patients with disorders of renal handling is three fold. First, is the proper assessment of glomerular filtration rate (GFR) since renal failure may be a cause of hypocalcemia or acute and chronic renal failure may be the result of calcium disorders especially hypercalcemia? For most clinical purposes, serum creatinine is an adequate measure of GFR and normally rises from 0.3 mg/dL after a few

weeks of age to adult levels of about 0.8–1 mg/dL by early adolescence. Secondly, assessment of renal calcium excretion gives valuable information about calcium balance and may point to the etiology of hypo- and hypercalcemia as well as the possible role of the kidney. Renal calcium excretion is equal to gastrointestinal calcium absorption minus skeletal calcium balance. In normal healthy children, calcium excretion is less than the calcium absorbed in the GI tract. Conditions associated with low calcium absorption are very low calcium intake, vitamin D deficiency, malabsorption (states possibly associated with hypocalcemia), and familial benign hypocalciuric hypercalcemia where the kidney contributes to the hypercalcemia. In contrast hypercalciuria is usually present in vitamin D induced hypercalcemia, hyperparathyroidism and immobilization and humoral hypercalcemia of malignancy. Under these conditions, hypercalcemia occurs when the kidney can no longer excrete calcium released from bone or absorbed from the GI tract.

Normal calcium excretion can be expressed in relation to body weight with the normal values being less than 4 mg calcium/kg body weight/day. Simultaneous measurement of creatinine should be performed to assess the completeness of the collection and should equal 15–25 mg/kg/day *(20)*. Alternatively, calcium excretion can be expressed as a ratio of creatinine excretion but these results are age dependent (Table 3). Finally, since calcium excretion is dependent on the filtered calcium load, a useful measure of calcium handling is the ratio of calcium clearance to creatinine clearance, which can be calculated in a spot urine sample where the urine volumes cancel out to equal: $Ca_{cl}/Cr_{cl} = (Ca_u \times Cr_s)/(Cr_u \times Ca_s)$. This index is especially helpful in evaluation of familial hypocalciuric hypercalcemia where the index is typically less than 0.01 *(26)*.

Table 3
Calcium Excretion by Age

Age (years)	*Ca/cr (mg/mg) 95th percentiles*
0.5–1.0	<0.81
1–2	<0.56
2–3	<0.5
4–5	<0.41
5–7	<0.3
7–17	<0.25

8. HYPOCALCEMIA – INTRODUCTION

Hypocalcemia in infants and children is a relatively common disorder especially in the neonate. Hypocalcemia is the result when the influx of calcium in the extracellular fluid does not keep pace with calcium efflux into bone, excretion into the urine or less commonly as deposits into the soft tissue. The level of intravascular calcium is regulated and protected by the parathyroid and vitamin D systems and their effects on bone resorption, renal excretion, and gastrointestinal absorption of calcium. Acute hypocalcemia can cause life-threatening events especially through disordered neuromuscular and cardiovascular physiology.

CASE SCENARIOS

Case Scenario 1: Hypocalcemia in a school aged child.

An 8-year-old boy has been admitted with cramping of his hands and feet that began with a recent illness. He has been healthy except for a chronic infection of his skin and nails for which he sees a dermatologist. Your physical exam of this normal appearing boy includes Chvostek's and Trousseau's signs, both of which are positive. Labs come back with a normal CBC, normal renal function, and electrolytes but a total serum calcium of 7.2 mg/dL, phosphorus of 7.9 mg/dL, and an albumin of 3.9 g/dL.

What is the most likely diagnosis and what studies would you like to perform next? What should your initial treatment be? What other illnesses do you need to be monitoring?

Case Scenario 2: Infant with new onset seizures and heart disease.

An 8-day-old full-term infant with the diagnosis of congenital heart disease from a VSD is found to have a creatinine of 1.4 mg/dL, calcium 6.9 mg/dL, and a phosphorus of 10.2 mg/dL. He is just starting to feed and has been on a standard infant formula. The mother is healthy and is on no medications. On physical exam he has an unusual facies and is extremely jittery. EKG shows an abnormal QT interval.

What is the most likely diagnosis and what studies would you like to order? What would your initial treatment be?

9. DEFINITION OF HYPOCALCEMIA

The lower limits of normal for total serum calcium in children range from 8.8 mg/dL in infants to 9.4 mg/dL in pre-adolescents and dropping back to 9 mg/dL in adolescents (Table 2) *(18)*. The most important fraction – ionized calcium – does not exactly follow total calcium with lower limits of normal of 1.22 mM or 4.9 mg/dL until age 6 years and then it drops slightly to 1.15 in older children and 1.12 in young adults. Some of the variation with age is due to changes protein-bound and complexed fractions of calcium. The latter occurs when serum concentrations of lactate, sulfate, and citrate are elevated. Measurement of total calcium is adequate in most stable out-patients but variations of low serum albumin are an important cause of "pseudohypocalcemia" in which total serum calcium is low but ionized calcium is normal *(27)*. In contrast, changes in pH or excessive levels of citrate can give a picture of normal or even high total calcium in the presence of significant drops in ionized calcium. Total serum calcium can be "corrected" for alterations in serum albumin and pH although in ill or complex patients or in those patients known to have changes in albumin, pH, or one of the complexing anions, ionized calcium should be measured directly.

10. CLINICAL FEATURES

The clinical symptoms related to hypocalcemia are mainly related to affects on the cardiac and neuromuscular systems (Table 4) *(28)*. Some signs and symptoms such as abnormal calcification may be more common in states of abnormal PTH function. The two classic signs are those of Chvostek and Trousseau *(27)*. Chvostek's sign is elicited

Table 4
Clinical Manifestations of Hypocalcemia

Cardiovascular
Prolonged QT interval on EKG
Heart failure
Neuromuscular
Parasthesias, perioral tingling
Muscle cramps, tetany
Laryngospasm
Trousseau's sign
Chvostek's sign
Seizures (all types)
Irritability, abnormal mental function
Basal ganglion calcifications
Other
Cataracts, papilledema
Coarse skin, brittle nails

by tapping with three fingers over the facial nerve anterior to the ear. A positive sign can be arranged from twitching of the lip at the angle of the mouth to twitching of nasolabial fold, lateral angle of the eye or finally all of the facial muscles on that side. The mildest response can be seen in 8% of normocalcemic individuals but more dramatic twitching is specific for hypocalcemia. Trousseau's sign is elicited by pumping a sphygmomanometer cuff 20 mmHg above the systolic BP for 5 min to produce ischemia of the ulnar nerve. A positive sign is when the metacarpophalangeal joints flex, interphalangeal joints extend, and the thumb adducts. Neither of these signs are 100% sensitive.

11. CAUSES OF HYPOCALCEMIA

Normally the body is protected from hypocalcemia by the actions of parathyroid hormone (PTH) and 1,25$(OH)_2$vitamin D (1,25$(OH)_2$D). Hypocalcemia results when there abnormal secretion of these two hormones or the body cannot adequately respond to them either because of congenital or acquired conditions *(29)*. PTH acts to lower phosphorus by its actions on the kidney and 1,25$(OH)_2$D increases it by its action on bone and the GI tract. The level of phosphorus therefore is a useful clue to the cause of hypocalcemia because it is elevated in abnormal parathyroid states and low in vitamin D dysfunction *(28)*. Other hypocalcemic conditions can be the result of hyperphosphatemia from endogenous and exogenous sources or be associated with hypophosphatemia as calcium and phosphorus are being deposited in bone (Table 5).

11.1. Hypoparathyroidism

Hypoparathyroidism is characterized by hypocalcemia, hyperphosphatemia, and inappropriately low PTH levels for the calcium level *(30, 31)*. There are transient hypoparathyroid states that are common in young infants and which will be covered

Table 5
Causes of Hypocalcemia

Hyperphosphatemia
- Hypoparathyroidism
  - Congenital hypoparathyroidism
    - DiGeorge and related syndromes
    - Maternal hyperparathyroidism
    - Calcium receptor activating mutations
  - Acquired hypoparathyroidism
    - Autoimmune
    - Surgical removal or damage
    - Hypomagnesemia
- PTH resistance
  - Pseudohypoparathyroidism
  - Hypomagnesemia
- Phosphorus loads
  - Endogenous
    - Tumor lysis, rhabdomyolysis
    - Renal failure
  - Exogenous
    - Phosphorus containing enemas
    - High phosphorous formulas

Hypophosphatemia
- Vitamin D deficiency
  - Lack of sun and dietary
  - Malabsorption
  - Renal failure
  - Increased metabolism
  - Vitamin D Dependent Rickets (VDDR) Type I
- Resistance to vitamin D – VDDR Type II
- Deposition of Ca and P into tissues
  - Hungry bone syndrome

Other
- Sepsis and other critical illness
- Drugs
- Pancreatitis
- Altered bound calcium-citrate

under Neonatal Causes (Section 11.5). The major categories of hypoparathyroidism are agenesis as in DiGeorge syndrome, destruction by surgery, radiation, infiltrative disease, or autoimmune processes and functional such as with severe hypomagnesemia. The causes of hypoparathyroidism can be often be recognized by history and associated findings. With acute surgical hypoparathyroidism, a sudden drop in the PTH level can lead to a condition called “hungry bone syndrome” can develop as result of interrupted

bone resorption in the presence of continued bone mineralization. In "hungry bone syndrome" there can be hypophosphatemia in addition to hypocalcemia, which is unusual for other hypoparathyroid states.

There are a number of syndromes associated with agenesis or hypoplasia of the parathyroid glands (Table 6) that usually present in the first week of life with hypocalcemia and tetany *(32)*. The most common is DiGeorge syndrome, which can occur in 1:500 live births. DiGeorge syndrome is due to abnormal development of the 3rd and 4th branchial pouches and can include hypoparathyroidism, immunodeficiency, congenital cardiac defects, and a distinctive facies. In greater than 90% of cases it is due to a microdeletion of chromosomal band 22q11.2 and has been termed "CATCH 22" to refer to the Cardiac, Abnormal facies, Thymic aplasia, Cleft palate, Hypocalcemia with 22q deletion *(33)*. The clinical spectrum may include a Shprintzen (velocardiofacial) syndrome or conotruncal anomaly face syndrome. Genetic diagnosis can be made in most cases with cytogenetic analysis for the 22q11.2 using fluorescence in situ hybridization (FISH). Other chromosomal abnormalities have been associated with a DiGeorge syndrome including deletions of 10p. The degree of the defects can vary in patients with DiGeorge syndrome including normocalcemic infants with normal PTH levels but who cannot respond adequately to a hypocalcemic stress with increased PTH secretion. Other syndromes associated with congenital hypoparathyroidism include Kenny–Caffey (skeletal dysplasia and dwarfism), Kearns–Sayre (mitochondrial myopathy, cardiac conduction defects, and ocular abnormalities), Barakat (nephrosis and sensorineural deafness), and Sanjad–Sakati (IUGR, dysmorphic facies, skeletal defects, and developmental delay) *(30)*.

An autosomal dominant form of hypoparathyroidism results from activating of the gene for the calcium receptor, CaSR. This disorder is the mirror image of familial hypocalciuric hypercalcemia (FHH) and is characterized by hypocalcemia, hypercalciuria, and hypoparathyroidism *(34)*. Recognition of the condition is important to avoid hypercalciuria and nephrocalcinosis with treatment. Another familial hypoparathyroid disorder that can present in either an autosomal dominant or recessive form is due to a PTH gene defect resulting in decreased secretion of normal PTH.

Table 6
Syndromes with Parathyroid Dysgenesis*

DiGeorge syndrome
Chromosomal – del(10p), del(22q)
Monogenetic – autosomal dominant, autosomal recessive, "Catch 22 syndrome"
Isolated hypoparathyroidism (11p15)
X-linked hypoparathyroidism
Kenny–Caffey syndrome
Barakat syndrome
Kearns-Sayre syndrome (mitochondrial)
MELAS (mitochondrial)

*chromosomal defect shown if known

In adults, relatively common causes of acquired hypoparathyroidism are due to damage after thyroid or parathyroid surgery, radiation to the neck or infiltration of the parathyroid by cancer, heavy metals, or granulomatous disease. In children, destruction by autoimmune disease is more common especially in a condition variably referred to as HAM (hypoparathyroidism, Addison's disease, monilial infection), APS1 (autoimmune polyendocrinopathy syndrome, type 1), or PGA (polyglandular autoimmune) disease, type 1 *(35)*. PGA type 1 is an autosomal recessive disorder caused by abnormalities of the AIRE-1 gene on chromosome 21q22.3 that regulates autoimmunity. Many endocrine and non-endocrine tissues can be affected but the classic triad is chronic mucocutaneous candidiasis followed by hypoparathyroidism followed by Addison's disease. It occurs equally in males and females and its incidence varies in different populations but has been reported to be as high as 1:25,000 among the Finnish and 1:9000 in Iranian Jews. The age of onset of the hypoparathyroidism is usually between 6 and 9 years and about 4 years after the onset of candidiasis. For those affected with Addison's disease, its onset is typically about 5 years after the hypoparathyroidism. In the classic study by Blizzard et al, in 32 patients with idiopathic hypoparathyroidism, 66% had candidiasis and 56% had Addison's disease. Other less common features of the syndrome include diabetes mellitus, gonadal failure, hypothyroidism, pernicious anemia, dermal abnormalities, and autoimmune hepatitis. The management of these patients includes careful surveillance for signs of other organ involvement. The manifestations of hypoparathyroidism are greatly influenced by those of untreated Addison's disease but with glucocorticoid replacement, hypocalcemia may become severe and life threatening.

An important cause of refractory hypocalcemia is that due to hypomagnesemia, which will be described in more detail in Chapter 8. Hypomagnesemia causes hypocalcemia by the dual mechanisms of inhibiting PTH secretion as well as blocking the action of PTH on bone and kidney *(27)*. Whereas mild decreases in the divalent cation magnesium stimulate PTH secretion in a similar fashion as calcium by decreasing the inhibition of secretion by the CaSR, severe hypomagnesemia (Mg < 1.0 mg/dL) blocks the ability of the parathyroid cell to secrete PTH. Hypomagnesemic hypocalcemia can be demonstrated in neonates such as in infants of diabetic mothers as well as in children such as in those with celiac disease and malabsorption. Treatment of hypocalcemia in these patients must begin with at least partial correction of the hypomagnesemia or other measures are likely to prove ineffective.

11.2. Parathyroid Resistance

Resistance to PTH can occur with severe hypomagnesemia or hypovitaminosis D but is usually associated with the genetic disorder pseudohypoparathyroidism (PHP). PHP is a disease in which abnormal components of the G protein-coupled receptors such as the PTH/PTHrP receptor for PTH prevent normal formation of second messengers such as cAMP *(36)*. In PHP Type 1a, deficiency of G_s is responsible for preventing the formation of the second messenger cAMP in response to activation of the PTH1 receptor by PTH as well as other G-protein-coupled receptors including those for TSH, gonadotropins, and glucagon. The chromosomal defect is on chromosomal fragment

20q13.3. Recent studies show that the tissue specificity is the result suppression of the paternal gene and expression only of the maternal gene due to imprinting in the affected tissues. Patients with PHP Type 1a also demonstrate a characteristic phenotype known as Albright's hereditary osteodystrophy (AHO), which includes a round face, short stature, obesity, mental retardation, subcutaneous calcifications, and brachydactyly. The latter is due to short metacarpals and metatarsals that result in the knuckle dimple sign when these individuals make a fist. In some kindreds with PHP Type 1a, there are individuals who express the AHO phenotype but have normal PTH responsiveness, a condition referred to as pseudo-pseudohypoparathyroidism. There are other types of PHP due to other genetic defects. PHP Type 1b lacks the features of AHO and whereas there is resistant to PTH in the kidneys, there is responsiveness in bone leading to osseous changes of hyperparathyroidism. PHP Type 1c is not due to a defect in G_s or G_i but there remains resistance to PTH. Finally, in PHP Type 2, there is normal cAMP excretion but no phosphaturia in response to PTH.

Biochemically, the affected individuals with PHP have hypocalcemia, hyperphosphatemia as in hypoparathyroidism but in contrast display elevated PTH levels. Magnesium and 25(OH)D levels should be measured to rule out these conditions as possible causes of PTH resistance. Formerly, tests for cAMP production by PTH were performed using the Ellsworth–Howard test but now for PHP Type 1a, genetic testing is now available.

11.3. Vitamin D Disorders

Hypocalcemia secondary to abnormalities of vitamin D are the result of the precursors of active $1,25(OH)_2D$ as result of nutritional or metabolic reasons or two rare genetic disorders termed vitamin D dependent rickets *(37)*. The features of hypovitaminosis D are typically hypophosphatemia, secondary hyperparathyroidism, elevated alkaline phosphatase and variably hypocalcemia. The reason for the latter is that secondary hyperparathyroidism is often able to compensate for deficiency of the precursors of $1,25(OH)_2D$. Once thought to be a condition of the past, classic vitamin D deficiency is reemerging due to the combination inadequate sun exposure and inadequate vitamin D in the diet, especially breast milk. Low vitamin D can be seen in a variety of GI disorders including Crohn's disease, celiac disease, pancreatic insufficiency, cystic fibrosis, and hepatobiliary disease. The etiology of hypovitaminosis D in these conditions is fat malabsorption or interruption of the enterohepatic circulation. In addition to malabsorption, vitamin D levels may be low due to increased metabolism to inactive metabolites by hepatic microsomal P-450 oxidases that can be induced by phenobarbital, Dilantin, and other agents. In each of these disorders, the diagnostic test of choice to evaluate vitamin D stores is that of circulating 25(OH)D and not the level of $1,25(OH)_2D$. Disorders affecting the renal proximal renal tubule including acute and chronic renal failure and Fanconi syndrome can cause decreased formation of $1,25(OH)_2D$ and contribute to hypocalcemia by this mechanism.

Two rare inherited disorders of vitamin D are so called vitamin D-dependent rickets type 1 (pseudo-vitamin D-deficiency) and vitamin D-dependent rickets type 2. The former is an autosomal recessive disorder the enzyme responsible for formation

of $1,25(OH)_2D$: 25-hydroxyvitamin D 1α hydroxylase. In this illness, there is low circulating $1,25(OH)_2D$ and the patient can be cured by physiologic doses of $1,25(OH)_2D$. In vitamin D-dependent rickets type 2, there is an abnormality of the vitamin D receptor leading to an end-organ resistance. The management of hypocalcemia in some of these patients with mild defects is with large doses of oral $1,25(OH)_2D$ and calcium but the most severely affected require parenteral calcium.

11.4. Critical Illnesses and Other Causes

Hypocalcemia is a common complication in a variety of severe illnesses including sepsis and toxic shock syndrome *(27, 38)*. Hypoalbuminemia is common in severe acute and chronic disease so pseudohypocalcemia with normal ionized calcium must be ruled out. Massive tissue breakdown as seen in tumor lysis syndrome and rhabdomyolysis releases intracellular phosphate which through precipitation of calcium in soft tissues and other mechanisms can cause hypocalcemia. Acute pancreatitis can cause hypocalcemia by several proposed mechanisms including fat necrosis and calcium soap formation as well as decreased PTH secretion. In all of these conditions, hypocalcemia is a bad prognostic sign.

Certain medications can lead to hypocalcemia *(38, 39)*. Phosphate containing enemas can lead to severe hypocalcemia and hyperphosphatemia, especially if there is concurrent renal failure. Citrate given parenterally as an anticoagulant with massive transfusions or during extracorporeal procedures like ECMO can cause an unusual situation in which the total calcium is elevated but the ionized calcium is low. This is because of an increase in the complexed fraction of calcium. Bisphosphonates are a useful class of drugs for the treatment of hypercalcemia but there may be an overshoot with the development of hypocalcemia. This is particularly true in the presence of other factors such as vitamin D deficiency.

11.5. Neonatal Causes

Neonates can suffer from hypocalcemia from many of the causes described above but there are also a group of disorders described under the term "neonatal hypocalcemia" *(40– 42)*. These conditions are largely due to abnormalities in the transition from fetal to postnatal life when the placenta that supplies the fetus with calcium is suddenly removed. The fetus goes from being hypercalcemic to a physiologic period of mild hypocalcemia in the first 2 days of life and returns to normal levels over the next several days. Premature infants often demonstrate a greater fall than term infants. Neonates who are sick, preterm, asphyxiated or are infants of diabetic mothers are at greatest risk for hypocalcemia. Due to a fall in serum albumin after birth as well, measurement of ionized calcium is important in the diagnosis of true hypocalcemia. A total calcium level less than 8 mg/dL in term infants and less than 7 mg/dL in preterm infants is considered abnormal but an ionized calcium less than 1.0 mM or 4 mg/dL in both is considered low. The symptoms of hypocalcemia in the neonate are similar to those in older children (Table 1) but also include apnea, cyanosis, tachypnea, tachycardia, and vomiting.

Table 7
Causes of Neonatal Hypocalcemia

Early (Days 1–4 of life)
Prematurity
Perinatal distress/asphyxia
Infants of diabetic mothers
Intrauterine growth restriction
Late (Days 5–10 of life)
High phosphate load
Transient hypoparathyroidism
Other hypoparathyroid conditions
Maternal hyperparathyroidism
Transient PTH resistance
Hypomagnesemia
RTA Type 1
Primary hypomagnesemia
Maternal hypomagnesemia
Maternal vitamin D deficiency
Late-Late hypocalcemia (2–4 mo of age if premature)
Other-low ionized calcium, normal total calcium
Alkalosis
Citrate from blood transfusions

Neonatal hypocalcemia has usually been described by time of onset (Table 7). Early hypocalcemia occurs in the first 3–4 days of life and is an exaggeration of the normal transition period. It occurs typically under 3 conditions: prematurity, infant of diabetic mothers (IDM), and intrauterine growth restriction (IUGR). The mechanism is usually a lack of response by the immature kidney to respond to PTH but lack of feeding, rise in calcitonin, renal failure, and hyperphosphatemia all may contribute. With IDM, an exaggerated physiologic drop is often seen with maternal and resultant neonatal hypomagnesemia play a causative role (Chapter 8). Hypocalcemia in IDM correlates with severity of maternal diabetes and can be particularly severe in preterm IDM with IUGR. Late neonatal hypocalcemia is defined as occurring after 4 days of age and is usually due to high dietary phosphate intake and an inadequate parathyroid response that may be transient or be the presentation of one of the disorders described in Section 11.1. Hypoparathyroidism at this point may also be the result of maternal hypercalcemia as seen with maternal hyperparathyroidism. Maternal hypercalcemia can lead to fetal hypercalcemia and fetal hypoparathyroidism that may take weeks to resolve after birth. Hypomagnesemia may be the result of IDM or of one of the conditions described in Chapter 8. Maternal vitamin D deficiency as a result of lack of sunlight or vitamin D intake is an important cause of neonatal hypocalcemia. Finally, hypocalcemia can be seen in infants, especially prematures, as a result of many other causes including sepsis, pancreatitis, and citrate administration with blood transfusions, or ECMO.

12. HYPOCALCEMIA – DIAGNOSTIC EVALUATION

The first step in the evaluation of a child with hypocalcemia is to confirm that they truly have the condition. We recommend direct measurement of ionized calcium in any patient who is acutely or chronically ill or is likely to have abnormalities of serum albumin or pH. The initial diagnostic studies should include electrolytes, magnesium, BUN, creatinine, and phosphorus. If associated clinical conditions do not point to the likely diagnosis then the laboratory studies can be helpful in narrowing down the diagnosis. Hypomagnesemia and renal failure are important diagnoses that should be recognized immediately. It must be remembered that mild decreases in serum magnesium stimulate PTH secretion but hypocalcemia is more likely associated with levels less than 1 mg/dL. Serum phosphorus can be used in a diagnostic strategy to narrow the diagnosis (Table 5). High phosphorus levels in the absence of renal failure suggest abnormal PTH function (decreased secretion or decreased action) or endogenous or exogenous phosphorus load. Low serum phosphorus suggests abnormalities of vitamin D action or movement of calcium and phosphorus into bone or the soft tissues.

The second level of testing includes PTH and 25(OH)D levels (Table 8). PTH levels are low or inappropriately normal in states of decreased secretion and are elevated with resistance to its action (pseudohypoparathyroidism) as well as most other states where its secretion is being stimulated. To investigate for vitamin D deficiency whether due to decreased intake, malabsorption or increased metabolism, 25(OH)D levels and not $1,25(OH)_2D$ levels are the test of choice to evaluate for vitamin D deficiency. $1,25(OH)_2D$ levels are usually in the normal range with classic rickets but inappropriately low in light of the hypocalcemia, hypophosphatemia, and secondary hyperparathyroidism that are usually present. Rarely in states of decreased proximal renal tubular function or even more rare vitamin D-dependent rickets type 1 are $1,25(OH)_2D$ diagnostic.

Table 8
Laboratory Features of Hypocalcemic Syndromes

Condition	*PO4*	*PTH*	*Vitamin D*
Hypoparathyroidism	⇑	⇓	$1,25(OH)_2D$ nl to ⇓
Pseudohypoparathyroidism	⇑	⇑	$1,25(OH)_2D$ nl to ⇓
Tumor lysis syndrome	⇑	⇑	⇔
Vitamin D deficiency	⇓	⇑	25(OH) D ⇓
Vitamin D dep. rickets type 1	⇓	⇑	$1,25(OH)_2D$ ⇓
Vitamin D dep. rickets type 2	⇓	⇑	$1,25(OH)_2D$ ⇑
Hypomagnesemia	nl to ⇑	⇓	$1,25(OH)_2D$ nl to ⇓

13. MANAGEMENT OF HYPOCALCEMIA

In children with severe, symptomatic hypocalcemia, emergency treatment with intravenous calcium is indicated (Table 9) *(40, 43)*. In older children and adults, 10–20 ml of

Table 9
Treatment of Hypocalcemia in Children-Common Forms of Calcium, Magnesium, Vitamin D

Agent	*Concentration*	*Dose*	*Comment*
Calcium carbonate*	100 mg/ml suspension	50–75 mg/kg/day÷q6 h	Oral-liquid
	200, 300, 400, 500 mg		Oral-tabs
*Calcium glubionate**	115 mg/5 ml	50–75 mg/kg/day÷q6 h	Oral-syrup
Calcium citrate*	53.5, 200 mg	50–75 mg/kg/day÷q6 h	Oral tabs-use with achlorhydria
Calcium gluconate*	100 mg/ml injection	10–20 mg/kg/dose	IV
Magnesium sulfate^	500 mg/ml injection	50–100 mg/kg/dose	IV
Ergocalciferol	8000 IU/ml	800–8,000 IU/day	Oral-liquid
	50,000 IU	50,000 IU/2–4 weak	Oral-tablet
Cholecalciferol	1000, 2000 IU	1000–8000 IU/day	Oral-tabs (OTC)
$1,25(OH)_2D$	0.25, 0.5 mcg	0.25–1 mcg/day	Oral-capsules
	1 mcg/ml		Oral-liquid
$1,25(OH)_2D$	1.0 mcg/ml	0.25–1 mcg/day	IV

* elemental calcium; ^ elemental magnesium

10% calcium gluconate (10 ml ampules) over 10–15 min is often sufficient to stop the acute manifestations including seizures. In younger children and neonates, the dose is 10–20 mg/kg or 1–2 ml/kg or 10% calcium gluconate at a rate no greater than 1 ml/min using constant cardiac monitoring. Hypomagnesemic hypocalcemia will be refractory to this treatment and should be treated with 0.1–0.2 ml/kg of 50% magnesium sulfate (50–100 mg/kg) IV over a 10-min period, a dose that can be repeated every 12–24 h. Calcium infusions can be given for persistent hypocalcemia in children by mixing ten 10 ml calcium gluconate ampules in 1 L D5W and given at a rate of 50–75 mg/kg/day *(44)*. It is imperative that it is only given in a well-functioning IV to avoid chemical burns with calcium extravasation into the tissues and with continuous cardiac monitoring to avoid bradycardia. Calcium can be given on the chronic basis orally at a dose 1–4 g of elemental calcium daily depending on the body size. The form of oral calcium generally is not clinically relevant except for states achlorhydria in the stomach where calcium carbonate does not dissolve and calcium citrate in preferable.

For infants with late hypocalcemia and hyperphosphatemia, low phosphorus feeding such as breast milk or Similac PM 60/40™ is important *(41)*. With severe acute hyperphosphatemia as with tumor lysis especially with renal failure, hemodialysis or other renal replacement therapy may be necessary. In vitamin D deficiency states, ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) can be given at a dose of 800–8000 units daily. In young infants the dose should be no more than 2000 units daily. Calcium,

phosphorus, and 25(OH)D levels are useful guides to therapy in hypocalcemia patients with severe hypovitaminosis D. In the presence of renal failure, hypoparathyroidism, active $1,25(OH)_2D$ can be given orally or by IV at a dose of 20–40 ng/kg/day or in older patients 0.25–1 μg/kg/day. In hypoparathyroidism, especially that due to CaSR disorders, hypercalciuria may develop with normalization of serum calcium. In those states, the minimal amount of calcium to keep the serum calcium in the low normal range should be give to avoid nephrocalcinosis or renal stones. Thiazide diuretics (1 mg/kg) can be given cautiously to increase calcium reabsorption and support the serum calcium in hypoparathyroidism.

CASE SCENARIO DISCUSSIONS

Case Scenario 1: Hypocalcemia in a school aged child. This child has symptomatic hypocalcemia with a low serum calcium and high serum phosphorus. The high phosphorus points to likely dysfunction of PTH secretion or function but the normal body habitus suggests that he does not have Albright's Hereditary Osteodystrophy (AHO) as with pseudohypoparathyroidism. He does not have renal failure and the normal CBC makes tumor lysis less likely. You look for hypomagnesemia that could cause this picture but the magnesium level is normal and an EKG shows prolonged QT interval. Other studies that are sent off with the initial labs are PTH and 25(OH)D levels. Because he is not having serious manifestations like seizures or tetany, you choose to start treatment with oral calcium to both raise the serum calcium and to act as a phosphate binder. You choose a dose of 500 mg of elemental calcium four times daily as calcium carbonate and you place the patient on a low phosphate diet of 800 mg/day or less. As soon as the phosphorus level starts to come down you start active $1,25(OH)_2D$ at a "physiologic" dose of 0.5 mcg daily. The PTH level comes back in the low normal range, which is inappropriate for the level of calcium consistent with hypocalcemia and the 25(OH)D level is normal. The rash turns out to be chronic Candida infection and the diagnosis of polyglandular autoimmune syndrome (PGA) type 1 is strongly suggested. Since a high percentage of PGA type 1 patients will go on to develop Addison's disease, you must carefully monitor for this potentially life-threatening condition, which can present with electrolyte abnormalities such as hyponatremia, hypokalemia, and acidosis. A random cortisol of less than 18 μg/dL is suggestive of adrenal insufficiency but a cortisol stimulation test may be required. In addition to Addison's disease, other disorders associated with PGA 1 should be suspected if other clinical abnormalities develop.

Case Scenario 2: Infant with new onset seizures and heart disease. This infant presents as a "late" neonatal hypocalcemia with a heart defect and an abnormal facies. The possibility of "late" neonatal hypocalcemia includes high-phosphate dietary load, maternal vitamin D, or magnesium deficiency, and maternal parathyroid disease do not appear to be present. Initial studies should include magnesium, ionized calcium, CBC with differential and PTH. In this case, the magnesium is normal but the ionized calcium confirms the hypocalcemia and the PTH comes back just above the lower limit of 10 pg/ml suggesting hypoparathyroidism with an inappropriate response to the hypocalcemia. The diagnosis of DiGeorge Syndrome should be considered even though the VSD is not one of the classic aortic arch or cardiac outflow lesions usually described

with this syndrome. Karyotypes with fluorescence in situ hybridization (FISH) studies should be sent to look for microdeletions in the 22q11.2 (CATCH-22) and 10p regions (HDR). The initial treatment was with 10 ml/kg of calcium gluconate (parenteral), which improved the serum calcium and the neuromuscular symptoms. This child also had renal failure with a normal renal ultrasound (pointing away from the renal dysplasia of Barakat syndrome), which improved as the hypocalcemia was corrected suggesting a prerenal (or decreased perfusion) etiology related to heart failure. Long term management is with oral calcium (up to 1000 mg/day in divided doses), low phosphorus diet (breast milk or Similac PM 60/40^{TM}), and possibly 1,25$(OH)_2$D (0.04–0.08 mg/kg/day).

14. HYPERCALCEMIA – INTRODUCTION

Hypercalcemia is a relatively uncommon disorder in children. The diagnosis is most commonly made with the incidental finding of elevated serum calcium on routine measurement of serum electrolytes. Clinical sign and symptoms of hypercalcemia are usually vague and non-specific but their recognition can be important in certain clinical settings. The determination of the etiology of the hypercalcemia requires investigation of the mechanisms that regulate the level of serum calcium and the known causes that disrupt these mechanisms. Treatment should include both non-specific measures to lower the level of serum calcium as well as specific therapies to address the primary cause.

CASE SCENARIOS

Case Scenario 1: Hypercalcemia in a healthy adolescent

You have consulted psychiatry on a 16-year-old male who is depressed and lethargic while in the hospital for an injury of his leg. He is very tearful about being kept in the hospital and not being able to go home to his friends and family. He is not eating and has not had a bowel movement in 3 days. This formerly athletic male had been admitted 4 weeks prior after being thrown from a four-wheeler and suffering a displaced femur fracture with soft tissue injury. He is in traction and on antibiotics for infection of the wound. He has a poor appetite and is constipated and has lost 8 kg since admission. His vital signs show a pulse of 110/min, BP of 140/95, temperature of 37.5, and normal respiratory weight. On examination, he appears somewhat cachectic despite the history of being on the football team prior to his injury. Routine labs which show a normal CBC are sent but the chemistry panel shows a BUN 22 mg/dL, creatinine 1.4 mg/dL, and a serum calcium 15.2 mg/dL, phosphorus 4.2 mg/dL, albumen 4.8 g/dL. Urinalysis shows a specific gravity of 1.005 and small blood on the dipstick.

What are the signs and symptoms that suggested the patient had hypercalcemia? What is the basic etiology of his hypercalcemia and what are the contributing factors in its development? What studies would you order? How would you treat him?

Case Scenario 2: Neonatal hypercalcemia

Thirty-four-week gestation SGA infant develops mild respiratory distress requiring oxygen on day 2 of life. Chest X-ray shows evidence of abnormal, washed out clavicles, and ribs. Skeletal survey shows diffuse demineralization of the long bones with no rachitic changes at the metaphyses and the skull shows no evidence of wormian bones.

Chemistry profile: sodium 135 mEq/L, potassium 4.8 mEq/L, bicarbonate 19 mEq/L, chloride 98 mEq/L, BUN 5 mg/dL, creatinine 0.9 mg/dL, calcium 12.5 mg/dL, phosphorus 3.8 mg/dL, albumen 2.9 g/dL.

What are the studies that you want to order? What is the most likely direct cause of the hypercalcemia? How would you manage this patient?

15. DEFINITION OF HYPERCALCEMIA

Hypercalcemia can be defined as a total serum calcium level in a child greater than 10.3 mg/dL but as has been explained in Sections 2.1 and 5.1, it is the ionized calcium that is physiologically and clinically significant *(18*, *34)*. Total serum calcium may not reflect the level of ionized calcium in states that alter either the protein-bound fraction with changes in the serum albumin level or the complexed fractions with changes in the concentrations of either serum phosphate or citrate. Methods to "correct" total serum calcium are too often inaccurate in the sick hospitalized patient and so it is recommended to at least initially directly measure serum ionized calcium and levels > 1.35 mmol/(5.5 mg/dL) in the child or >1.4 mmol/L (5.6 mg/dL) in the neonate can be considered elevated. The degree of hypercalcemia has diagnostic, prognostic and therapeutic significance with more severe hypercalcemia requiring more aggressive diagnosis and treatment. In terms of total calcium (mg/dL), hypercalcemia can therefore be classified as mild (10.5–11.2), moderate (11.3–13.5) and severe (>13.5).

16. HYPERCALCEMIA – CLINICAL FEATURES

The signs and symptoms of hypercalcemia are typically vague and non-specific but do relate to the severity of the hypercalcemia with the patient with more severe hypercalcemia (calcium > 14 mg/dL) being more likely to be symptomatic *(45*, *46)*. The symptoms are listed in Table 10 and can be broken down into cardiovascular, gastrointestinal, neuromuscular, renal, and general. By increasing cardiac repolarization, high calcium can cause a shortened Q–T interval, which can be a classic sign. The gastrointestinal symptoms are a very common presentation but are totally non-specific as are the neuromuscular symptoms. The renal manifestations of polyuria, polydipsia, and nocturia are not so significant for their prominence but the ensuing dehydration can lead to increasing inability of the kidney to excrete calcium leading to a vicious cycle of worsening hypercalcemia and renal dysfunction. This sequence can be especially important in the presence of poor oral intake that can exacerbate the dehydration. Prolonged severe hypercalcemia can cause renal calcification in the form of stones and nephrocalcinosis. In young children unlike adults, a common presentation of chronic hypercalcemia is poor growth and failure to thrive.

17. CAUSES OF HYPERCALCEMIA

17.1. Parathyroid Disorders

There are two disorders whose pathophysiology is an inappropriately elevated secretion of PTH for the level of serum calcium, which is due to the loss of the normal

Table 10
Clinical Manifestations of Hypercalcemia

Cardiovascular
Shortened QT interval on EKG
Hypertension
Bradycardia
Gastrointestinal
Nausea and vomiting
Constipation
Peptic ulcer
Pancreatitis
Neuromuscular
Lethargy
Depression
Stupor
Confusion
Muscle weakness
Renal
Polyuria and polydipsia
Decreased concentrating ability
Hypercalciuria
Nephrocalcinosis
Nephrolithiasis
General
Weakness
Metastatic calcifications
Failure to thrive

feedback by calcium on PTH secretion (Table 11). The first is primary hyperparathyroidism (HPT), one of the two most common causes of hypercalcemia in adults but a fairly rare cause of hypercalcemia in children. The second condition is familial hypocalciuric hypercalcemia (FHH), a generally benign disorder of the calcium receptor CaSR with the exception being when it presents in the neonatal period (see Section 17.6.1).

17.1.1. Primary Hyperparathyroidism

The incidence of HPT in children is 2–5 per 100,000, which is only about 1% of that in adults *(47*, *48)*. This may contribute to the fact that there is often a delay in the diagnosis of HPT in children who present with non-specific symptoms (Table 1) as compared to adults. As a result, almost 79% of the children were symptomatic in one study and 44% had some sort of end-organ involvement, which is different from adults who most often have asymptomatic hypercalcemia. Also in children, only 65% of children are found to have an adenoma of a single parathyroid gland versus 80% in adults leaving about 30% children with four-gland hyperplasia *(49)*. The reason is the

Table 11
Infections and Granulomatous Causes of 1,25(OH) Mediated Hypercalcemia

Infectious
Tuberculosis
Coccidiomycosis
Cat-scratch disease
Histoplasmosis
Candidiasis
Inflammatory
Sarcoidosis
Wegener's granulomatosis
Crohn's disease
Silicone-induced granulomatosis
Subcutaneous fat necrosis
Lymphoproliferative
B-cell lymphoma
Hodgkin's disease

relatively higher incidence of familial HPT in children that accounts for over 50% of the children with four-gland hyperplasia. In contrast to other causes of hypercalcemia, children with HPT are more likely to present with kidney stones or bone involvement including fractures.

Primary HPT can present as one of several familial disorders *(50)* including the multiple endocrine neoplasia Types 1 (MEN1) and 2A (MEN2A), hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial isolated hyperparathyroidism, and fore-mentioned neonatal severe HPT (NSHPT), which will be discussed below. MEN1 is a rare autosomal dominant disorder in which there is an inactivating germ-line mutation of the tumor suppressor gene *MEN1* on chromosome 11q13 leading to the development of tumors of the parathyroid, anterior pituitary, pancreatic islets as well as other tissues. HPT in this condition can begin as young as 8 years of age, often with symptomatic hypercalcemia. MEN 2A is more associated with medullary thyroid carcinoma (90%) but can also have HPT (20%) and pheochromocytoma (40%). This autosomal dominant disorder arises from a germ-line mutation of the *RET* proto-oncogene and is more likely to be associated with asymptomatic HPT. HPT-SJ, a is a very rare syndrome in which there may be ossifying fibromas of the mandible or maxilla as well as possibly renal cysts, hamartomas or even Wilm's tumor. The mutation in this condition is on chromosome 1q.

The diagnosis of HPT is based on the presence of an elevated PTH level in the presence of hypercalcemia *(47)*. The standard test for PTH is measurement of intact PTH by IRMA or ICMA (see Section 6.1). About 15% of children with HPT may have PTH values in the upper range of normal and high serum calcium levels, which should be associated with PTH levels below the mean. Other associated laboratory findings include low or low normal serum phosphorus; elevated markers of bone formation and bone

resorption such as serum alkaline phosphatase and urinary N-telopeptide/creatinine, respectively, and increased urinary calcium excretion as result of increased circulating $1,25(OH)_2$vitamin D ($1,25(OH)_2D$). Measurement of serum phosphate and urinary calcium is clinically useful, measurement of markers of bone turnover and $1,25(OH)_2D$ are not since they do not distinguish between other causes of hypercalcemia (see Section 5). Other studies in HPT may include X-rays for bone involvement but these are not cost effective and do not add to the direct measurement of PTH.

Treatment of HPT includes the non-specific management of hypercalcemia (Section 19) but in children should include surgical removal of the abnormal parathyroid tissue *(32*, *48)*. Controversy remains over the role of pre-operative imaging of the parathyroid, which can include ultrasound, CT, MRI, and scintigraphy with technetium-99m-sestamibi. The latter is the most common study because of its ability to localize a single adenoma but it can be combined with adjunctive modalities such as single photon emission computed tomography (SPECT) to more precisely localize the parathyroid tissue. An axiom of parathyroid surgery has been that the most important factor is to have an experienced surgeon perform the exploration because of the great variability in location of the parathyroids, which can include the mediastinum or multiple locations in the neck. The surgical procedure of choice is to remove any adenomas, a procedure that should be accompanied by a drop of PTH levels intraoperatively by 50%. If the drop in PTH levels is less, there is likely to be more hyperplastic parathyroid glands, especially in children. In multiglandular disease the choice is to mark and leave a small piece of parathyroid tissue in situ or to remove all of the parathyroid tissue and autotransplant a portion in the non-dominant forearm. After surgery a brief period of hypocalcemia is expected requiring either oral or intravenous calcium or possibly $1,25(OH)_2D$. If both severe, prolonged hypocalcemia and hypophosphatemia develop post-operatively, this is a likely sign of "hungry bone" syndrome in which there is a transient high turnover of bone. After surgery bone resorption is suppressed with the loss of PTH stimulation but activated bone mineralization continues for a period of time.

17.1.2. Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH), which is also know as familial benign hypercalcemia, is an autosomal dominant loss of function abnormality of the calcium receptor (CaSR) *(51)*. The majority of cases have abnormalities of the CaSR locus on chromosome 3q. Most patients who have a heterozygous CaSR defect in the parathyroid and the renal tubule require a higher serum calcium levels to suppress PTH secretion (increased set point) and demonstrate increased tubular reabsorption of calcium. The latter defect helps maintain serum calcium levels at a higher level even in the absence of PTH but is also responsible for the relative hypocalciuria in this condition. Homozygous CaSR defects result in the massive, life-threatening neonatal severe primary hyperparathyroidism covered under "Hypercalcemia in Infants" (Section 17.6.1).

Children with FHH present with mild asymptomatic hypercalcemia with serum magnesium levels in the high normal range and phosphorus levels in the low range. Characteristically, calcium excretion is low for the level of serum calcium and can be measured by the ratio of calcium clearance to creatinine clearance. Similarly, magnesium

excretion is also increased, leading to the mild hypermagnesemia. The diagnosis of FHH can usually be made in the presence of autosomal dominant inheritance of hypercalcemia, hypocalciuria and normal PTH levels. Currently genetic testing for FHH is only able to detect 70% of affected kindreds so false negatives remain a possibility. The management for most cases of FHH is to avoid parathyroidectomy except for the neonatal form covered below and rare cases with serum calcium greater than 14 mg/dL. There is a possible future role for calcimimetics that has yet to be determined.

17.2. Vitamin D Mediated

Vitamin D can cause hypercalcemia by stimulating calcium absorption from the GI tract and resorption from bone *(52, 53)*. Toxicity can result from intoxication by vitamin D or one of its active analogues can result from endogenous formation of active $1,25(OH)_2D$ in a variety of disease states. Characteristically, both serum calcium and phosphorus will be elevated since the actions of vitamin D elevate both minerals, and serum PTH levels should be suppressed. Another effect is increased excretion of calcium, which may precede hypercalcemia, but other factors such as thiazide diuretic use may trigger frank hypercalcemia by limiting the ability of the kidneys to excrete the excess calcium. The measurement of vitamin D metabolites may be helpful in these disorders. In states of intoxication by regular vitamin D_2 or D_3, the level of 25(OH)D but not $1,25(OH)_2D$ is high, whereas in other vitamin D disorders described below, the formation and serum levels of $1,25(OH)_2D$ are elevated.

17.2.1. Vitamin D Intoxication

Hypercalcemia from vitamin D supplements is a fairly rare disorder *(54)*. Despite recommended upper limits of intake of 2000 IU/day, intakes of 10,000 IU/day are well tolerated in adults. Most reported cases are due to consumption of vitamin D in amounts greater than 100,000 units daily for a period of time as a result of an error in the production of supplemented products or a bizarre intake of huge amount of vitamin D. In these cases, it is the level of 25(OH)D but not $1,25(OH)_2D$ that is elevated, and recent expert opinion suggests that levels greater than 100 ng/ml are necessary for toxicity. The mechanism is unclear but likely includes competition for the vitamin D receptor, elevated free $1,25(OH)_2D$, interference with vitamin D metabolism and upregulation of the vitamin D receptor. The half-life of $25(OH)D_3$ is 7–30 days and so the duration of the hypercalcemia may be for weeks. In cases where the parent compound, vitamin D2 or vitamin D3 is elevated, the duration of hypercalcemia can last as long as 18 months due to large stores of fat soluble vitamin in adipose tissue. Treatment for severe cases can include the use of corticosteroids and low calcium diet. More commonly, hypercalcemia from vitamin D intoxication is the result of administration of active forms of vitamin D in renal failure or other metabolic conditions. In these cases, $1,25(OH)_2D$ or another active metabolite are the culprits. Due to their short half lives of more like 24 h, resolution of the hypercalcemia will occur in days after discontinuation of the medication and is usually all that is required in the treatment.

17.2.2. Granulomatous Disorders

Hypercalcemia has been long associated with certain infectious and granulomatous disorders with sarcoidosis as the classic example *(55)*. The enzyme responsible for formation of 1,25$(OH)_2$D, 25(OH)D-1α-hydroxylase is known to be expressed in many extra-renal tissues including monocytes and macrophages. In these tissues, formation of 1,25$(OH)_2$D is not stimulated by PTH, low calcium and low phosphorus as in the kidney rather by immune mediators and cytokines such as IL-2 and γ-interferon. In a number of these states (Table 11), increased levels of 1,25$(OH)_2$D appear to be the cause of the hypercalcemia and its measurement can be diagnostic. Hypercalcemia in certain lymphoproliferative diseases and subcutaneous fat necrosis in infants appear to have a similar pathogenesis. The malignancies most often associated with increased 1,25$(OH)_2$D formation are Hodgkin's and non-Hodgkin's lymphomas. Treatment of 1,25$(OH)_2$D mediated hypercalcemia includes control of the primary disease or reduction of 1,25$(OH)_2$D production by the macrophages/monocytes by glucocorticoids or in refractory cases by chloroquine, hydroxychloroquine, and ketoconazole.

17.3. Bone-Related

Release of calcium from bone is associated with most hypercalcemic disorders but under certain conditions this is not secondary to increases in PTH or vitamin D. Increased resorption of bone by osteoclasts combined with the suppression of mineralization by osteoblasts (uncoupling) can lead to massive release of calcium from bone, which can overwhelm the homeostatic mechanisms to maintain normal serum calcium.

17.3.1. Hypercalcemia of Malignancy

Hypercalcemia associated with malignancy is much less common in children than adults where it is one of the two most common causes of hypercalcemia *(56)*. Malignancy associated hypercalcemia is often severe (total calcium >14 mg/dL) and can be life threatening. Unlike adults where 30-day survival is only about 50% with this condition, the prognosis in children appears to be better which is related to the kind of associated cancers in children *(57)*. There are several described mechanisms, including 1,25$(OH)_2$D formation described with certain lymphomas (Section 3.2.2). Local osteolytic hypercalcemia (LOH), typified by breast cancer with extensive metastatic disease to bone, is caused by local production by the cancer cells of cytokines and PTHrP, which activate local resorption of bone by osteoclasts. Leukemias, including ALL, which cause hypercalcemia, may have a similar mechanism. The biochemical features of LOH are hypercalcemia, normal to high serum phosphorus, low PTH, hypercalciuria, and suppressed 1,25$(OH)_2$D levels.

The second syndrome is "humoral hypercalcemia of malignancy" in which there is little evidence of direct skeletal metastases. Once thought due to ectopic secretion of PT, it was found in the majority of cases to be due to PTHrP. The majority of tumors associated with PTHrP such as squamous cell carcinoma of the lung, esophagus, head and neck, and cervix, are rare in the pediatric age group but there are still many reported

cases of cancer in children due to PTHrP. Whereas PTH and PTHrP act through similar receptors, patients with HHM share with those with HPT of having hypercalcemia, and hypophosphatemia but differ in that $1,25(OH)_2D$ formation is not elevated and that bone formation by osteoblasts is suppressed by PTHrP in contrast to PTH.

There are some non-malignant illnesses that have been associated with PTHrP and hypercalcemia including SLE, HIV, lymphedema, massive mammary hyperplasia, and certain benign tumors including pheochromocytoma.

17.3.2. Immobilization

Hypercalcemia in children who have been immobilized is a relatively common and is the result of the sudden suppression of osteoblastic bone mineralization simultaneous with a striking increase in osteoclastic bone resorption *(58)*. With a growing child or adolescent who is physically active, this uncoupling of bone mineralization and resorption in a skeleton that is rapidly turning over can lead to hypercalciuria in a few days and hypercalcemia in a few weeks. The immobilization may be the result of spinal cord injury, femur fractures, or other acute injury. Symptoms of nausea, loss of appetite, lethargy, and depression caused by the hypercalcemia are often attributed to the circumstances and missed as a sign of hypercalcemia. The laboratory evaluation should show hypercalcemia, hypercalciuria along with a suppressed PTH level. The treatment is remobilization but treatment with hydration and bisphosphonates may be required (Section 19).

17.3.3. Other

Thyrotoxicosis or excessive administration of thyroid hormone can lead to hypercalcemia by accelerating bone turnover with bone resorption exceeding mineralization *(58)*. Vitamin A intoxication can also stimulate osteoclastic activity and cause hypercalcemia. Enhanced osteoclastic reabsorption has also been reported with type 1 Gaucher's disease, juvenile idiopathic arthritis, and other non-specific inflammatory disorders.

17.4. Renal Induced

Excretion of calcium by the kidneys acts as an essential defense by ridding the body of excess calcium absorbed by the GI tract or released by bone *(46)*. Hypercalciuria is often an early warning of impending hypercalcemia when the calcium entering the extracellular fluid exceeds the ability of the kidney to excrete it. Hypercalcemia can cause a decrease in its own excretion by direct effects on glomerular filtration and by disrupting urinary concentrating ability leading to a dehydration and increased calcium reabsorption. In any acute or chronic renal failure disorder, the loss of normal calcium excretion makes the individual more susceptible to hypercalcemia. Other causes of hypercalcemia described above including PTH and PTHrP activate renal reabsorption of calcium as part of the mechanism by which they increase serum calcium. Thiazide diuretics, which enhance renal tubular reabsorption of calcium, have been associated with hypercalcemia when given to patients on vitamin D or other potential causes of hypercalcemia.

17.5. Diet

Increases in dietary calcium leads to decreased fractional absorption by feedback mechanisms involving PTH and vitamin D. An exception is the once common entity milk–alkali syndrome in which massive amounts of milk was consumed for peptic ulcer disease *(59)*. With the advent of H_2-antagonists and proton pump inhibitors, this syndrome is rarely seen today but still reported with the ingestion of calcium carbonate in amounts of 2–8 g of day. The clinical features are hypercalcemia, alkalosis with hyperphosphatemia, and progressive renal failure. The pathophysiology involves the effect of inhibition of calcium excretion by alkalosis and renal failure. Another dietary cause of hypercalcemia is with total parenteral nutrition, when there are excessive amounts of calcium or vitamin D in the formulation. Aluminum contamination of amino acids in TPN solutions was once a common cause of hypercalcemia but this should be a condition of the past.

17.6. Hypercalcemia in Infants

The causes of hypercalcemia that present in infancy deserves special consideration because many of the conditions are unique to that period because of such factors as maternal influences on the fetus, decreased ability of the immature kidneys to excrete a calcium load and the role of high bone turnover. There are other conditions in which the severity is so great that potentially life-threatening hypercalcemia presents during the first few weeks to months of life *(1*, *60)*.

17.6.1. Neonatal Hyperparathyroidism

Hyperparathyroidism (HPT) in the neonate is the result of diminished calcium transport across the placenta resulting in stimulation of fetal parathyroid tissue and disorders of the CaSR, especially the homozygous form *(51*, *60)*. In addition to the non-specific signs of hypercalcemia that include dehydration, hypertension, lethargy, hypotonia, constipation and respiratory distress, neonates with HPT also present with bone manifestations including decreased mineralization, fractures, and assorted bone deformities. The biochemical features of HPT besides elevated PTH levels include hypercalcemia that can be in the 15–30 mg/dL in neonatal severe primary hyperparathyroidism (NSHPT), mild hypophosphatemia, high alkaline phosphatase, and anemia. In the most severe cases, nephrocalcinosis may be present.

Neonatal HPT can be a secondary adaptive phenomenon as result of inadequate transport of calcium across the placenta. The most common reason for this is maternal hypocalcemia as result of such conditions as poorly controlled maternal hypoparathyroidism, pseudohypoparathyroidism, or renal tubular acidosis. We recently described three cases of neonatal HPT in infants with mucolipidosis II disease where the primary disorder appeared to interfere directly with placental calcium transport *(61)*. Infants with secondary HPT due to maternal hypocalcemia characteristically are not as hypercalcemic as other causes of neonatal HPT but can have severe demineralization. With good supportive care, the secondary hyperparathyroidism usually resolves, as does the bone disease by 6 months of age.

Disorders of the CaSR, which are discussed under FHH (Section 17.1.2), are the most common cause of neonatal HPT *(1, 51)*. Infants are more likely than adults to have symptomatic hypercalcemia and bone disease with the heterozygous form of the CaSR defect, especially if the infant is the offspring to an affected father but normal mother. In this setting the normocalcemic mother cannot transport adequate calcium across the placenta to maintain the fetal calcium concentration at a level that will suppress the fetal parathyroid glands expressing the abnormal CaSR. Infants expressing homozygous CaSR abnormalities have neonatal severe primary hyperparathyroidism that should be considered a life-threatening emergency because of the extreme degree of hypercalcemia coupled with renal and skeletal findings. The diagnosis may be suspected due to family history or prenatal skeletal changes and will develop the most profound symptoms as described above. With a reported mortality rate of 25% in the literature, the treatment of choice has been emergency total parathyroidectomy. However a role for intravenous pamidronate to stabilize the patient has recently been suggested.

17.6.2. Subcutaneous Fat Necrosis

Subcutaneous fat necrosis (SFN) is a relatively common disorder observed in full term infants after a traumatic or difficult delivery with resulting areas of indurated subcutaneous nodules typically found on the buttocks, trunk, thighs, cheeks, or extremities *(60)*. Monocytic infiltrates are typically found in the areas of induration and in a minority of infants, hypercalcemia develops over a period of days to weeks. The mechanism, which can be severe, may be due to prostaglandin E_2 or in other instances secondary to $1,25(OH)_2D$ formation as described in Section 17.2.2 in other granulomatous disorders. In addition to hypercalcemia and possibly high $1,25(OH)_2D$, other biochemical features include low PTH and high phosphate levels. The treatment of these infants until the inflammation resolves includes typical treatments (Section 6) corticosteroids, saline, and furosemide but also low calcium and vitamin D formula (CalciloXD, Ross Laboratories, North Chicago, IL). One must monitor for vitamin D deficiency if this formula is used.

17.6.3. Williams Syndrome

Williams syndrome is a chromosomal abnormality of 7q11.23 characterized by infantile presentation of supravalvular aortic stenosis, mental defects, a distinctive "elfin" facies, and in 15% of the cases hypercalcemia *(60)*. The hypercalcemia when present usually resolves in the first year of life but there can also be more persistent hypercalciuria and nephrocalcinosis. Although the affected gene defect appears to be the elastin gene, studies suggesting abnormalities in vitamin D function suggest a possible contiguous gene defect. The diagnosis can usually be made by a fluorescent in situ hybridization (FISH) for the elastin gene. Treatment is usually with dietary restriction of calcium and vitamin D.

17.6.4. Idiopathic Infantile Hypercalcemia

First described in the 1950s by Lightwood, idiopathic infantile hypercalcemia (IIH) first appeared to be a disorder causes by excessive maternal vitamin D supplementation *(60)*. This syndrome, which shares features with Williams syndrome but is not associated with a positive FISH test for elastin, has been associated with elevated PTHrP. Hypercalcemia with IIH is usually more persistent that with Williams syndrome and may require treatment with glucocorticoids and a low calcium and vitamin D formula like Calcilo XD.

17.6.5. Skeletal Dysplasias

Two rare skeletal dysplasias have been associated with hypercalcemia *(60, 62)*. The severe, infantile form of hypophosphatasia in which there is a deficiency of tissue non-specific alkaline phosphatase is associated with a defect in skeletal mineralization, rachitic changes on X-ray and hypercalcemia. The latter is likely the result of poor osteoblast function in the face of continued osteoclastic bone resorption. Besides low serum alkaline phosphatase, the classic biochemical changes are an increase in both urinary phosphoethanolamine and serum pyridoxal-5-phosphate. The second condition is Jansen syndrome associated with hypercalcemia and metaphyseal dysplasia and later development of a characteristic X-ray picture. The etiology appears to be due to constitutively active PTH/PTHrP receptors.

17.6.6. Dietary And Iatrogenic Causes

Neonates, especially premature infants are particularly susceptible to a variety of imbalances that can lead to hypercalcemia *(60)*. Probably the most common cause of moderate hypercalcemia in premature infants is phosphorus deficiency with insufficient phosphorus to allow normal bone mineralization leading to excess serum and urinary calcium. This is most commonly seen when very low birth weight infants fed unsupplemented human milk or inappropriate term formulas deficient in phosphorus. In addition to very low levels of serum phosphorus, this disorder features osteopenia and elevated alkaline phosphatase and can be treated with appropriate supplementation. Hypercalcemia may occur with excessive calcium during ECMO, exchange transfusion or excessive vitamin D supplementation. Vitamin A if given in excess can stimulate bone turnover and hypercalcemia.

17.6.7. Other

There are a number of other conditions that are rare or are common but rarely reported to be associated with hypercalcemia in infants (Table 12) *(6, 51)*.

Table 12
Rare Causes of Neonatal Hypercalcemia

Primary oxalosis
Congenital lactase deficiency
Down's syndrome
Renal tubular acidosis
Thyrotoxicosis
Infantile hypothyroidism
Congenital mesoblastic nephroma
Adrenal insufficiency
Prostaglandin E syndrome

18. DIAGNOSTIC EVALUATION OF HYPERCALCEMIA

Identification of the cause of hypercalcemia requires a detailed history and physical in combination with an appropriate use of the laboratory studies (Table 13). Section 5 describes in more detail the interpretation of studies of divalent ion metabolism. The first step in laboratory evaluation of the child or infant with suspected hypercalcemia is to confirm the diagnosis with total serum calcium, electrolytes, BUN, creatinine, phosphorus, and albumin. We do not recommend the use of "corrected" serum calcium but the albumin and electrolytes may point to the need for ionized calcium measurement. In a patient with hypoalbuminemia, acidosis or severe illness, ionized calcium should be measured to confirm the diagnosis. The severity of the diagnosis is important for treatment but may also point to likely etiologies. In patients with confirmed hypercalcemia, the serum phosphorus may help to identify the cause. In disorders involving PTH or PTHrP, the stimulation of renal phosphorus excretion may lead to a low serum phosphate concentration. Normal to high serum phosphate concentrations is seen with vitamin D mediated states, renal failure, and disorders described above as related to bone. The next step is the measurement of PTH, which will be increased in PTH-mediated conditions but should be suppressed in other causes of hypercalcemia.

Table 13
Laboratory Features of Hypercalcemic Syndromes

Condition	*PO_4*	*PTH*	*1,25$(OH)_2$D*	*Special test*
1° Hyperparathyroidism	⇓	⇑	nl to ⇑	Urine Ca/cr ⇑
Familial hypercalciuric hypercalcemia	nl to ⇓	nl to ⇑	nl to ⇓	Urine Ca/cr ⇓
Vitamin D intoxication	⇑	⇓	nl to ⇑	25(OH)D ⇑
Granulomatous disorders	nl to ⇑	⇓	⇑	1,25$(OH)_2$D ⇑
Humoral hypercalcemia of malignancy	⇓	⇓	nl to ⇓	PTHrP ⇑
Immobilization	nl to ⇑	⇓	⇓	Urine Ca/cr ⇑
Subcutaneous fat necrosis	⇑	⇓	nl to ⇑	

The measurement of 25(OH)D is diagnostic in states of vitamin D intoxication and the more esoteric 1,25(OH)2D and PTHrP are helpful in patients in whom the history and other clinical information point to the possibility of their involvement. The urinary concentrations of calcium and creatinine can be a useful indicator of hypercalciuria as seen in most states or can be used to detect hypocalciuria in FHH patients and family members by measuring the ratio of calcium clearance to creatinine clearance.

19. MANAGEMENT OF HYPERCALCEMIA

The management of hypercalcemia in children will depend on the severity and cause of the hypercalcemia (Table 14). Ideally, the therapy should be directed at treatment of the underlying disorder. Otherwise the management is directed to lower serum calcium non-specifically by increasing renal excretion, reducing calcium absorption, or decreasing the flux out of bone *(45*, *46*, *63)*. These processes may be affected in differing degrees depending on the etiology of the hypercalcemia. Renal calcium excretion can be increased by hydration, preferably with isotonic saline to first treat any ongoing dehydration and then to establish a saline diuresis with an infusion of isotonic saline at 2–3 times maintenance requirements. These measures with increase calcium filtration by increasing the glomerular filtration rate and decreasing the sodium dependent calcium reabsorption. Calcium reabsorption at the thick ascending limb can be further decreased with the addition of the loop diuretic furosemide but the intravascular volume status must be maintained with careful fluid balance or tubular reabsorption may increase worsening the hypercalcemia. Furosemide can lead to electrolyte disturbances such as hypokalemia if not monitored closely. Maximizing calcium excretion with these maneuvers has the ability to lower serum calcium approximately 1–3 mg/dL, but by itself cannot totally correct severe hypercalcemia. Gastrointestinal calcium absorption can be decreased by limiting the calcium and vitamin D in the diet especially in disorders mediated by $1,25(OH)_2D$, using glucocorticoids, which block the action of

Table 14
Treatment of Hypercalcemia in Children*

Agent	*Dose*	*Comment*
Furosemide	0.5–1 mg/kg/dose IV q6–24 h	Avoid volume depletion
Methylprednisolone	1 mg/kg/day IV	Useful in vitamin D mediated hypercalcemia
Salmon Calcitonin	4–8 IU/kg q 12 h	Give IM or SQ
Pamidronate	0.5–1 mg/kg IV	Give in 10 ml/mg over 4 h minimum
Zoledronic acid	0.025–0.05 mg/kg IV	Give over 15–30 min

*Patient must be made euvolemic before and during therapy with normal saline 150–250 ml/kg/day.

vitamin D. The most severe hypercalcemic states generally involve increase bone resorption, so measures that decrease bone resorption are the most powerful in lowering serum calcium. The bisphosphonates, which inhibit osteoclast function, are the most potent agents in treating hypercalcemia. In children, the greatest experience is with intravenous pamidronate. There is a more potent analogue zoledronic acid, which has been introduced for hypercalcemia of malignancy in adults. Pamidronate has been given safely to children with metabolic bone disease at a dose of 1 mg/kg given intravenously in 10 ml isotonic saline per mg pamidronate to be given over 4 h. There is limited experience with the use of zoledronic acid in children although it has been reported to be safe when given at a dose of 0.025–0.05 mg/kg up to a maximum dose of 4 mg. An advantage of zoledronic acid is that it can be given over a minimum of 15–30 min rather than the 4 h required for pamidronate. Both agents should be avoided in the presence of renal failure and can be associated with transient fever and hypophosphatemia, and possibly an overshoot hypocalcemia. A much older agent to inhibit bone resorption is calcitonin. Calcitonin works to lower calcium in hours but a resistance to its effects develops over 24–48 h. Therefore it is useful when given in combination with one of the bisphosphonates. Several agents given in the past that are no longer recommended are plicamycin, gallium nitrate, and intravenous phosphate. Each of these agents has significant toxicities and has been replaced by the bisphosphonates.

With mild hypercalcemia (total serum calcium < 12 mg/dL, ionized < 1.5 mM), asymptomatic children often do not require treatment other than avoiding dehydration and reducing the calcium in the diet. In patients with moderate hypercalcemia (total serum calcium 12–14 mg/dL), dehydration should be expected and aggressive rehydration with normal saline should be instituted. Hydration is unlikely to normalize the serum calcium and the next step should be directed to treat the primary etiology if known. Bisphosphonates should be used only with caution with moderate hypercalcemia to avoid an over shoot hypocalcemia. In patients with severe hypercalcemia (total serum calcium > 14 mg/dL or who are symptomatic) are at greater risk for morbidity and mortality. In addition to the hydration, the careful addition of furosemide at a dose of 0.25–0.5 mg/kg can be given every 12 h after the patient is adequately hydrated with isotonic saline. Caution to avoid dehydration or hypokalemia must be exercised. Many of these patients will have increased bone resorption as part of their pathophysiology so the use of bisphosphonates, possibly preceded by calcitonin may be considered. There are rare patients with severe hypercalcemia with renal failure in whom peritoneal or hemodialysis using a low calcium dialysate as an emergency measure is indicated.

CASE SCENARIO DISCUSSIONS

Case Scenario 1: Hypercalcemia in a healthy adolescent. This young man is suffering from immobilization hypercalcemia with sudden turn off of his active bone mineralization simultaneous with an increase in bone resorption releasing large amounts of calcium into the blood stream. His lethargy and depression is a direct result as are his GI symptoms. He is hypertensive as result of the effect on the vascular system and his renal manifestations include acute renal failure and a urinary concentrating defect.

The combination of poor intake and renal water wasting has led him to be dehydrated which is exacerbating the direct inhibition of GFR by hypercalcemia. The cause of this patient's hypercalcemia appears to be fairly straightforward but a minimum work-up to look for any surprises in this patient with severe hypercalcemia would be a serum PTH level, which should be suppressed and a spot urine calcium/creatinine which should be elevated.

The definitive treatment would be to get the patient mobilized but that is not likely to be successful anytime soon and intermediate measures such as use of a tilt-table is not effective. The first step would be to correct the dehydration with isotonic saline and to maintain fluid balance by infusing the calcium at 2–3× maintenance. Whereas this is likely to help correct the acute renal failure and decrease the calcium, it is unlikely to lower the total calcium more than about 2 mg/dL. One can add furosemide at a dose of about 0.5–1.0 mg/kg IV every 12 h, the total fluid balance must stay positive or the calcium will start to go back up again. To lower the calcium to the normal range, a bisphosphonate may have to be used. The choices are pamidronate 0.5–1.0 mg/kg IV over 4 h or possibly the newest agent in the class, zoledronic acid 4 IV over 15 min. The patient's calcium, phosphorus, renal function, and electrolytes need to be monitored closely through the treatment phase.

Case Scenario 2: Neonatal hypercalcemia. This infant with the washed-out bones and hypercalcemia either could have a primary abnormality of the skeleton but more likely has neonatal hyperparathyroidism, which is supported by the low phosphorus level. The calcium level is lower than what is generally reported with NSHPT but a CaSR defect cannot be ruled out. Maternal hypocalcemia whether from hypoparathyroidism is an important cause but abnormalities of placental transport of calcium are possible as well. The first step in the diagnosis is to measure an ionized calcium PTH levels on the mother and infant. Urine calcium and creatinine levels may help in the evaluation of a CaSR disorder. In this case, the mother had low calcium and PTH levels because of idiopathic hypoparathyroidism that was not being medically controlled and her infant had an elevated PTH as result. The management of the moderate hypercalcemia was supportive with fluids; initially 150–200 ml/kg/day of normal saline given parenterally followed by oral intake of 2 times the normal maintenance requirements of fluid. With time, the hyperparathyroidism resolved and the skeleton remineralized.

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