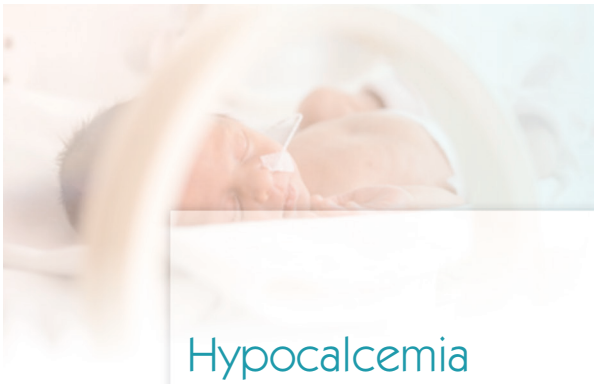

CHAPTER

27

# Hypocalcemia

Hypocalcemia is a common clinical and laboratory abnormality in neonates. Ionized calcium is essential for many biological processes, including coagulation, neuromuscular functioning, integrity of cell membrane, and many cellular enzymatic reactions.

## CALCIUM HOMEOSTASIS DURING THE FETAL AND NEONATAL PERIOD

Calcium (Ca) is actively transferred from mother to fetus during the last trimester, as demonstrated by a significantly higher level of total Ca concentration in cord blood compared to maternal serum.[1] Serum Ca (SCa) in the fetus is 10 –11 mg/dl at term that maintains a gradient of maternal-to-fetal calcium of 1:1.4. Parathyroid hormone (PTH) and calcitonin (CT) do not cross the placental barrier. PTH-related peptide (PTHrP) is the primary regulator of the positive Ca balance across the placenta. Though vitamin D is critical for mineral ion homeostasis and bone development during adult life, fetal mineral ion homeostasis is mostly independent of it.

After birth, the SCa levels in neonates depend on PTH secretion, dietary calcium intake, renal calcium reabsorption, and skeletal calcium and vitamin D status. Hence, after delivery, SCa levels start decreasing—the rate and extent of decrease are inversely proportional to the gestation—and reach a nadir of 7.5–8.5 mg/dl in healthy term neonates by day 2 of life. This postnatal drop in SCa may be related to decreased PTH level, end-organ unresponsiveness to PTH,[2] abnormalities of vitamin D metabolism, hyperphosphatemia, hypomagnesemia, and hypercalcitonemia, which occur by 12–24 hours of age.[3] PTH levels increase gradually in the first 48 hours of life, and normal levels of SCa are achieved by the 3rd to 4th day of life.[4] Efficacy of the intestinal absorption and the renal handling of Ca mature by 2–4 weeks. This transition phase is responsible for the increased risk of early-onset hypocalcemia in high-risk neonates.

## DISTRIBUTION OF CALCIUM IN THE BODY

Body Ca exists in two major compartments: skeleton (99%) and extracellular fluid (1%). Ca in the extracellular fluid is present in three forms[5]—bound to albumin (40%), bound to anions like phosphorus, citrate, sulfate, and lactate (10%), and as free ionized form (50%). Ionized serum calcium (iSCa) is crucial for many biochemical processes, including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity.

Measurement of the total serum Ca (tSCa) concentration alone can be misleading because the relationship between tSCa and iSCa is not always linear. The correlation between the two is poor when the serum albumin concentration is low and, to a lesser degree, with disturbances in acid-base status, which occur frequently in premature or sick infants. With hypoalbuminemia, tSCa is low, while iSCa is normal. Falsely low iSCa may be recorded in alkalosis and with heparin contamination of blood samples. The tSCa falls by about 0.8 mg/dl (0.2 mmol/L) for every 1.0 g/dl fall in the plasma albumin concentration.

*Therefore, the estimation of tSCa is a poor substitute for measuring the iSCa.*

## DEFINITION

Hypocalcemia is defined by different tSCa and iSCa cutoffs in preterm and term infants (Table 27.1).[6]

Hypocalcemia is usually classified into two categories based on the age of onset. Early-onset hypocalcemia presents within the first 72–96 hours and usually requires short-term calcium supplementation. In contrast, late-onset hypocalcemia usually presents after 96 hours and requires long-term therapy.

**Table 27.1: Definition of hypocalcemia**

| *Gestation* | *Total serum calcium* | *Ionic serum calcium* |
|---|---|---|
| Preterm | <7 mg/dl (1.75 mmol/L) | <4 mg/dl (1 mmol/L) |
| Term | <8 mg/dl (2 mmol/L) | <4.8 mg/dl (1.2 mmol/L) |

SCa is usually reported in different units viz. mg/dl, mEq/l, and mmol/l. The relationship among these units is related to the following equations:
mmol/L = [mg/dl × 10] ÷ molecular wt; mEq/L = mmol/L × valency
Since the molecular weight of Ca is 40, and the valence is +2, 1 mg/dl is equivalent to 0.25 mmol/L and 0.5 mEq/L. Thus, values in mg/dl may be converted to molar units (mmol/L) by dividing it by 4.

## EARLY-ONSET NEONATAL HYPOCALCEMIA (ENH)

This condition is relatively common and seen within the first 3–4 days of life in the following clinical settings (Table 27.2).

There is no universal recommendation regarding routine screening of at-risk infants for ENH. However, it may be considered in the following categories of infants:

a. Preterm infants born before 32 weeks of gestation.
b. Infants of diabetic mothers.
c. Infants born after severe perinatal asphyxia (defined as an Apgar score <4 at 1 minute of age)

*Schedule for screening:* at 24 and 48 hours of age.

### Clinical Presentation

**Asymptomatic:** ENH is usually asymptomatic (unlike the late onset hypocalcemia) and is incidentally detected.

**Symptomatic:** The symptoms may be neuromuscular irritability – myoclonic jerks, jitteriness, exaggerated startle, and seizures. They may represent cardiac involvement like tachycardia, heart failure, prolonged QT interval, and decreased contractibility. More often, they are nonspecific and unrelated to the severity of hypocalcemia. Apnea, cyanosis, tachypnea, vomiting, and laryngospasm are other symptoms.

### Diagnosis

**Laboratory:** by measuring total or ionized serum calcium. Ionized calcium is the preferred mode for the diagnosis of hypocalcemia.

**ECG:** QoTc >0.22 seconds or QTc >0.45 seconds

$$QTc = \frac{\text{QT interval in seconds}}{\sqrt{\text{R - R interval in seconds}}}$$

**Table 27.2: Causes of early-onset hypocalcemia**

| |
|---|
| Prematurity |
| Preeclampsia |
| Infants of diabetic mother |
| Perinatal stress/asphyxia |
| Maternal intake of anticonvulsants (phenobarbitone, phenytoin sodium) |
| Maternal hyperparathyroidism |
| Iatrogenic (alkalosis, use of blood products, diuretics, phototherapy, lipid infusions, etc.) |

$$QoTc = \frac{\text{QT interval in seconds}}{\sqrt{\text{R - R interval in seconds}}}$$

(QT interval is measured from the origin of the q wave to the end of the T wave on ECG; QoT is measured from the origin of the q wave to the origin of the T wave).

A diagnosis of hypocalcemia based only on ECG criteria is likely to yield a high false-positive rate. Although these parameters have a reasonable correlation with hypocalcemia in LBW infants (sensitivity of 77% and specificity of 94.4%), [7] neonates suspected to have hypocalcemia by ECG criteria should have the diagnosis confirmed by measurement of serum calcium levels.

## Treatment

**Asymptomatic hypocalcemia:** Infants detected to have hypocalcemia on screening but are otherwise asymptomatic should receive 80 mg/kg/day of elemental calcium (8 ml/kg/day of 10% calcium gluconate; 1 ml = 9.4 mg of elemental calcium) for 48 hours. This may be tapered to a 50% dose for another 24 hours and then discontinued. Neonates tolerating oral feeds may be treated with oral calcium (IV preparation may be used orally).

**Symptomatic hypocalcemia:** These infants should receive a bolus dose of 2 ml/kg/dose diluted 1:1 with 5% dextrose over 10 minutes under cardiac monitoring. When there is severe hypocalcemia with poor cardiac function, calcium chloride 20 mg/kg may be given through a central line over 10–30 minutes (because calcium chloride, unlike gluconate salt, does not require metabolism by the liver for the release of free calcium). This should be followed by continuous IV infusion of 80 mg/kg/day elemental calcium for 48 hours. Continuous infusion is preferred to IV bolus doses (1 ml/kg/dose q 6 hourly). Calcium infusion should be dropped to 50% of the original dose for the next 24 hours and then discontinued. Normal calcium values should be documented at 48 hours (i.e. before weaning the infusion). The infusion may be replaced with oral calcium therapy on the last day.

## Precautions and Side Effects

Bradycardia and arrhythmia are known side effects of bolus IV calcium administration. Hence, bolus doses of calcium should be diluted 1:1 with 5% dextrose and given slowly over 10–30 minutes

under cardiac monitoring. Continuous infusion is preferred to IV bolus. An umbilical venous catheter (UVC) may be used to administer calcium after ensuring that the tip is positioned in the inferior vena cava. Hepatic necrosis may occur if the tip of the UVC lies in a branch of the portal vein. The umbilical artery catheter (UAC) should never be used for giving calcium injections. Accidental injection into the umbilical artery may result in arterial spasms and intestinal necrosis.

Skin and subcutaneous tissue necrosis may occur due to extravasation. Hence, IV sites where calcium is infused should be checked at least two hourly to monitor for extravasation.

### Prolonged or Resistant Hypocalcemia

This condition should be considered in the following situations:

- Symptomatic hypocalcemia unresponsive to adequate doses of calcium therapy.
- Infants needing calcium supplements beyond 72 hours of age.
- Hypocalcemia presenting at the end of the first week.

*These infants should be investigated for causes of LNH (see below).*

## LATE ONSET NEONATAL HYPOCALCEMIA (LNH)

It usually presents at the end of the first week of life. It is usually symptomatic in the form of neonatal tetany or seizures and is generally caused by high phosphate intake (iatrogenic). The common causes are listed in Table 27.3.

### Examination

Neonates with LNH should have an examination with particular emphasis on cataracts, hearing, and any evidence of basal ganglia involvement (movement disorder) in the follow-up.

### Investigations

Investigations listed in Table 27.4 should be considered in LNH or if the hypocalcemia does not respond to adequate doses of calcium. The workup is vital to determine the etiology.

Hypoparathyroidism should be strongly suspected if hypocalcemia is present with hyperphosphatemia and a normal renal function (*See* Table 27.5 for interpretation of diagnostic investigation).

| Table 27.3: Causes of late-onset hypocalcemia |
|---|
| 1. Increased phosphate load: cow milk, renal insufficiency |
| 2. Hypomagnesemia |
| 3. Vitamin D deficiency |
| 4. Maternal vitamin D deficiency |
| 5. Malabsorption |
| 6. Hepatobiliary disease |
| 7. PTH resistance |
| 8. Transient neonatal pseudo-hypoparathyroidism |
| 9. Hypoparathyroidism<br>a. *Primary:* hypoplasia/aplasia (DiGeorge's syndrome, CATCH 22 syndrome), activating mutations of the calcium sensing receptor (CSR)<br>b. *Secondary:* maternal hyperparathyroidism, metabolic syndromes (Kenny–Caffey syndrome, long-chain fatty acyl CoA dehydrogenase deficiency, Kearns–Sayre syndrome. |
| 10. Autosomal dominant hypocalcemic hypercalciuria |
| 11. Iatrogenic: Citrated blood products, lipid infusion, bicarbonate therapy, loop diuretics, glucocorticoids, phosphate therapy, aminoglycosides (mainly gentamicin), viral gastroenteritis, phototherapy |

| Table 27.4: Investigations required in infants with persistent/late-onset hypocalcemia | |
|---|---|
| *First line* | *Second line* |
| Serum phosphate<br>Serum alkaline phosphatase (SAP)<br>Liver function tests<br>Renal function tests (RFT)<br>X-ray chest/ wrist<br>Arterial pH | Serum magnesium (Mg)<br>Serum parathormone levels (PTH)<br>25-hydroxyvitamin D levels (25-OH D)<br>Urine calcium creatinine ratio<br>Maternal calcium, phosphate, and alkaline phosphatase |

| Table 27.5: Interpretation of investigations | |
|---|---|
| *Disorder causing hypocalcemia* | *Findings* |
| Hypoparathyroidism | High: phosphate<br>Low: SAP, PTH, 25-OH D |
| Pseudohypoparathyroidism | High: SAP, PTH, Phosphate<br>Low: 25-OH D |
| Chronic renal failure | High: phosphate, SAP, PTH, deranged RFT<br>Low: 25-OH D, pH (acidotic) |

(*Contd.*)

| Table 27.5: Interpretation of investigations (*Contd.*) | |
|---|---|
| *Disorder causing hypocalcemia* | *Findings* |
| Hypomagnesemia | High: PTH<br>Low: phosphate, Mg, 25-OH D |
| VDDR I | High: SAP, PTH<br>Low: Phosphate, 25-OH D |
| VDDR II | High: SAP, 25-OH D, PTH<br>Low: Phosphate |

*VDDR:* Vitamin D dependent rickets

## Treatment

The initial treatment of LNH is the same as that of ENH. This should be followed by specific management according to the etiology and may, in certain conditions, be life-long.

1. **Hypomagnesemia:** Symptomatic hypocalcemia unresponsive to adequate doses of IV calcium therapy is usually due to hypomagnesemia. It may present either as ENH or later as LNH. The neonate should receive two doses of 0.2 ml/kg of 50% $MgSO_4$ injection 12 hours apart, deep IM, followed by a maintenance dose of 0.2 ml/kg/day of 50% $MgSO_4$ PO for 3 days.
2. **High phosphate load:** These infants have hyperphosphatemia with near-normal calcium levels. This results from feeding animal milk with a high phosphate load (e.g. cow's milk). Exclusive breastfeeding should be encouraged, and animal milk should be discontinued. Phosphate-binding gels must be avoided.
3. **Hypoparathyroidism:** High phosphate levels in the absence of high phosphate intake (cow's milk) and normal renal functions suggest hypoparathyroidism.[8]

   Supplementing calcium may lead to calcium deposition and tissue damage if the phosphate level is high. Thus, reduction of the phosphate load must be attempted to keep the calcium and the phosphate product less than 55.[9] These neonates should be supplemented with calcium (50 mg/kg/day in 3 divided doses) and $1,25(OH)_2$ vitamin $D_3$ (0.5–1 µg/day). Therapy may be stopped in hypocalcemia secondary to maternal hyperparathyroidism after 6 weeks.
4. **Vitamin D deficiency states:** These infants have hypocalcemia associated with hypophosphatemia due to an intact parathormone response in the kidneys. They benefit from $1,25(OH)_2$ vitamin $D_3$ supplementation in a dose of 30–60 ng/kg/day.

After starting treatment, neonates with LNH must be monitored for SCa, phosphate, 24-hour urinary calcium, and calcium creatinine ratio. Try to keep the calcium in the lower range, as defective distal tubular absorption leads to hypercalciuria and nephrocalcinosis.[10]

## PROGNOSIS AND OUTCOME

Most cases of ENH resolve within 48–72 hours without any significant sequelae. LNH caused by exogenous phosphate load and magnesium deficiency also responds well to phosphate restriction and magnesium repletion, respectively. When caused by hypoparathyroidism, hypocalcemia requires continued therapy with vitamin D and calcium. The treatment period depends on the nature of the hypoparathyroidism, which can be transient, last several weeks to months, or be permanent.

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