Selected Macro/Micronutrient Needs of the Routine Preterm Infant

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Requirements for optimal nutrition, especially for micronutrients, are not well defined for premature infants. The "reference fetus," developed by Ziegler et al,[1] has served as a model to define nutritional needs and studies designed to determine nutrient requirements. Revision of nutrient requirements and provision of optimal nutrition may lead to improved outcomes in preterm infants. Appropriate provision of nutrients also may help prevent nutritional disorders, such as metabolic bone disease and anemia. In this review, we discuss calcium, phosphorus, magnesium, vitamin D, iron, and copper, and define optimal intakes based on the available published data. *(J Pediatr 2013;162:S48-55)*.

Optimal micronutrient requirements for preterm infants are not well defined. Increasing numbers of these infants survive after birth at progressively lower gestational ages. It is important to define micronutrient needs and provide appropriate amounts of these nutrients to prevent nutritional disorders, such as metabolic bone disease and neonatal anemias. In this article we review current data from preterm infants and recommend the micronutrient intake necessary to meet the estimated requirements for calcium, phosphorus, magnesium, vitamin D, copper, and iron.

Calcium and phosphorus homeostasis and formation of bone matrix are complex processes that require an adequate supply of protein and energy, as well as calcium, phosphorus, magnesium, and vitamin D. Vitamin D is important for bone mineralization, supports physiological processes that affect neuromuscular and immune functions, and plays a role in the heart, lung, pancreas, and brain. Iron is the oxygen-binding moiety of hemoglobin and myoglobin, which are essential for oxygen transport. It is also a cofactor for cytochrome C and other enzymes, which are necessary for cellular energy metabolism. Iron is critically important for normal brain development, including myelin formation and neurotransmitter synthesis. Zinc is essential for multiple enzymes involved in gene expression, signal transduction, apoptosis, cellular proliferation, differentiation, and growth. Copper is essential for enzymes in the electron transport chain and the antioxidant systems; anemia, neutropenia, and osteoporosis may result from copper deficiency.

Background: Calcium, Phosphorous, Magnesium, and Vitamin D

Physiology of Mineral Accretion and Bone Formation

The majority of fetal mineral accretion occurs during the third trimester.[1] Peak calcium accretion rate, typically 120-160 mg/kg/day (3-4 mmol/kg/day) in late gestation, is maintained through active transplacental calcium influx. Parathyroid hormone (PTH), PTH-related peptide, and 25-hydroxy vitamin D [25(OH)D] play important roles in the transplacental transport of calcium and bone remodeling.[2] After birth, dramatic physiological changes in bone metabolism result from disruption of the maternal mineral supply, stimulation of calciotropic hormone secretion, changes in the hormonal environment, and a relative reduction in mechanical stress. These events stimulate the remodeling process, leading to increased bone resorption and decreased bone density.[3]

Calcium, Phosphorus, and Magnesium Intake

Low birth weight (LBW) infants, either preterm or infants with intrauterine growth restriction, have significantly lower calcium and phosphorus stores compared with infants who are born at term and appropriate for gestational age. This might be the result of low total body mineral content at birth, which is subsequently worsened by a suboptimal postnatal dietary calcium supply, transient hypoparathyroidism, lack of mechanical stimulation, and the use of diuretics and other calciuric drugs.

Estimated daily enteral calcium and phosphorus requirements in preterm infants are 120-230 and 60-140 mg/kg/day, respectively. These values may be overestimates, however, because the unique postnatal environment of preterm infants might modify their mineral needs. Bone accretion in early infancy is not likely to occur at rates observed during the third trimester in utero. Furthermore, bone remodeling increases after birth, and released minerals become available to the pool of precursors necessary for early postnatal bone growth and turnover. Recent studies suggest that calcium retention in the range

25(OH)D	25-hydroxy vitamin D
ELBW	Extremely low birth weight
LBW	Low birth weight
PTH	Parathyroid hormone
VLBW	Very low birth weight

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of 60-90 mg/kg/day ensures appropriate bone mineralization in very low birth weight (VLBW) infants.[4] An enteral intake of 120-140 mg/kg/day will support this level of calcium retention, given an estimated absorption rate of 50%-65%.

Phosphorus accretion is linked to calcium and nitrogen retention. Phosphorus absorption is efficient (up to 90%) in infants fed either human milk or formula. If calcium retention is 60-90 mg/kg/day and nitrogen retention is 350-450 mg/kg/day, then phosphorus intake sufficient to meet accretion by bone and soft tissues can be achieved by an intake of 65-90 mg/kg/day of a highly absorbable phosphate source, and the resultant calcium:phosphorus would be 1.5-2.0:1. Similar to calcium, magnesium has a high accretion rate in utero during the third trimester. Thus, preterm infants have a higher magnesium requirement than term infant, estimated as 8-15 mg/kg/day.

Requirement for Vitamin D

The ideal definition of optimal vitamin D levels would be based on functional biomarkers, such as intestinal calcium absorption, extent of bone mineralization, and PTH concentrations. Recent studies based on adult vitamin D physiology indicate that a serum 25(OH)D concentration <50 nmol/L is consistent with vitamin D deficiency, and a concentration 50-80 nmol/L is consistent with vitamin D insufficiency. 25(OH)D concentrations >80 nmol/L are considered sufficient. However, because no similar studies in preterm infants are currently available, values from adult and pediatric populations are extrapolated to neonates.

Low vitamin D level is not uncommon in neonates fed either breast milk or infant formula. Preterm neonates are at particular risk for metabolic bone disease, for reasons that include: difficulty achieving adequate enteral intake of calcium, phosphorus, and vitamin D; relative immobility; dependence on total parenteral nutrition; use of unfortified human milk; and adverse effects of medications (ie, diuretics and steroids) administered during hospitalization. Metabolic bone disease may be present in >50% of extremely low birth weight (ELBW) infants and in up to 25% of VLBW infants.

Impact of Vitamin D Supplementation in Preterm and Term Infants

Total and free 25(OH)D concentrations in cord blood of preterm and full-term neonates are lower than those in maternal blood. Early supplementation with vitamin D has been studied in neonates. Salle et al[5] evaluated 25(OH)D levels in 17 preterm infants who received 1000 IU of vitamin D daily from birth. Mean levels increased from 20 nmol/L (range, 10-40 nmol/L) at birth to 92 nmol/L (range, 71-116 nmol/L) at 6 months. This dosage is sufficient to raise vitamin D levels to the desired range when administered for 6 months. Whether this leads to any functional benefits is unclear, however. Several other clinical studies have evaluated the relationship between vitamin D3 intake and 25(OH)D concentrations.[6-12] These findings support the consensus opinion that a vitamin D intake of 800-1500 IU/day is necessary to increase 25(OH)D concentrations to above 75 nmol/L in preterm infants of mothers with vitamin D deficiency. At best, 400 IU/day of vitamin D—the amount recommended for term infants—is provided in some US neonatal intensive care units.[13] It is likely that an intake far lower than this is currently provided, given that clear criteria for vitamin D sufficiency in preterm infants have not yet been established.

Evidence from Randomized Controlled Trials

A randomized controlled trial investigating the effect of vitamin D supplementation on bone density and biochemical indices in preterm infants has demonstrated that doses of 200-400 IU/kg body weight/day is sufficient to maintain normal vitamin D status.[14] However, a more recent trial that compared 3 doses (200, 400, or 800 IU/kg/day) led the authors to conclude that higher doses might accelerate bone turnover.[15] Although vitamin D provides clear short-term benefits to preterm infants, the benefits of increased vitamin D intake on bone mineral status in preterm-born children are no longer evident at age 9-11 years.[16]

Factors Affecting Enteral Absorption of Calcium and Phosphorus

Intestinal absorption of calcium and bone accretion are affected by numerous factors. Calcium phosphate has low solubility compared with calcium chloride, citrate, and carbonate. Organic calcium salts, such as calcium gluconate and glycerophosphate, are more soluble and readily absorbed. A high palmitate content in fat reduces calcium absorption, secondary to the formation of insoluble calcium soaps.

Supplementation of human milk with phosphorus improves calcium retention and reduces calciuria in infants. Human milk has an excellent calcium:phosphorus and, thus, high bioavailability; however, it is relatively low in calcium and phosphorus and requires fortification to achieve adequate mineralization in preterm infants. When human milk fortifier is provided with adequate amounts of calcium and phosphorus, calcium retention reaches 60 mg/kg/day. The use of human milk fortifiers containing highly soluble calcium glycerophosphate improves calcium retention by up to 90 mg/kg/day in formula-fed infants, although the percentage of net calcium absorption is less than that seen with human milk. Because the poor bioavailability of preterm formula is compensated for by a higher calcium and phosphorus content, routine mineral supplementation is not required in infants fed preterm infant formula.

The reported effects of vitamin D supplementation on calcium absorption have been inconsistent due to differences in study design. Bronner et al[17] showed that calcium absorption in LBW infants was directly proportional to daily calcium intake and independent of vitamin D supplementation. In contrast, Senterre et al[18] reported that calcium absorption in preterm infants increased from 50% to 71% when human milk was supplemented with 1200 IU/day of vitamin D3 with no additional calcium. This latter result suggests that