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Hypocalcemia in Infants and Children

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In Brief


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 (predomi-nantly albumin), and 10% is complexed with anions (eg, citrate). It is the plasma ionized calcium (iCa) fraction that is biologically active, and its concen-tration is tightly controlled.

Ca concentrations in blood are re-ported in various units: mg/dL, mmol/L, and mEq/L. Because Ca is found as the divalent cation in humans, the conver-sion factor between mmol/L and mEq/L is 2; that is, 1 mmol/L=2 mEq/L. Be-cause 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 imme-diately.

The range of normal Ca concentra-tion varies somewhat with age. Concentrations decrease immediately after birth, recovering after the first post-natal week and rising slightly more in infancy than in childhood. Ca values also vary because of laboratory meth-odology. Usual reported ranges of nor-mocalcemia 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 gener-ally are not considered to have hypo-calcemia 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 mem-brane-bound molecule found in multiple tissues, including cells of the parathyroid glands. When plasma iCa concentrations are sufficient to stimu-late the CaSR, the result is inhibited PTH release. When the iCa concentra-tion 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-de-pendent. In hypocalcemic states, PTH induces bone mineral release, thereby increasing circulating Ca and phos-phate (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 ef-fect: stimulating the conversion of rel-atively 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)2D). When released into the circulation, 1, 25(OH)2D results in increased intesti-nal Ca and P uptake.

Historically, calcitonin also was con-sidered a Ca-regulating hormone that could lower extracellular Ca by diminish-ing bone resorption. However, the absence of calcitonin, as occurs in post-thyroidectomy patients, does not result in hypercalcemia, suggesting that cal-citonin 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 contrac-
tions 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 main-
taining 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. Arrhyth-
mias are even rarer, but hypocalcemia
is associated with hypotension and im-
paired cardiac contractility. Electrocardi-
ography may reveal a prolonged QTc
interval. Most patients who have mild
hypocalcemia are asymptomatic. Neo-
nates may present only with nonspe-
cific symptoms such as apnea, tachy-
cardia, lethargy, poor feeding, vomiting,
and abdominal distension.

Hypocalcemia occurring in the neo-
natal period is divided into early- and
late-onset types. Early-onset hypocal-
cemia refers to the first few days after
birth, when Ca concentrations are nat-
urally falling, but in this situation, they
decrease more than normal. Affected
neonates are stressed from asphyxia-
tion or sepsis, or by being infants of a
neonates are stressed from asphyxia-
tion or sepsis, or by being infants of a
diabetic mother (IDMs). For IDMs, hy-
pomagnesemia, which interferes with
PTH release and possibly PTH respon-
siveness, has been implicated as a ma-

Late neonatal hypocalcemia occurs
after the fifth postnatal day, also can be
transient, and often is related to imma-
turity 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 for-
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 hypoparathy-
roidism, which include a spectrum of
abnormalities from the absence of para-
thyroid 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 para-
thyroid gland developmental problems
is the DiGeorge sequence, in which the
hypoparathyroidism may be associated
with cardiovascular abnormalities and
thymic hypoplasia.

Some neonatal causes of hypocal-
cemia cross the early/late boundary.
Maternal hypercalcemia and blood trans-
fusion 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, hypocal-
cemia is observed most often in
an intensive care setting, usually re-
lated to an acute illness or stress such
as sepsis, cardiac surgery, rhabdomyol-
ysis, 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: dis-
orders 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 re-
sponsiveness to PTH (pseudohyopopa-
thyroidism). Each form has its own set
of causes. Hypoparathyroidism can be
distinguished from pseudohyopopa-
thyroidism 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 phospha-
tase, and low 1, 25(OH)2D values.

An appropriate PTH response may
not be adequate to correct hypocal-
cemia if there is an abnormality in the
vitamin D pathway. Disorders of vita-
min 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-hydroxyl-
ation step required for vitamin D acti-
vation (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 phospha-
tase, and high PTH concentrations. In
cases of vitamin D deficiency or liver
dysfunction, the 25-hydroxylvitamin D
concentration is low. When there is a
renal cause, the 1, 25(OH)2D concen-
tration is low while the 25-hydroxylvitamin
D concentration may be normal. With
end-organ resistance, the concentration
of 1, 25(OH)2D is very high.

Renal failure presents a special sit-
uation, with hypocalcemia occurring
because of an inadequate kidney re-
sponse to PTH, a lack of 1-alpha hy-
droxylase activity resulting in low 1,
25(OH)2D concentrations, and hyper-
phosphatemia from diminished glom-
erular filtration. The typical biochemical
profile is elevated serum urea nitrogen
and creatinine, elevated serum P, de-
creased serum Ca, increased PTH, and
decreased 1, 25(OH)2D concentrations.

Thus, the evaluation of a patient

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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 anti-convulsant 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 morbidsly 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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