Metabolic Bone Disease of Prematurity

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Educational Gaps

1. Clinicians should be aware of current screening guidelines to evaluate bone health in neonates.
2. Clinicians should use biomarkers and imaging modalities appropriately to diagnose and follow patients with metabolic bone disease.

Abstract
Advances in neonatal care have led to increased survival rates in preterm infants. Optimizing postnatal nutrition has been a critical factor for improved growth and outcomes in very low-birth-weight infants. Despite rapid progress in the field, obtaining comparable mineral delivery to fetal rates has been challenging. Metabolic bone disease of prematurity is a multifaceted condition primarily resulting from inadequate mineral supply compounded by chronic illness, an immature digestive system, and hormonal imbalance. The aim of this review is to discuss the pathophysiology, diagnosis, prevention, and treatment of metabolic bone disease.

Objectives
After reviewing this article, readers should be able to:

1. Understand the physiologic mechanisms of underlying bone formation and mineralization.
2. Describe the hormonal and extrinsic factors that regulate skeletal development.
3. Provide an overview of current screening guidelines to evaluate bone health in neonates.
4. Discuss biomarkers and imaging modalities used to diagnose and follow up patients with metabolic bone disease.

Introduction
Metabolic bone disease (MBD), formerly known as rickets or osteopenia of prematurity, has become an increasingly interesting neonatal morbidity. For instance, the American Academy of Pediatrics (AAP) Committee on Nutrition released a report in 2014 that focused on mineral and hormonal balance and its effects on bone health in preterm infants. (1) The current rate of MBD in very low-birth-weight (VLBW) infants is unknown because there is no universal consensus on its definition, yet the literature reports estimates as high as 40%. (2) This condition has been difficult to define because of its silent nature that clinically presents with poor extrauterine growth, increased ventilator dependency, and fractures. (3)(4) In addition, MBD has long-term consequences, including short stature and osteopenia, in young adulthood. (5)(6)(7)(8)

Definitions
MBD is best defined by Calabria et al (9) as a reduction in bone mineral content relative to the expected level of mineralization for an infant of comparable size or gestational age in combination with radiographic and biochemical changes. Bone mineralization is a 2-phase process: (1) osteoblasts form osteoid (organic bone matrix) followed by (2) incorporation

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of minerals (calcium and phosphorus) into newly formed osteoid. Osteomalacia is failure of incorporation of minerals into osteoid. Bone mineral content is a measurement of the amount of minerals in a segment of bone. Bone mineral density is the amount of minerals per square centimeter of bone. Bone mineral density results are reported as T-scores and Z-scores. T-scores are the number of SDs above or below the mean of a healthy adult of the same sex. Z-scores are the number of SDs above or below the mean compared with someone with the same age, sex, weight, and ethnicity. Osteopenia is a defined as a T-score of −1 to −2.5 (at risk for developing osteoporosis). Osteoporosis is defined as a T-score of −2.5 or below.

Pathophysiology

Bone Formation

The ectoderm and mesoderm are the 2 germ layers that give rise to the skeletal system. The ectodermal neural crest cells give rise to the craniofacial bones, whereas the paraxial and lateral plate mesoderm form the axial (head and trunk) and appendicular (limb) skeleton (Figure 1). During the third and fourth weeks of gestation, the paraxial mesoderm organizes into segments and somites. By the fifth week of gestation, the axial skeleton has a rudimentary appearance, and by the second month of gestation, the lateral plate mesoderm begins to branch into limb buds. (10)

Mesenchymal stem cells, derived from mesoderm, dictate the method of bone formation: membranous (osteoblast induced) vs endochondral (chondrocyte induced). Osteoblasts are extensions of mesenchymal stem cells, whereas osteoclasts originate from the hematopoietic cell lineage. Osteoblasts are responsible for building the bone matrix where minerals will embed. Most cells in the bone are osteocytes, or terminally differentiated osteoblasts, that serve as mechanoreceptors. (11) The main function of osteoclasts is to resorb bone under the control of osteoblasts (Figure 2).

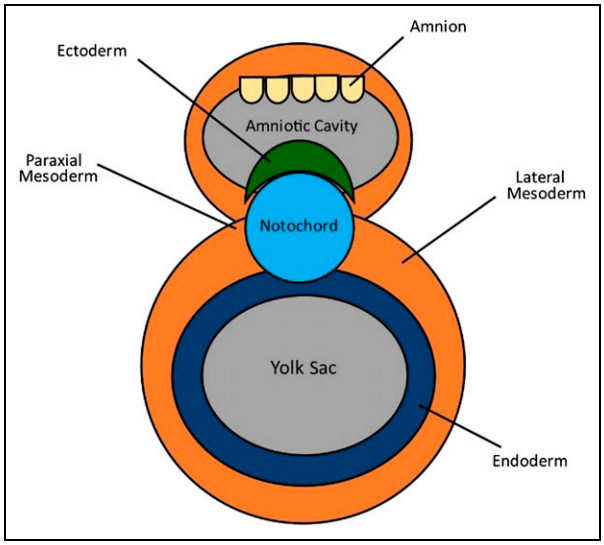

Figure 1. Bone embryology.

Fetal Physiology

Ninety-nine percent of whole-body calcium, 85% of phosphorus, and 65% of magnesium are contained in the skeletal system. (12) During the third trimester, 80% of calcium and phosphorus are actively transferred across the placenta into the fetus and are constant despite maternal nutritional status. Estimated accretion rates approach 120 mg/kg/d of calcium and half that rate for phosphorus between 24 weeks' and term gestation. (12)(13)(14) As a result, preterm infants will not achieve optimal bone mineralization.

In utero, the fetus is in a bone-forming environment with high concentrations of estrogen and calcitonin and low levels of parathyroid hormone (PTH). (15) Calcium transport across the placenta is an energy-dependent process that relies on PTH-related protein, the placental conversion of vitamin D to its active form, and PTH. On the other hand, phosphorus transport has not been clearly defined, but most experts believe PTH is an important mediator. (16)

Neonatal Physiology

All newborns experience a hypocalcemic phase shortly after birth. Calcium reaches its nadir 24 to 48 hours after birth due to a reversal of fetal physiologic mechanisms: low estrogen and calcitonin production and elevated PTH secretion. (17)

Risk Factors for MBD

Prenatal

Inadequate maternal vascular supply of nutrients to the fetus results in poor intrauterine weight gain. (18)(19) Likewise, measurements of fetal weight gain have been correlated with fetal mineral accrual. (5)(20) Therefore, any condition that affects placental sufficiency, such as hypertension, diabetes, anemia, smoking, or cocaine exposure, can negatively affect bone growth.

Postnatal

Prematurity is the greatest risk factor for MBD because most calcium and phosphorus deposition occurs during the third trimester. Although human milk is considered the best nutritional diet for a preterm infant, it has limited concentrations of calcium and phosphorus, approximately one-fifth the amount included in specialized preterm formulas. (21)(22) In addition to decreased mineral amounts

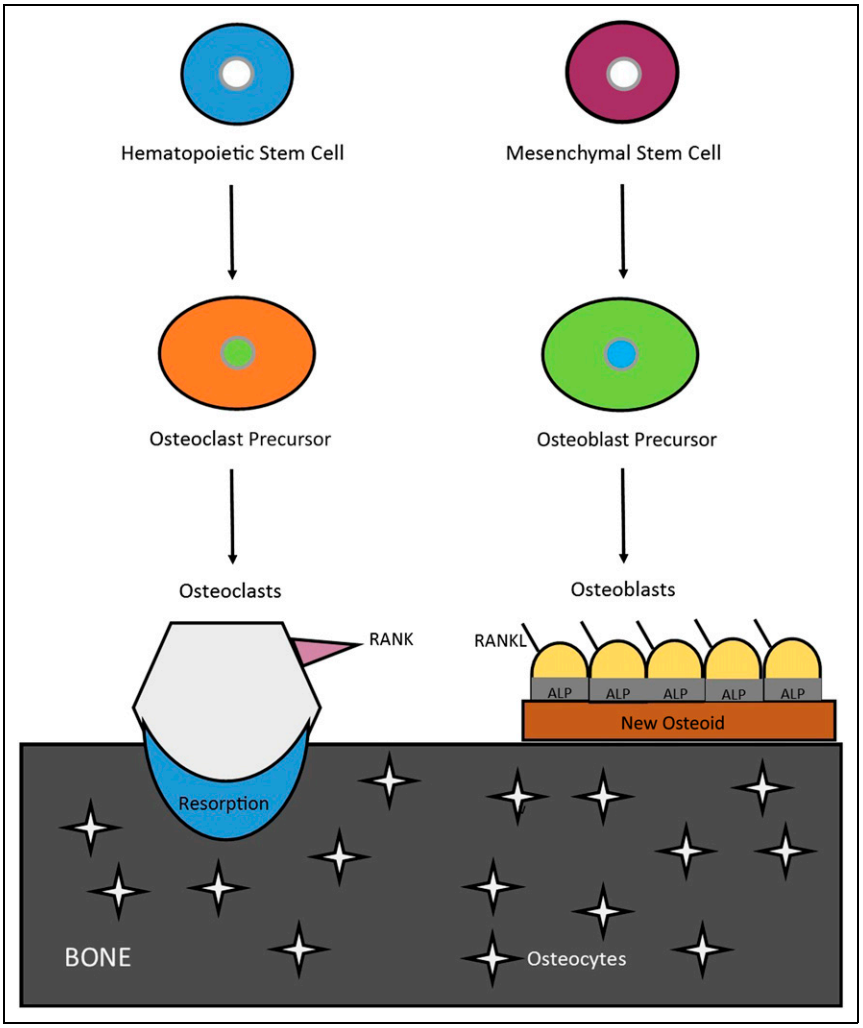

Figure 2. Origin of bone cells.
RANK = receptor activator of nuclear factor κB; RANKL = receptor activator of nuclear factor κB ligand.

Bone as a Metabolic Organ

The skeletal system has many roles in the body, including mineral homeostasis, acid-base buffer, detoxification, hematopoiesis, and energy storage. In mineral homeostasis, mobilization of calcium, magnesium, and phosphorus to maintain mineral balance is a priority, even if it is at the cost of losing bone integrity. Therefore, preterm infants with an already weakened skeletal system will mobilize minerals into the blood and consequently lose more bone strength. (28) Through its release of calcium and phosphorus, bone buffers acidic environments into sodium bicarbonate, calcium carbonate, and dicalcium phosphate. As a result, chronic acidosis is a risk factor for MBD. (29) Bone tissue is able to remove toxic metals from the bloodstream (ie, aluminum in parenteral nutrition). Most infants have red marrow that produces red blood cells, platelets, lymphocytes, granulocytes, and monocytes. Throughout life adipocytes are stored in yellow marrow.

Hormones That Regulate Bone Mineralization

The regulation of mineral metabolism takes place in 3 major organs: bone, kidney, and intestine. The regulation is under the control of 3 hormones: PTH, vitamin D, and calcitonin

in unfortified human milk, the digestive system of preterm neonates has poor absorptive properties.

Because of solubility issues, parenteral nutrition is unable to provide comparable in utero rates of calcium and phosphorus. Lack of physical activity and the loss of mechanical stimulation against the uterine muscle also hinder bone strength and development. (23)(24) Infants with medical conditions, such as bronchopulmonary dysplasia, are treated with osteolytic medications: methylxanthines, diuretics, and glucocorticoids. (25)(26) Likewise, infants with necrotizing enterocolitis and/or short bowel syndrome require prolonged parenteral nutrition, need sedation, and have difficulty absorbing calcium and phosphorus. (27)

PTH

PTH is an 84–amino acid peptide that is released by the parathyroid glands in response to serum calcium. (29) Parathyroid glands contain calcium-sensing receptors that trigger PTH secretion when extracellular calcium decreases. PTH has a half-life of approximately 5 minutes, 20% is found in its intact form in the blood, and the active portion is the 34-N terminal amino acids. (30) PTH stimulates bone resorption through stimulation of the PTH receptor on osteoblasts. (31) On binding to the osteoblast, there is an upregulation of the receptor activator of nuclear factor κB ligand (RANKL). Osteoclast proliferation, and subsequent resorption of bone, occurs when its membranous RANK binds to RANKL on osteoblasts. (11)(31)

PTH increases calcium reabsorption in the distal convoluting tubule of the kidney and inhibits phosphorus reabsorption in the proximal nephron. This hormone also increases calcium and phosphorus reabsorption in the digestive system via activation of vitamin D in the kidney (Figure 3). (32)

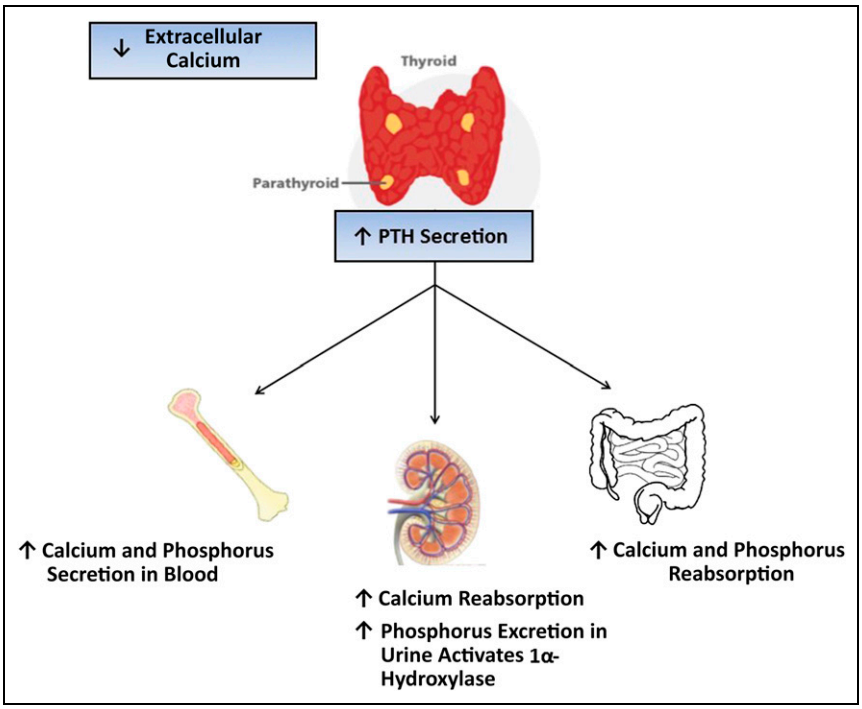

Figure 3. Parathyroid hormone (PTH) effects on bone minerals.

Vitamin D

Vitamin D is a fat soluble secosteroid hormone that is present in 2 forms: D_3 (cholecalciferol) and D_2 (ergocalciferol). (15)(33) Most vitamin D_3 is produced in the skin from exposure to sunlight in the 300-nm range (UV-B). Vitamin D_2 is predominantly obtained in the diet from plant sources (ergosterol). Vitamin D_3 and D_2 are not biologically active until they undergo enzymatic digestion in the liver and kidney. In the liver, 25-hydroxylase converts vitamin D to 25-hydroxyvitamin D (25[OH]D_3 or calcidiol), which is the primary form of vitamin D in the blood. Then in the kidney, 1α-hydroxylase converts calcidiol to the biologically active calcitriol (1,25[OH]$_2D_3$). Even though calcitriol is the most active form of vitamin D, the best indicator of vitamin D status is 25(OH)D_3 because its half-life is longer (15 days vs 15 hours). (34)(35)(36)

Vitamin D increases calcium and phosphorus absorption in the duodenum and jejunum of the intestinal tract. PTH increases 1α-hydroxylase in the kidney, producing more calcitriol with subsequent increased reabsorption of calcium and phosphorus in the gut (Figure 4).

Calcitonin

Calcitonin is a 32–amino acid peptide that inhibits bone resorption. It is produced in the parafollicular cells of the thyroid and is stimulated by an increase in calcium. (37) This hormone counters the effects of PTH by inhibiting osteoclast activity in bone, inhibiting calcium reabsorption in the intestine and in the kidneys. Similar to PTH, it has a phosphaturic effect.

Biomarkers

The 2 most commonly used biomarkers to assess bone mineralization are phosphorus and alkaline phosphatase (ALP). (38) Backström et al (39) evaluated serum ALP and phosphorus levels in preterm infants and correlated their values with dual energy x-ray absorptiometry (DEXA) at a corrected age of 3 months. A combination of phosphorus less than 4.6 mg/dL (<1.49 mmol/L) and ALP greater than 900 IU/L (>15.0 μkat/L) yielded a sensitivity of 100% and a specificity of 70% for low bone mineral density. Phosphate deficiency is considered the earliest manifestation of poor bone mineralization, and measurement of the tubular reabsorption of phosphate (TRP) [1-[(urine phosphorus × serum creatinine)/(serum phosphorus × urine creatinine)]] × 100 in this setting would be greater than 95%. (9)

ALP production is found in the kidney, intestine, placenta, bone, and liver. Total ALP, or tissue nonspecific ALP, is the marker generally used by most laboratories and for the most part is composed of the bone isoform of ALP. It is a marker of bone turnover and is found on the membrane of osteoblasts (Figure 2). (38) In preterm infants, ALP levels continuously increase during the first month after birth as the preterm skeleton is trying to support bone mineralization. Although ALP is routinely used to evaluate bone health status and has been strongly correlated with phosphorus deficiency, its use as a sole biomarker has had conflicting outcomes when compared with bone mineral content and density. (38)

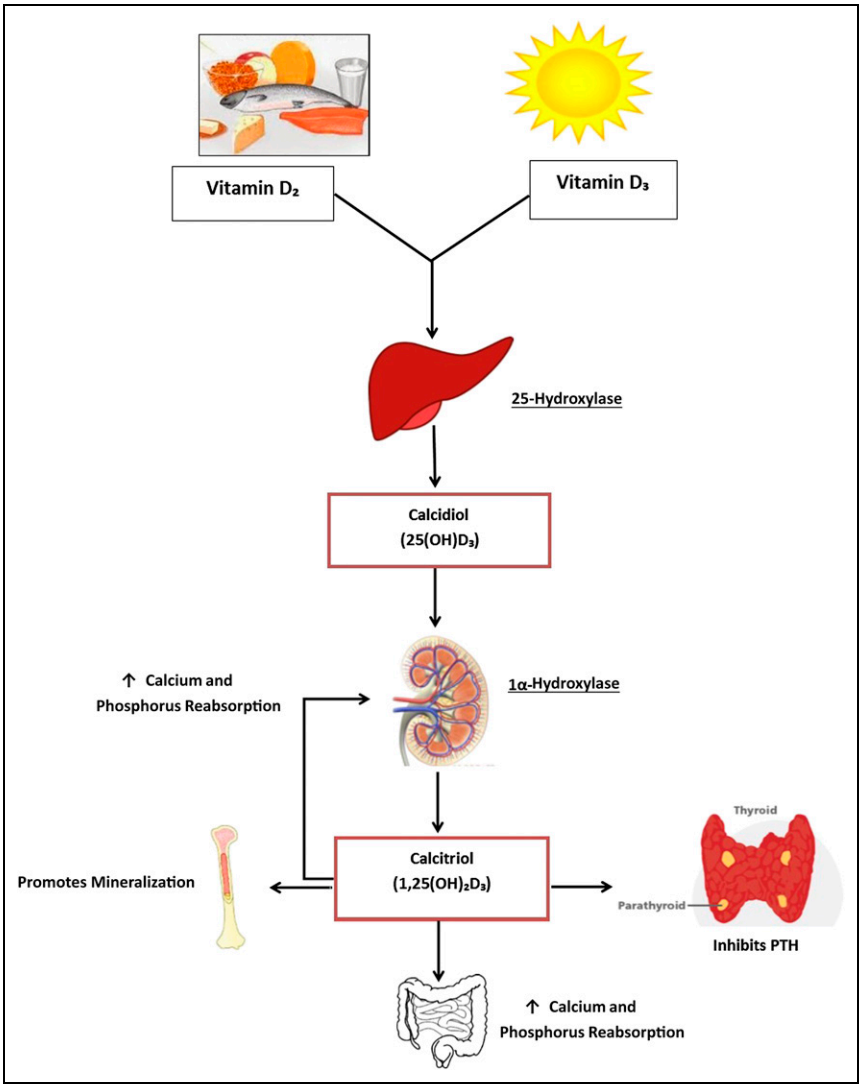

Figure 4. Vitamin D effects on bone minerals.
PTH = parathyroid hormone.

Serum calcium levels are typically normal in infants with MBD because of the rapid response of the calcium-sensing receptors in the parathyroid glands. Preterm infants with a chronic depletion of calcium (glucocorticoid, diuretic, and methylxanthine use) may develop secondary hyperparathyroidism. These patients would also have hypophosphatemia but a low TRP. Therefore, serum calcium is not a sensitive marker in screening for MBD.

There has been recent interest in PTH and $25(OH)D_3$ as supplementary markers used to assess bone health status. (34)(40) The AAP released a statement advising a target calcidiol level of greater than 20 ng/mL. (1) Nevertheless, Mimouni et al (41) found that $25(OH)D_3$ levels in infants was frequently normal in infants with MBD. In a prospective study, VLBW infants with PTH levels greater than 180 pg/mL (>180 ng/L) at age 3 weeks had a high risk of severe MBD diagnosed on radiography. (42) Lack of robust reference values for PTH in preterm infants makes interpretation of results challenging. In addition, emerging studies on PTH and vitamin D as biomarkers for MBD need to be corroborated with quantitative ultrasonography and/or DEXA imaging. Osteocalcin, procollagen peptide, and cross-linked collagen are other markers of bone formation and resorption but are currently used for investigational purposes only.

Imaging

Multiple imaging modalities have been proposed for assessing bone health in preterm infants. Each technique offers differing advantages and disadvantages.

Radiography

Experts recommend radiography of the wrist and/or knee because these regions are of high metabolic activity. Unfortunately, bone demineralization may not be easily apparent in this imaging technique until at least 20% of bone loss has occurred. Koo et al (17) developed the following scheme for assessing severity:

- Normal: normal density with white line at metaphyseal region;
- Grade 1: loss of dense white line at metaphyses, thinning of cortex;
- Grade 2: loss of dense white line at metaphyses, thinning of cortex, irregular frayed or cupping to metaphyses; and
- Grade 3: bone changes seen in grade 1 and grade 2 in addition to fracture (Figure 5).

Clinically, this classification is useful and easy to perform, but it has not been validated with absorptiometry and exposes neonates to radiation.

Quantitative Ultrasonography

Quantitative ultrasonography (QUS) is an emerging noninvasive technique that is routinely used in adults and

now gaining acceptance in the pediatric population. (43)(44) Advantages of QUS include portability, simplicity, low cost, and lack of radiation. (45)(46) Reference intervals for preterm infants are available and directly correlate with gestational age. Most centers use QUS for investigative purposes to measure tibial speed of sound, bone transmission time, or broadband ultrasonographic attenuation. These measures indicate qualitative and quantitative properties of bone. Drawbacks to QUS are small window of variation of results (approximately 2,800 m/s in extremely preterm infants vs 3,100 m/s in term infants), and additional studies are needed to compare QUS and DEXA in preterm infants.

Quantitative Computed Tomography

Quantitative computed tomography offers a 3-dimensional assessment of bone and the ability to separate cortical from trabecular bone. Radiation dose has been decreased with the use of peripheral quantitative computed tomography, but both these techniques are not widely used in neonates because of transport needs of the patient out of the unit.

DEXA

DEXA is considered the gold standard for assessing bone mineralization and fragility. DEXA focuses on a region of skeletal interest and yields bone mineral content and density. Normative data and guidelines for use in infants are lacking, making DEXA interpretation challenging. Disadvantages also include expense, radiation, and possible need for sedation. Unlike in adults, the Z-score (not the T-score) is the variable used to assess bone health in children. (47)

Screening Guide and Follow-up

Even with the AAP guidelines for screening, prevention, and treatment of MBD, clinical practice in the United States and United Kingdom are wide-ranging. (48)(49) A summary of suggested MBD screening is outlined in Table 1.

Prevention and Treatment

Different pediatric societies have provided daily recommendations for enteral calcium and phosphorus needs in preterm infants (Table 2). It has been universally accepted that premature neonates should be fed fortified human milk or preterm formula to optimize bone mineralization. It is imperative to closely monitor calcium and phosphorus levels in VLBW infants coupled with periodic calculation of these minerals from all sources. Minimal use of osteolytic medications is also beneficial in the

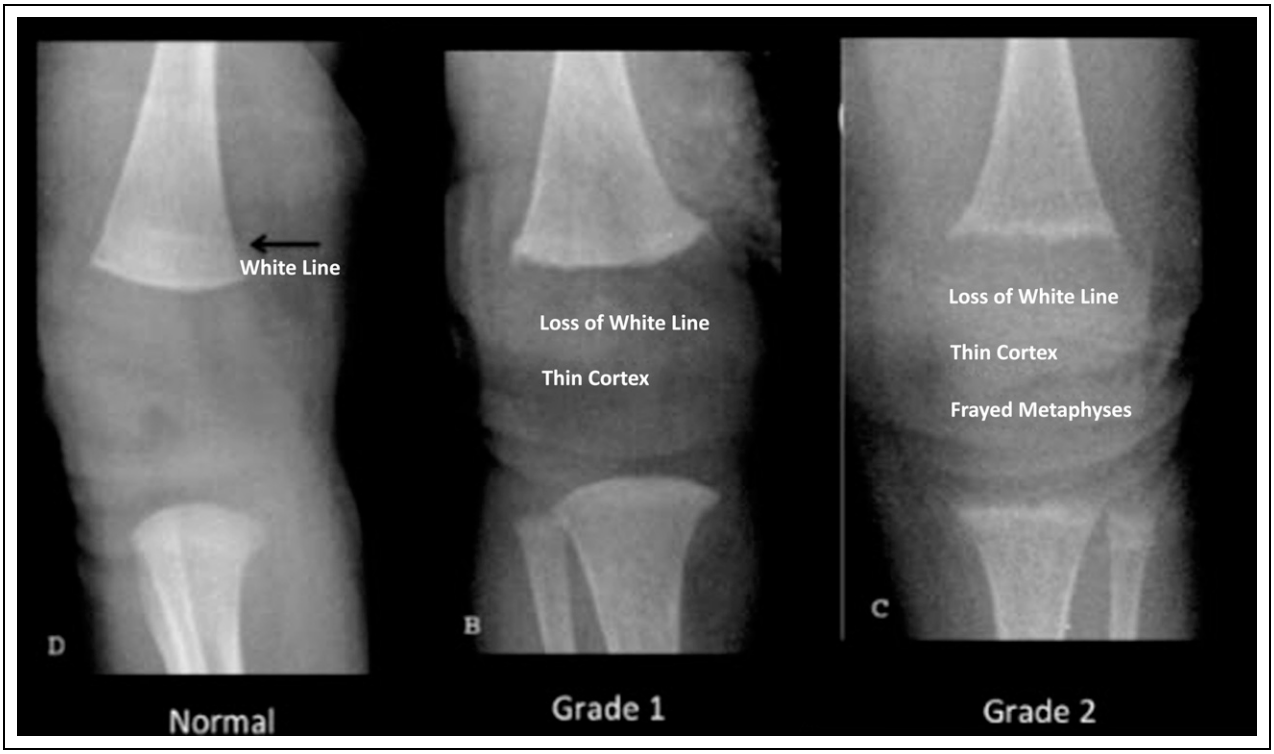

Figure 5. Knee radiographs.

Table 1. **Screening Recommendations**

Category	Abrams (1)	Mitchell et al (50)	Harrison et al (48)	Rustico et al (9)
Target	<1,500 g	600–1,000 g	1. <1,500 g 2. <28 weeks 3. TPN >4 weeks 4. Diuretic or steroid therapy	1. <1,500 g 2. <28 weeks 3. TPN >4 weeks 4. Unable to reach full fortified feed 5. Use of bone active medications
Biomarkers and recommendations	1. ALP >800–1,000 IU/L→ radiographic evaluation	1. ALP every 1–2 weeks	1. Weekly calcium, phosphorus, ALP	1. Screen with calcium, phorphorus, ALP, TRP at 4–6 weeks of age
	2. Phosphorus <4.0 mg/dL→ supplementation for persistent hypophosphatemia	2. ALP <1,000 IU/L and no clinical suspicion for MBD→ monitor ALP until <500 IU/L	2. If phosphorus <5.6 mg/dl and ALP >500 IU/L→ check TRP	2. Normal results, then continue to monitor
	3. Vitamin D supplementation of approximately 400 IU/L when >1,500 g	3. ALP >1,000 IU/L and clinical suspicion of MBD, fracture, TPN >3–4 weeks, or ALP >800 IU/L on 2 occasions→ perform knee/wrist radiography	3. If TRP >95% → start phosphorous supplementation	3. Abnormal results at 4–6 weeks→ consider radiography, PTH, and calcidiol levels
	4. If exclusive breastfeeding obtain ALP 2–4 weeks after discharge		4. If no increase in phosphorus and ALP continues to rise→ start ergocalciferol or calcidiol	4. If requires calcium and/or phosphorus supplementation → monitor calcium, ALP, TRP, and PTH every 1–2 weeks
			5. Encourage daily passive exercises	5. Monitor urine calcium-creatinine ratio if receiving calcium supplements or calcitriol therapy

ALP=alkaline phosphatase; PTH=parathyroid hormone; TPN=total parenteral nutrition; TRP=tubular reabsorption of phosphate.

prevention of developing MBD. Physical activity and passive massage have improved biomarkers of bone formation.

The AAP recommends 150 to 220 mg/kg/d of enteral calcium, 75 to 140 mg/kg/d of phosphorus, and 200 to 400 IU/d of vitamin D. (1) Early and higher amino acid intakes in VLBW infants improve growth; however, recent studies have found that these practices create imbalances in minerals during the first week after birth (hypophosphatemia, hypercalcemia).

Calcium and Phosphorus Supplementation

There are multiple options for calcium and phosphorus supplementation, and this supplementation should be customized for each patient. Infants with a high TRP levels, low to normal PTH levels, and hypophosphatemia will benefit from phosphorus supplementation. In turn, neonates with hypophosphatemia, low TRP levels, and high PTH levels have a chronic calcium deficiency and would gain bone mineralization with calcium supplementation. Calcium gluconate and sodium or potassium phosphate are suitable choices for infants who require intravenous administration. (56)(57) Enteral forms include calcium carbonate and potassium or sodium phosphate, as well as the compound calcium tribasic phosphate. Most experts recommend starting at a dose of 10 to 20 mg/kg/d of enteral or parenteral calcium and phosphate, with an

Table 2. **Enteral Recommendations**

Source	Calcium, mg/kg/d	Phosphorus, mg/kg/d	Vitamin D, IU/d
Abrams (1)	150–220	75–140	400
ESPGHAN (51)	70–140	50–90	800–1,600
LSRO (51)	150–220	100–130	135–340
CPS (52)	160–240	80–120	400–800
Tsang (53)	100–220	60–140	150–400
Rigo et al (35)	100–160	60–90	800–1,000
Atkinson (54)	120–200	60–140	200–1,000
Agostoni et al (55)	120–140	65–90	800–1,000
Mimouni et al (41)	120–200	60–140	400–1,000

CPS=Canadian Pediatric Society; ESPGHAN=European Society for Paediatric Gastroenterology, Hepatology and Nutrition; LSRO=Life Sciences Research Organization.

ideal calcium-phosphorus ratio of 1.5:2.0. Serum and urine electrolytes should be monitored frequently while the patient is receiving supplementation.

Conclusion

In summary, bone tissue is an important organ that supports multiple body functions. Preterm infants are at risk for developing metabolic bone disease secondary to chronic illnesses, poor nutrition, decreased movement, and long-term use of diuretics and glucocorticoids. MBD has long-term complications that may affect bone health in adulthood. Recommendations to prevent MBD include fortification of nutrition, monitoring of the disease, and early supplementation of minerals and vitamin D. There is a need to continue to explore best practices to reduce long-standing skeletal sequelae.

American Board of Pediatrics Neonatal–Perinatal Content Specifications

- Know normal calcium, phosphorus, and magnesium metabolism during the prenatal and postnatal periods, including fetal accretion rates.
- Know the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate.
- Know the etiology, clinical manifestations, radiographic features, and approach to treatment of osteopenia of prematurity.

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NeoReviews Quiz Requirements

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1. A mother delivers a female infant prematurely at 28 weeks' gestational age. Which of the following statements regarding factors related to bone formation during the fetal and neonatal stages is correct?
   A. Ninety-nine percent of whole-body calcium is contained in the skeletal system.
   B. During the second trimester, 80% of calcium and phosphorus are actively transferred across the placenta into the fetus.
   C. In utero, the fetus is in an environment of low calcitonin and high parathyroid hormone.
   D. The transfer of phosphorus across the placenta into the fetus in the third trimester is heavily dependent on maternal nutritional status.
   E. The estimated accretion rate of both calcium and phosphorus from 24 weeks' gestational age to term in utero is 250 to 500 mg/kg/d.

2. The neonate is admitted to the neonatal intensive care unit (NICU) and soon after is administered parenteral nutrition. The mother starts to obtain expressed breast milk. Which of the following risk factors for metabolic bone disease is correctly described?
   A. Parenteral nutrition is able to provide adequate amounts of calcium, providing rates similar to in utero rates but suboptimal amounts of phosphorus.
   B. Although human milk is considered the best nutritional diet for preterm infants, it contains approximately one-fifth the amount of calcium and phosphorus as that of specialized preterm infant formulas.
   C. Bundling and movement restriction with minimal stimulation during the first month are preventive measures for bone disease because excessive movement after preterm birth can hinder bone strength.
   D. Chronic alkalosis is a strong risk for metabolic bone disease because it causes release of calcium and phosphorus from bone tissue.
   E. Excessive vitamin D provided in parenteral nutrition or formula can cause decreased absorption of calcium and phosphorus in the small intestine.

3. The infant receives routine nutritional laboratory testing to monitor nutrition and bone health status. Which of the following statements correctly describes the biomarkers used for bone disease?
   A. Phosphate deficiency only occurs relatively late in the disease process for metabolic bone disease.
   B. In preterm infants, alkaline phosphatase levels gradually decrease during the first month, and any rise in levels during that time is a 100% sensitive marker for metabolic bone disease.
   C. Serum calcium levels are typically normal in infants with metabolic bone disease.
   D. Alkaline phosphatase is only found in bone tissue on the membrane of osteoclasts and therefore is a useful sole biomarker for bone mineralization.
   E. Low parathyroid levels at age 3 weeks are highly correlated with radiographic findings consistent with metabolic bone disease.

4. The neonate has laboratory findings that lead to concerns that there may be high risk of metabolic bone disease. Which of the following statements regarding imaging modalities to assess bone health in preterm neonates is correct?
   A. Radiography of the wrist and knee can assess bone health, but bone demineralization may not be easily apparent until at least 20% of bone loss has occurred.
   B. Grade 2 bone disease is classified when a fracture is noted in addition to thinning cortex and loss of dense white line at metaphyses.

C. Quantitative computed tomography is an inexpensive modality that can be used for preterm infants, but it is not able to separate cortical from trabecular bone.
D. Quantitative ultrasonography is useful to track bone health due to the very broad range of tibial speed of sound measurements that are 10 times higher in term infants compared with preterm infants.
E. The T-score is the measure assessed when bone health is assessed using dual energy x-ray absorptiometry for infants.

5. A multidisciplinary team at your hospital is reviewing measures to prevent and treat metabolic bone disease for preterm infants in the NICU. Which of the following statements regarding current recommendations is correct?
   A. The American Academy of Pediatrics recommends 350 to 500 mg/kg/d of enteral calcium nutrition.
   B. Infants with high tubular reabsorption of phosphate, low to normal parathyroid hormone levels, and hypophosphatemia will benefit from phosphorus supplementation.
   C. An ideal ratio of calcium to phosphorus is 2.5 to 5.0 for preterm infants who require supplementation.
   D. Early and higher amino acids provided through parenteral nutrition usually cause hyperphosphatemia and hypocalcemia during the first week after birth.
   E. Neonates with hypophosphatemia and low tubular reabsorption of phosphate, with high parathyroid hormone levels, have excessive calcium intake.