Hypocalcemia in Infants and Children

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In Brief

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Author Disclosure

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Approximately 99% of the total body calcium (Ca) is in the form of hydroxyapatite crystal in the skeleton; the remaining 1% resides in extracellular fluid. About 50% of the Ca in the circulation is in the free ionized form, 40% is bound to protein (predominantly albumin), and 10% is complexed with anions (eg, citrate). It is the plasma ionized calcium (iCa) fraction that is biologically active, and its concentration is tightly controlled.

Ca concentrations in blood are reported in various units: mg/dL, mmol/L, and mEq/L. Because Ca is found as the divalent cation in humans, the conversion factor between mmol/L and mEq/L is 2; that is, 1 mmol/L=2 mEq/L. Because the molecular weight of Ca is approximately 40, the conversion factor between mmol/L and mg/dL is 4; that is, 1 mmol/L=4.0 mg/dL. For example, a value of 9.0 mg/dL is the equivalent of 2.25 mmol/L or 4.5 mEq/L. Despite the iCa fraction being the biologically important component, total serum Ca is measured most commonly. iCa values should be determined when abnormalities in Ca homeostasis are suspected. iCa is measured on whole venous blood samples that are anticoagulated and handled similarly to a blood gas sample, that is, capped airtight, no air bubbles, and kept on ice if not analyzed immediately.

The range of normal Ca concentration varies somewhat with age. Concentrations decrease immediately after birth, recovering after the first postnatal week and rising slightly more in infancy than in childhood. Ca values also vary because of laboratory methodology. Usual reported ranges of normocalcemia are 8.5 to 10.5 mg/dL (2.1 to 2.6 mmol/L) for total Ca and 4.0 to 5.0 mg/dL (1.0 to 1.3 mmol/L) for iCa in children. Preterm infants generally are not considered to have hypocalcemia until serum total Ca values fall below 7.0 mg/dL (1.8 mmol/L).

The extracellular Ca concentration has three primary regulators: Ca-sensing receptor (CaSR), parathyroid hormone (PTH), and vitamin D. The CaSR is a membrane-bound molecule found in multiple tissues, including cells of the parathyroid glands. When plasma iCa concentrations are sufficient to stimulate the CaSR, the result is inhibited PTH release. When the iCa concentration is low, PTH is released and is carried in blood to its target tissues: bone and kidney.

The effects of PTH on bone are complex and dose- and duration-dependent. In hypocalcemic states, PTH induces bone mineral release, thereby increasing circulating Ca and phosphate (P) concentrations. In the kidney, PTH increases renal tubular Ca reabsorption, which adds the filtered Ca back into blood, but PTH also increases P excretion.

The net effect of PTH on bone and kidney is to increase plasma Ca and decrease plasma P concentrations. PTH has an additional important renal effect: stimulating the conversion of relatively inactive 25-hydroxyvitamin D, itself a product of liver hydroxylation of vitamin D, to its most active form, 1, 25-dihydroxyvitamin D (1, 25$[OH]_2$D). When released into the circulation, 1, 25$(OH)_2$D results in increased intestinal Ca and P uptake.

Historically, calcitonin also was considered a Ca-regulating hormone that could lower extracellular Ca by diminishing bone resorption. However, the absence of calcitonin, as occurs in postthyroidectomy patients, does not result in hypercalcemia, suggesting that calcitonin does not have an important role in regulating blood Ca concentrations in humans.

Hypocalcemia is associated with neuromuscular excitability leading to muscle contractions. The term tetany is applied to the contractions, and a typ-

ical manifestation is sustained contractions in the hands and feet. The fingers are in extension; they can be bent but spring back into the same position when released. Muscle contractions can be provoked when eliciting a Chvostek or Trousseau sign. A positive Chvostek sign is a twitch at the ipsilateral corner of the mouth with a light tap over the facial nerve just below the maxilla. A positive Trousseau sign is carpal spasm in the hand produced by inflating a blood pressure cuff around an arm and maintaining pressure at just above systolic for 3 to 5 minutes.

Central nervous system irritability from hypocalcemia can cause anticonvulsant-resistant seizures. Such spells often are brief, lasting a few seconds or minutes, but may recur frequently. Initially, there may be no postictal phase, although clinical experience shows increasing lethargy with repeated seizures. Rarely, the initial presentation is stridor or cyanosis from laryngospasm. Arrhythmias are even rarer, but hypocalcemia is associated with hypotension and impaired cardiac contractility. Electrocardiography may reveal a prolonged QTc interval. Most patients who have mild hypocalcemia are asymptomatic. Neonates may present only with nonspecific symptoms such as apnea, tachycardia, lethargy, poor feeding, vomiting, and abdominal distension.

Hypocalcemia occurring in the neonatal period is divided into early- and late-onset types. Early-onset hypocalcemia refers to the first few days after birth, when Ca concentrations are naturally falling, but in this situation, they decrease more than normal. Affected neonates are stressed from asphyxiation or sepsis, or by being infants of a diabetic mother (IDMs). For IDMs, hypomagnesemia, which interferes with PTH release and possibly PTH responsiveness, has been implicated as a major contributor. Correcting the underlying problem results in the resolution of hypocalcemia, although temporary support with Ca infusions may be necessary.

Late neonatal hypocalcemia occurs after the fifth postnatal day, also can be transient, and often is related to immaturity of the parathyroid glands, which results in intolerance of the P load found in cow milk and derived infant formulas. In such cases, a low-P formula that is supplemented with Ca to achieve a 4:1 Ca:P ratio by weight should correct the hypocalcemia.

Failure to achieve normocalcemia with this regimen raises the concern of other, possibly permanent causes of hypocalcemia. Among these disorders are the genetic forms of hypoparathyroidism, which include a spectrum of abnormalities from the absence of parathyroid gland development to gain-of-function mutations in the gene coding for the CaSR, defects in production or processing of PTH, or abnormal response to PTH. The most common of the parathyroid gland developmental problems is the DiGeorge sequence, in which the hypoparathyroidism may be associated with cardiovascular abnormalities and thymic hypoplasia.

Some neonatal causes of hypocalcemia cross the early/late boundary. Maternal hypercalcemia and blood transfusion with citrated blood both can cause hypocalcemia in a neonate who has a transient episode but may need short-term therapeutic intervention.

Among infants and children, hypocalcemia is observed most often in an intensive care setting, usually related to an acute illness or stress such as sepsis, cardiac surgery, rhabdomyolysis, pancreatitis, hepatitis, or tumor lysis. With resolution of the underlying condition, the hypocalcemia ends.

Chronic causes of hypocalcemia can be divided into two major groups: disorders involving PTH and those related to vitamin D. PTH-related disorders, in turn, can be divided into two major categories: insufficient circulating PTH (hypoparathyroidism) or insufficient responsiveness to PTH (pseudohypoparathyroidism). Each form has its own set of causes. Hypoparathyroidism can be distinguished from pseudohypoparathyroidism simply by measuring serum PTH. If PTH is inappropriately low for the Ca value, hypoparathyroidism can be diagnosed. The serum biochemical profile of PTH disorders consists of low Ca, high P, normal alkaline phosphatase, and low 1, 25$(OH)_2$D values.

An appropriate PTH response may not be adequate to correct hypocalcemia if there is an abnormality in the vitamin D pathway. Disorders of vitamin D can result from lack of exposure to ultraviolet B radiation, inadequate intake, fat malabsorption, lack of liver activity to promote 25-hydroxylation, genetic deficiency of the renal 1-alpha hydroxylase to assist in the 1-hydroxylation step required for vitamin D activation (vitamin D-dependent rickets type I), or resistance to the actions of vitamin D (vitamin D-dependent rickets type II). The serum biochemical profile for the vitamin D disorders is distinct from that of hypoparathyroidism and includes low P, high alkaline phosphatase, and high PTH concentrations. In cases of vitamin D deficiency or liver dysfunction, the 25-hydroxyvitamin D concentration is low. When there is a renal cause, the 1, 25$(OH)_2$D concentration is low while the 25-hydroxyvitamin D concentration may be normal. With end-organ resistance, the concentration of 1, 25$(OH)_2$D is very high.

Renal failure presents a special situation, with hypocalcemia occurring because of an inadequate kidney response to PTH, a lack of 1-alpha hydroxylase activity resulting in low 1, 25$(OH)_2$D concentrations, and hyperphosphatemia from diminished glomerular filtration. The typical biochemical profile is elevated serum urea nitrogen and creatinine, elevated serum P, decreased serum Ca, increased PTH, and decreased 1, 25$(OH)_2$D concentrations.

Thus, the evaluation of a patient

who has hypocalcemia should include serum electrolyte measurement; liver function tests; and assessment of alkaline phosphatase, P, PTH, vitamin D metabolites, and magnesium (Mg). The iCa value may be normal when the total Ca value is high or low, depending on serum albumin concentrations. As a rough estimate, Ca concentration falls 0.8 mg/dL (0.2 mmol/L) for every 1.0-g/dL decrease in albumin concentration. Ca binding to albumin is pH-dependent. Acidemia releases Ca from albumin; alkalosis increases binding. A change of 0.1 pH unit may alter the concentration of ionized calcium by 10% without altering the total Ca concentration.

Urine tests that may be helpful in the face of hypocalcemia include pH, Ca, Mg, P, and creatinine evaluation. Normally, the kidney reabsorbs about 99% of filtered Ca. Approximately 80% to 85% of filtered Ca is reabsorbed passively in the proximal tubules, and the remaining Ca is reabsorbed in the distal cortical tubules under PTH stimulation. A random urine calcium/creatinine ratio (UCa/Cr) is a helpful test for diagnosis and making decisions about treatment. The median UCa/Cr value ranges from 0.04 to 0.26 mg/mg, depending on age and ethnicity, with the youngest children demonstrating the highest values. A ratio of 0.2 mg/mg or greater usually defines hypercalciuria in older children, but the age-dependent 95th percentile of UCa/Cr can be as high as 0.70 for white infants.

A patient who has symptomatic hypocalcemia should receive intravenous (IV) Ca to increase the Ca concentration above symptom threshold and subsequently to maintain that concentration to prevent symptom recurrence. Seizures usually do not respond to anticonvulsant medications but stop when IV Ca is administered. Although no single protocol has been adopted universally, one common regimen recommends the IV infusion of 20 mg/kg elemental Ca over 10 to 20 minutes, with careful monitoring for cardiac arrhythmias, which means administering approximately 2 mL/kg of 10% Ca gluconate or 0.7 mL/kg of 10% Ca chloride. In the experience of one of the authors (MM), a much smaller dose of 0.5 mL/kg of 10% Ca gluconate often is sufficient to eliminate hypocalcemia-related symptoms and has not been associated with arrhythmias.

A secure IV line is essential for any Ca infusion to avoid subcutaneous necrosis from extravasation. The bolus dose can be repeated as needed to control symptoms attributable solely to hypocalcemia.

Immediately after the bolus infusion, a continuous Ca infusion should be strongly considered. The dose varies with age. For neonates, 500 mg/kg of 10% Ca gluconate infused over 24 hours is a common recommendation. For older infants and children, a starting dose of 200 mg/kg per 24 hours of 10% Ca gluconate should be provided. In all cases, the Ca infusion should be titrated to a target normal Ca concentration. Serum Ca must be monitored frequently during the infusion, and Ca should not be mixed with fluids containing P or bicarbonate to avoid precipitation.

Hypomagnesemia (<1.0 mg/dL) may need to be corrected to restore PTH activity. This goal may be accomplished with infusion of 1 mmol/kg Mg as the sulfate over 24 hours, followed by an additional 1 mmol/kg over the next 48 hours, again with frequent monitoring of the serum Mg concentrations.

After hypocalcemia-related symptoms are controlled, follow-up treatment with oral therapy can be provided. Vitamin D, in one of its various forms, also may be indicated, depending on the cause of the hypocalcemia. The most important aspect of management is resolution of the primary cause of hypocalcemia when possible.

Comment: Not aware of a study that confirms my impression, I can offer only anecdote in place of data. Over the past few years, as the epidemic of childhood obesity has burgeoned, we have seen several adolescents in our primary care practice whose laboratory assessment, performed in response to their body mass indexes, showed abnormally high alkaline phosphatase and low calcium values. Their clinically unsuspected rickets was confirmed by low concentrations of vitamin D. Our speculation is that their high-fat junk food diets are morbidly low both in vitamin D and calcium. Also, when it comes to ultraviolet B exposure, sitting in front of TV and computer screens does not match running around in sunshine.

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Editor, In Brief

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