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Review

Metabolic bone disease of prematurity☆

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ABSTRACT

Metabolic bone disease (MBD) of prematurity remains a significant problem for preterm, chronically ill neonates. The definition and recommendations for screening and treatment of MBD vary in the literature. A recent American Academy of Pediatrics Consensus Statement may help close the gap in institutional variation, but evidence based practice guidelines remain obscure due to lack of normative data and clinical trials for preterm infants. This review highlights mineral homeostasis physiology, current recommendations in screening and monitoring, prevention and treatment strategies, and an added perspective of a bone health team serving a high volume referral neonatal intensive care center.

Background/definition

Despite notable nutritional and medical improvements, metabolic bone disease (MBD) of prematurity remains a significant comorbidity in preterm, low birth weight, and chronically ill neonates. MBD has been estimated to occur in 16–40% of very low birth weight (VLBW, <1500 g) and extremely low birth weight (ELBW, <1000 g) infants [1,2]. The exact incidence remains unknown, in part from a lack of consensus on the definition of MBD (also known as osteopenia or rickets of prematurity). We define MBD as decreased bone mineral content relative to the expected level of mineralization for a fetus or infant of comparable size or gestational age seen in conjunction with biochemical and/or radiographic changes (Figure 1). Most commonly, MBD occurs as a result of inadequate calcium and phosphorus stores exacerbated by inadequate intake and the high degree of skeletal growth occurring in the weeks following birth [3]. The etiology of MBD is multifactorial with numerous associated risk factors, including but not limited to the degree of prematurity, low birth weight, exposure to medications that can alter mineral levels, immobilization, long term parenteral nutrition, and delayed establishment of full feeds. MBD typically presents within 6–16 weeks after birth [1]. As MBD advances, biochemical changes intensify. These changes commonly include hypophosphatemia, hyperphosphatasia, and secondary hyperparathyroidism, which may be accompanied by rachitic changes and/or fractures. However, it may go unrecognized as a significant loss of bone mineralization is needed before characteristic changes are visible on radiograph [4]. Inadequate bone mineralization during this period may compromise pulmonary status and contribute to poor growth.

Fetal skeletal development

The fetal skeleton develops early in gestation with the proliferation and differentiation of cartilaginous precursors and progressive ossification. These processes are tightly regulated by hormones [e.g. growth hormone and parathyroid hormone (PTH)], cytokines, and vitamins (A, D, C) [5]. An adequate nutritional and vascular supply is also critical. Indeed, conditions associated with chronic placental damage, such as preeclampsia, intrauterine growth restriction, and chorioamnionitis, are associated with an increased risk of MBD potentially via decreased *in utero* phosphate transport [6].

Abbreviations: MBD, Metabolic bone disease; TRP, Tubular reabsorption of phosphate; PTH, Parathyroid hormone; ALP, Alkaline phosphatase; VLBW, Very low birth weight; ELBW, Extremely low birth weight.

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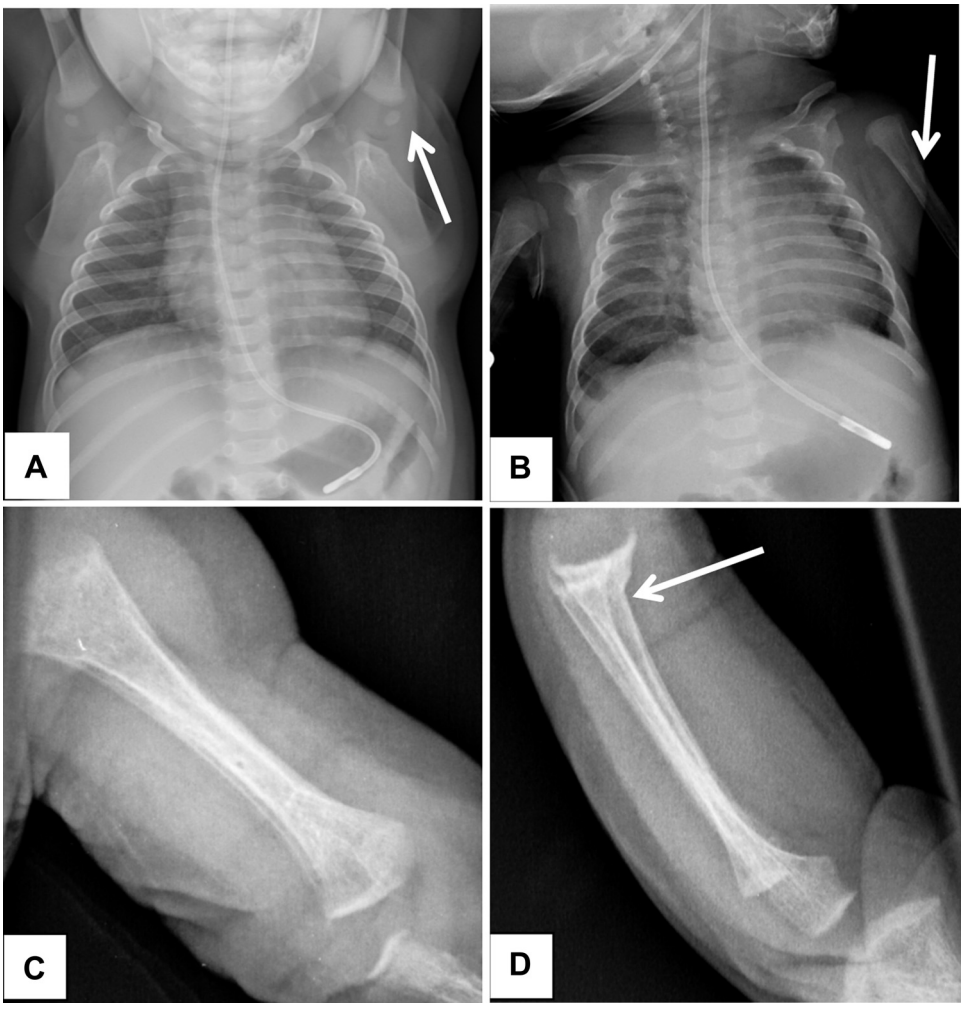

Figure 1. Radiographs – A) Normal mineralization of the proximal humerus in a six month old former full term infant; growth plate formation is shown (arrow), B) Early demineralization in the humerus of a six month old former ELBW preterm infant with periosteal reaction (arrow), C) and D) Severe demineralization with features of rickets including cupping and fraying of metaphyses, healing fracture (arrow), and cortical thinning. Images are courtesy of Dr. Janet Reid, The Children's Hospital of Philadelphia.

Bone mineralization occurs predominantly in the third trimester with calcium and phosphorus being the main minerals required. Levels of both are higher in the fetus due to active transport from mother to fetus. The main regulator of calcium transport appears to be parathyroid hormone-related peptide, though PTH also plays a role. The conversion of 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the active form of vitamin D, from its precursor 25-hydroxyvitamin D [25(OH)D], also promotes calcium flow across the placenta. The mechanisms for phosphorus transfer are less clearly understood though an active transport process mediated in part by PTH is suspected [7]. The end result is that nearly 80% of calcium and phosphorus transfer occurs between the 24th week of gestation and term [8]. Not surprisingly, infants born prematurely often fail to achieve adequate stores of these minerals.

Postnatal mineral homeostasis

Regardless of gestational age and despite continued mineral demand, there is an immediate drop in calcium at birth, with a nadir reached by 24–30 h in preterm infants [9]. PTH levels increase in response to decreased plasma calcium levels. In the kidney, PTH enhances calcium reabsorption while decreasing phosphate reabsorption, leading to urinary phosphate wasting. It also increases the synthesis of $1,25(OH)_2D$, which leads to intestinal calcium and phosphate absorption. In bone, PTH stimulates resorption and subsequent release of calcium and phosphate. Overall, as its actions are greatest in the kidney, the net effects of increased PTH levels are hypercalcemia and hypophosphatemia. With insufficient calcium intake over time, these biochemical changes can persist and accompany MBD.

The most common biochemical changes of MBD include hypophosphatemia and hyperphosphatasia and are frequently associated with insufficient mineralization. Hypophosphatemia manifests as the earliest marker of disrupted mineral metabolism, as early as 7–14 days after birth [10]. Phosphate deficiency suppresses PTH, thereby preventing urinary phosphate wasting but activates synthesis of $1,25(OH)_2D$ to increase intestinal calcium and phosphate reabsorption. Thus, phosphate deficiency disrupts calcium balance, potentially leading to hypercalcemia, hypercalciuria, and nephrocalcinosis. The kidney responds to phosphate deficient states by increasing phosphate reabsorption. Tubular reabsorption of phosphate (TRP) is a measure of the fraction of filtered phosphate that is reabsorbed and is a calculated from the ratio of phosphorus and creatinine in serum and urine (Table 1). As such, an elevated TRP with hypercalcemia and hypercalciuria can suggest inadequate phosphorus intake.

These changes are often accompanied by hyperphosphatasia. Alkaline phosphatase (ALP) is the sum of bone, liver and intestinal

Table 1
Screening and monitoring of MBD

	Level of interest	Key points
ALP	>800 IU/L or >600 and trending up	High values associated with MBD Can be elevated in liver disease and may consider bone specific alkaline phosphatase if etiology unclear
Calcium (albumin corrected)	<8.5 or > 10.5 [37]	Often normal (compensation). High levels indicate over-treatment. Low values suggest low intake or increased losses
Phosphorus	<5.5 mg/dl (1.8 mmol/l) [14,38]	Low levels correlate with MBD
TRP 1-($U_{phos}/S_{phos} \times S_{cr}/U_{Cr}$)	>95% [14] in setting of lower phosphorus (phos < 5.5)	Should be obtained at the same time as the serum sample. High TRP suggests low urinary phosphate wasting (low serum phos, or low PTH). Low TRP suggests increased urinary phosphatase wasting (often from high PTH in this population)
Urine Ca:Cr (spot)	3.8 mmol/mmol (95%tile) [14] (1.3 mg/mg)	Screen for hypercalciuria due to excess calcium/calcitriol intake or side effect of meds (ex. Loop diuretic, methylxanthine)
PTH	>100 pg/ml	No reference range for preterm infants Adult ULN ranges from 50 to 88 pg/ml [8,16] Elevated in subclinical hypocalcemia
25(OH) Vitamin D	<30 ng/ml	Values < 20 ng/ml indicate deficiency
Additional screening tests		
1,25-$(OH)_2$ vitamin D	c-terminal procollagen peptide	Osteocalcin
X-ray	Bone specific alkaline phosphatase	
DXA	Tibial quantitative ultrasound	

isoforms, with the bone isoform contributing about 90% and representing a marker of bone mineralization [5]. While ALP physiologically increases over the first few weeks and plateaus around 5–6 weeks, hyperphosphatasia beyond 6 weeks typically represents inadequate mineral intake and often accompanies MBD. However, ALP levels have not been shown to correlate to the degree of hypomineralization. Rachitic changes are more commonly associated with greater ALP levels (>800 IU/l) but can also be seen at lower levels (<600 IU/l) [11]. ALP levels may be deceivingly low in the setting of zinc deficiency or glucocorticoid exposure and should not be the only factor used in screening for MBD.

In a subset of high risk infants (e.g. chronic lung disease on long term furosemide), calcium deficiency can accompany MBD and lead to metabolic changes associated with secondary hyperparathyroidism. In these neonates, elevations in PTH lead to urinary phosphate wasting and an associated low TRP with hypophosphatemia. Increased PTH levels will trigger increased plasma calcium levels due to increased bone resorption and increases in renal and intestinal calcium absorption. As such, isolated plasma calcium levels may not be a helpful screening marker for infants at risk for MBD as a normal plasma level does not ensure adequate mineral intake.

Less commonly, renal tubular damage can cause urinary phosphate wasting and an associated low TRP and hypophosphatemia. However, unlike those with calcium deficiency, PTH levels are typically normal in this subset of patients.

Screening and monitoring

The American Academy of Pediatrics (AAP) recently released guidelines for calcium and vitamin D requirements of enterally fed preterm infants [12]. Many screening tests are available (Table 1) and neonatologists recognize the importance of maximizing bone health. Yet, there is a lack of consistency with regards to optimal screening, treating, and prevention of MBD. Indeed, wide practice variation in the United Kingdom was reported by Harrison et al. [6] Encouragingly, a survey by Kelly et al. of U.S. providers in Level 3 neonatal intensive care units (NICUs) done prior to the release of the AAP guidelines revealed that practices were nearly in line with the AAP recommendations. However, there was a no consensus regarding both diagnosis and timing of treatment initiation [13].

Choosing whom to screen is driven by risk factors (Figure 2) [12,14]. Deciding the best screening test can be a challenge. ALP has been shown to be suggestive of rickets at very high levels >1000 IU/l [11]; specificity improves when ALP is used in combination with serum phosphorus levels. ALP >900 IU/l with serum phosphorus levels <5.6 mg/dl (<1.8 mmol/l) yields 100% sensitivity with 70% specificity [15]. Given lack of consensus on screening, Harrison et al. has recommended weekly measurement of serum calcium, phosphorus, ALP, and TRP [6].

In addition, serum PTH levels may be a useful marker in identifying ELBW neonates at risk for MBD (Table 1) [16]. Not only can PTH be a marker of secondary hyperparathyroidism, but in conjunction with TRP can help distinguish the underlying cause of hypophosphatemia. A low TRP with a high PTH would suggest an underlying calcium deficiency. Meanwhile, a high TRP with low or normal PTH would indicate phosphorus deficiency.

Monitoring of biochemical markers is not only necessary for diagnosis and assessment of individual therapeutic response, but also to screen for complications of mineral supplementation. Complications can arise when mineral supplies are increased too quickly or after prolonged periods of interrupted enteral nutrition, leading to electrolyte imbalance and rapid augmentation of calcium and phosphorus absorption [17]. There are no clear monitoring guidelines, though it seems reasonable to monitor labs every 1–2 weeks. Abrams et al. recommend following serum phosphorus and ALP weekly or biweekly [12]. Land et al. recommend calcium and phosphorus measurements, accompanied by urinary calcium and phosphorus excretion, weekly in premature infants under 3 weeks and biweekly in those over 3 weeks [17]. Once mineral supplementation or other treatment is started, monitoring and therapeutic goals are individualized to the underlying deficiency and specific treatment. For infants with hypophosphatemia, phosphorus supplementation can be adjusted to reach a target serum phosphorus of >5.5 mg/dl. For infants on calcium or calcitriol, goals are to normalize PTH levels, monitor for hypercalciuria, and to normalize phosphorus levels by limiting urinary phosphorus wasting, as evidenced by increases in TRP.

Vitamin D typically can be assessed less frequently. While health experts have focused on vitamin D in recent years, much remains unknown regarding its physiology in preterm infants. As vitamin D is readily transferred across the placenta, newborn 25(OH)D levels are about 50–70% of maternal levels regardless of gestational age [18]. In the majority of cases of MBD, 25(OH)D levels are normal, and interestingly, serum 25(OH)D levels have been shown to be similar in premature infants with and without rickets [19]. As such

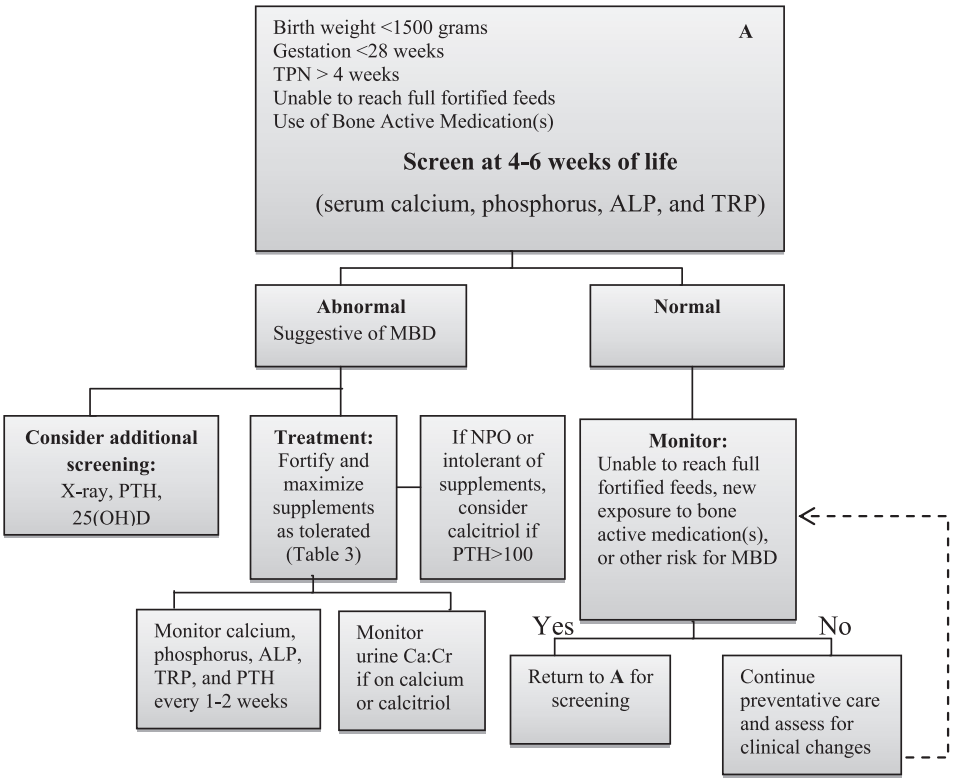

Figure 2. Algorithm for screening and monitoring MBD.

the role of vitamin D deficiency in MBD remains to be seen. To date, prior research has emphasized supplementation rather than vitamin D status, with no uniform consensus defining levels of insufficiency and adequacy [18]. Ongoing efforts will hopefully clarify some of these unknowns.

Indications for screening for vitamin D deficiency in preterm infants include maternal vitamin D deficiency (if known), short gut syndrome and other malabsorptive conditions that may impact vitamin D absorption, and anticonvulsant therapies that may increase vitamin D catabolism (e.g. phenobarbital). Further, screening is beneficial to identify the subset of infants who are at risk of developing vitamin D intoxication. In particular, those receiving preterm formulas and fortified breast milk where total vitamin D intake may exceed 1000 units/day when receiving concurrent supplementation are at greatest risk of intoxication. When measured, 25(OH)D rather than $1,25(OH)_2D$ should be the marker measured exclusively for vitamin D status as the latter is not closely associated with overall outcomes of vitamin D exposure [12]. In addition, $1,25(OH)_2D$ levels can be normal until profound depletion occurs.

Radiographs, typically done as part of standard clinical care, can reveal various degrees of MBD, including demineralization or "osteopenia," rachitic changes, and/or fractures (Figure 1). While some fractures can be acute with associated pain or diminished movement, fractures are more commonly healing and without associated symptoms [20]. The AAP Clinical Report recommends rechecking radiographs every 5–6 weeks until improved mineralization [12].

Prevention and treatment of MBD

The primary prevention and treatment strategy for MBD is similar: optimizing nutrition, specifically calcium, phosphorus, and vitamin D. Limiting prolonged exposure to commonly prescribed medications that further reduce mineral stores (e.g. loop diuretics and methylxanthines) or increase bone resorption (e.g. glucocorticoids) is equally important [5].

The goal is not only to maintain normal serum levels but also mimic *in utero* bone accretion rates for calcium and phosphorus. Recommendations for calcium, phosphorus, and vitamin D vary globally with higher calcium and phosphorus and lower vitamin D goals for intake in the United States compared to Europe (Table 2). Fortified breast milk and preterm formulas are generally preferred as formulas not designed for premature infants (e.g. soy or elemental formulas) lack the adequate calcium and phosphorus content needed by a preterm infant [12].

Fortification remains essential to provide adequate mineral intake. Even 180–200 ml/d feedings of unfortified human milk likely only provide 1/3 the level of *in utero* calcium and phosphorus accretion [21]. This is despite 60% calcium and 80% phosphorus absorption from human milk by the newborn. Care must also be taken when using unfortified banked human donor milk due to its lower phosphorus content than unbanked human milk [5]. Infants on full feeds with preterm formula or fortified maternal breast milk reach an optimal level of mineral intake with approximately 180–220 mg/kg/day calcium and 100–130 mg/kg/day phosphorus [12]. Despite reaching this degree of intake, some children still develop MBD, especially in the setting of critical illness, and may require targeted mineral supplementation with calcium and/or phosphorus (Table 3).

More aggressive feeding strategies aimed at promoting growth and avoiding a catabolic state, such as earlier introduction of protein supplementation in TPN and enteral feedings, have become commonplace in NICUs. One effect of the increased protein intake is an increased cellular uptake of phosphorus. Recent observational studies by Ichikawa et al. and Bonsante et al. demonstrated lower serum phosphorus levels in the first week of life associated with a

Table 2
Recommended enteral calcium, phosphorus, and vitamin D intakes

	Calcium (mg/kg/day)	Phosphorus (mg/kg/day)	Vitamin D (IU/day)
LSRO 2002 [39]	150–220	100–130	90–320 IU/kg/day
Atkinson and Tsang 2005 [40]	120–200	70–120	200–1000
Canadian Paediatric Society 1995 [41]	4–6 mmol/kg *(160–240)*[a]	2.5–3.8 mmol/kg *(78–118)*[b]	400–800
Rigo and Senterre 2006 [3]	100–160	60–90	800–1000
Abrams (AAP) 2013 [12]	150–220	75–140	200–400

[a] Calcium mmol to mg: multiply by 40.
[b] Phosphorus mmol to mg: multiply by 32.

higher amino acid intake, especially in small for gestational age premature infants [22,23]. The impact of this decrease in circulating phosphorus in contributing to MBD and whether it can be prevented with phosphorus supplementation is unknown.

Biochemical markers can help determine the most appropriate form of supplementation. Phosphorus supplementation should be considered with hypophosphatemia in the setting of low or normal PTH levels and high TRP, which suggests a lack of urinary phosphate wasting due to inadequate intake. Treatment is indicated for values consistently less than 4 mg/dl but can be considered if values fall below 5.5 mg/dl, especially with associated hyperphosphatasia. Correcting this imbalance is critical to promote bone mineralization and prevent hypercalciuria [12]. Individual responses may vary depending on clinical status, gut pH, and absorption and tolerance of the individual supplement. Potassium phosphate, typically the intravenous formulation administered enterally as solution, is the preferred form of phosphorus supplementation due to gut intolerance of other available phosphate salts. Due to national shortages, alternative formulations, such as tablet or powder forms, may be used. Children, especially those on potassium-sparing diuretics, must be monitored closely for electrolyte abnormalities due to additional sodium and potassium in these alternative formulations. Calcium supplementation can be considered in the setting of secondary hyperparathyroidism and low TRP. Again, serum calcium levels typically remain normal or even high due to a compensatory secondary hyperparathyroidism.

For those on parenteral nutrition, normal serum levels can be achieved but mineral intake fails to reach even 50% of rates of *in utero* mineral retention due to the poor solubility of available mineral salts in the U.S. Prior studies have shown that parenteral mineral retention is affected by greater mineral intake and calcium:phosphorus ratio, with a preferred ratio of 1.7:1 providing greater retention when compared to 1.3:1 or 2:1 [24].

The most recent AAP recommendation for daily vitamin D intake is 200–400 IU/day for preterm infants, but among various sources the amount ranges from 90 IU/day to 1000 IU/day (Table 2). For VLBW and ELBW infants, TPN in the U.S. will provide 160 IU/kg which could lead to deficiency in those infants requiring prolonged TPN without enteral feedings. Even with full enteral nutrition, supplementation beyond human milk fortification or higher caloric density preterm formulas may still be required to achieve a targeted intake. This can be achieved through the use of a multivitamin or individual vitamin D supplement.

For the subset of patients on TPN with secondary hyperparathyroidism, calcitriol may provide adjunctive therapy [25]. Calcitriol (starting dose 0.05 mcg/kg/day, max dose 0.2 mcg/kg/day) may suppress PTH and minimize phosphorus wasting while increasing intestinal calcium and phosphorus. This may be a particularly useful adjunct in this subset of patients that cannot receive enteral supplements.

Nonpharmologic therapies also play an integral part in the treatment of MBD. The role of mechanical stimulation to promote bone growth cannot be overlooked. Fetal movements against the uterine wall help ensure appropriate bone mineral content and muscular development [26]. These loading movements cannot be replicated in the extrauterine environment of the NICU. Physical therapy may provide necessary stimulation lost in the absence of the uterine wall resistance that helps ensure appropriate bone mineral content and muscular development. Programs reviewed by Schulze done in “well” preterm infants with activity ranging from 5 to 15 min per day for 3–8 weeks duration showed an increase in weight and length and improved short-term bone mineralization [27]. Similarly, Tosun et al. found improved tibial strength (measured by ultrasonography) and mid-upper arm circumference in VLBW infants [28].

Post-discharge

Discharge timing is dependent on clinical status, with the majority of stable VLBW and ELBW infants discharged home between 36 and 40 weeks post–conception. Extrauterine growth failure continues to be problematic in neonatal follow-up. Poor growth has been correlated with poor development and chronic diseases in adulthood [29–31], with the greatest risk in those with intrauterine or postnatal growth retardation. Bone mineralization generally improves rapidly in the first few months of life, reaching values appropriate for body size and similar to healthy term infants [32,33]. Thus, post discharge nutrition will often be driven by growth parameters. Many infants with BW >1500 g do well with exclusive breastfeeding or routine infant formula after discharge [12]. On the other hand, most VLBW and ELBW infants are discharged home on transitional formula and/or continued fortification. This is often an individualized approach based on clinical experience as there is limited research with which to guide providers. Enhanced formula continued until term benefits growth and bone health in otherwise well former preterm infants, but the data

Table 3
Supplementation with calcium and phosphorus when further increase cannot be made in diet alone

	Starting dose (mg/kg/day)	Maximum dose (mg/kg/day)	Dosage forms
Elemental calcium Enteral (E) Parenteral (P)	20	70–100 [12,16]	E: calcium glubionate, calcium carbonate P: calcium gluconate
Phosphorus	10–20	40–50	E/P: potassium phosphate

Clinical correlation is warranted (this may not be suitable for all). Monitoring of serum calcium (ionized and/or albumin corrected), serum phosphorus, urinary calcium are critical.

is insufficient for those with more comorbidities [34]. Transitional formula or breast milk fortification may be empirically provided until 40–52 weeks post-conceptional age [33] or up to 6 months if ongoing concerns for growth exist [35]. There are indications for transitioning to term formula or exclusive breastfeeding sooner. Some consider cutting back once weight reaches 3 kg due to concerns of Vitamin A exceeding the upper limit of recommended intake [12,36].

While growth parameters drive decisions on nutritional support, the frequency of biochemical monitoring for MBD is based on severity. ALP measured 2–4 weeks post discharge is appropriate in exclusively breastfed former VLBW infants with consideration of direct mineral supplementation if ALP >800–1000 IU/l [12]. Closer follow-up is warranted in those with moderate to severe MBD or with ongoing risk for poor bone mineralization (i.e. TPN dependence, loop diuretics, glucocorticoids, etc.) as they may require extended fortification or direct mineral supplementation. Those with ongoing use of direct calcium and/or phosphorus supplementation or those on calcitriol at discharge should have biochemical markers monitored as previously suggested (Figure 2). Clinical context will determine frequency of monitoring. The supplements should be weaned as biochemical markers normalize to avoid therapeutic consequences including hypercalciuria and nephrocalcinosis. In these more complex cases, we recommend a multidisciplinary approach that includes a registered dietitian with expertise in neonatal and/or bone health.

Conclusion

While the exact incidence remains unknown, MBD of prematurity remains a significant problem for preterm, chronic ill neonates. Treatment strategies include the optimization of nutrition, supplementation with calcium, phosphorus and vitamin D, and promotion of age appropriate physical therapy. Early identification and prevention of MBD remains important to prevent short-term and potential long-term complications, but up until the 2013 AAP recommendations, a lack of consensus existed on screening strategies. Given the significant knowledge gaps regarding screening, prevention, and long-term sequelae as infants survive at increasingly earlier gestational ages and lower birth weights, we hope that new AAP guidelines will provide consistency in clinical practice and promote research that generates evidence upon which to refine these guidelines.

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