Mineral Homeostasis and Effects on Bone Mineralization in the Preterm Neonate

Heidi E. Karpen, MD

KEYWORDS

• Calcium • Phosphorus • Parathyroid hormone • Bone mineralization • Bone density • Rickets of prematurity • Nutrition

KEY POINTS

- Accretion of adequate mineral content in utero is essential for normal bone mineralization.
- Placental mineral transport is accomplished via active transport and does not require fetal hormone input.
- Most mineral accretion occurs during the last trimester of gestation, placing the preterm infant at particular risk for metabolic bone disease.
- Postnatal mineral homeostasis requires a carefully orchestrated balance of actions of parathyroid hormone, calcitonin, and vitamin D on target organs.
- Preterm birth, asphyxia, acidosis, and prolonged parenteral nutrition increase the risk of mineral imbalance and metabolic bone disease.

MINERAL HOMEOSTASIS IN THE FETUS

Mineral accretion by the skeleton before birth depends directly on the adequacy of mineral supply in utero. This mineral supply also regulates the functional activity of the osteoblasts and osteoclasts. Although the bone (through mineral turnover), the intestines, and kidneys are the major source of mineral supply for the adult, the placenta actively transports calcium, phosphorus, and magnesium from the maternal circulation to meet the needs of the growing fetus.

Calcium

The full-term fetus typically accrues approximately 30 g of calcium (~120–150 mg/kg/d during the third trimester) and up to 300 mg/d during the last month of gestation. Similarly, phosphorus is accrued at rates of approximately 70 mg/kg/d.[1,2]

Because such high levels of mineral concentrations are necessary for normal fetal skeletal development, the placenta is capable of operating against a steep

Pediatrics, Emory University School of Medicine, 2015 Uppergate Drive Northeast, ECC Room 324, Atlanta, GA 30345, USA
E-mail address: heidi.karpen@emory.edu

Clin Perinatol ■ (2017) ■–■
https://doi.org/10.1016/j.clp.2017.11.005
perinatology.theclinics.com

concentration gradient importing calcium via a transcellular, active transport process.[2] This influx of calcium to the fetus is preserved even in circumstances of low mineral concentrations in the maternal circulation caused by severe dietary restriction, vitamin D deficiency, or in more serious conditions, such as combined thyroid/parathyroidectomy or loss of the vitamin D receptor.[3] Animal studies have shown that these high calcium levels are not necessary for survival of the fetus to term but that bones will be undermineralized at birth.[1]

Most (>99%) of the total body calcium stores are associated with hydroxyapatite or other components of collagen and bone matrix or in a noncrystalline calcium phosphate form, whereas less than 1% of the stores are contained in the extracellular fluid (ECF) and soft tissues. Calcium that exists at the edge of the bone mineral crystals is available for exchange with this ECF pool, serving as a ready reservoir for available free calcium.[4] Plasma calcium exists in 3 major forms:

- Free calcium ion (Ca^{2+}) accounts for approximately 50% of the serum calcium pool.
- Calcium is bound to plasma proteins, most of which is albumin, and totals approximately 40% of this pool.
- Diffusible complexes, such as bicarbonate, phosphate, or citrate, account for only approximately 10%.

As the only physiologically active form of calcium in the blood, ionized calcium is integral for many critical cellular functions and is, thus, under tight hormonal regulation, particularly by parathyroid hormone (PTH). It is also subject to acute changes due to blood pH, which decreases protein binding, and the serum albumin concentration, which can affect both the total and ionized calcium levels. Although there is a general correlation between total and ionized calcium levels, this correlation is often poor in neonates. Ca^{2+} balance is maintained via uptake from the intestinal tract, excretion and reabsorption at the kidney, and flux into and out of the bones.

At the time of birth, there is an acute disruption of the maternal-fetal calcium supply. In the absence of an exogenous source of calcium, the infant must increase the flux from bone to the ECF space in order maintain calcium homeostasis and normal serum calcium levels. Calcium levels begin to fall at 2 hours of life and nadir at 24 to 36 hours of age, with more significant declines seen in very-low-birth-weight (VLBW) preterm infants (**Fig. 1**).

The relatively high serum calcium levels in the fetus may also provide protection against neonatal tetany, arrhythmias, and seizures, as these calcium levels decline in the first 48 hours after birth. The deeper nadir seen in preterm infants may be due to gestational unresponsiveness of the parathyroid gland or to uncorrected hypomagnesemia, although hypomagnesemia is not usually associated with tetany or cardiovascular compromise. Interestingly, although serum calcium concentrations at birth are unaffected by sex, race, or weight for gestational age,[5] serum calcium does seem to be affected by mode of delivery (lower for elective caesarean delivery without labor than with labor or for vaginal delivery) and season of birth (lower in summer births than winter births).[6]

Phosphorus

The total body phosphorus in term newborns is approximately 16 g, distributed in a wide array of tissues. In addition to being a primary component of bone, phosphorus plays a major role in almost all metabolic processes through its association with nucleotides in DNA, energy-containing units, such as adenosine-triphosphate, lipid