

## Metabolic Bone Disease of Prematurity: A Review of Minerals Supplementation and Disease Monitoring

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### Abstract

Metabolic bone disease is a frequent condition in very low birth weight (VLBW) infants. In order to prevent the disease, the provision of high amount of calcium and phosphate in parenteral nutrition solutions and during transition to the full enteral feedings is crucial. Current practice supports early aggressive mineral supplementation. In this review, we will discuss data from the recent literature regarding the recommendation for supplementation of calcium, phosphate and vitamin D in VLBW infants and the interpretation of indirect markers of bone metabolism for screening, diagnosis and monitoring high risk infants, as well as to guide treatment.

**Keywords:** Preterm infants; Calcium; Phosphorus; Osteopenia; Bone mineralization

### Introduction

Metabolic bone disease of the prematurity (MBDP), also known as preterm newborn osteopenia or neonatal rickets, is a leading cause of pathological fractures in very low birth weight infants (VLBW, birth weight <1500 g), and in the long-term has been implicated with poor growth during childhood. It is characterised by a reduction of bone mineral density resulting from either increased bone reabsorption or decreased bone mineralisation [1].

MBDP affects up to 23% of VLBW newborns [1], and up to 55% of those extremely low birth weight (ELBW, birth weight <1000 g) [2]. MBDP mainly occurs between ten and sixteen weeks postnatally and may be under-recognized until demineralisation is severely established. Factors contributing to the development of MBDP include preterm birth given the reduced transplacental mineral release to the fetus, and chronic conditions related to prematurity, such as bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis, because of reduced nutritional and mineral intake associated to these conditions. Indeed, providing adequate supply of calcium and phosphate in preterm infants has always been a challenge for neonatologists, because of feed intolerance and inadequate mineral content in human or formula milk. Further restrictions are due to the solubility of calcium and phosphorus in parenteral nutrition (PN) solutions limiting the amount of minerals that can be supplemented, along with the side effects of prolonged fluid restrictions, diuretics, high dose systemic steroids, and immobilisation [3].

Diagnosis of MBDP is established upon radiographic evidence of reduced bone mineral density. While no biochemical tests are diagnostic, a number of easily accessible serum and urinary markers of bone metabolism have been used for early detection and monitoring of osteopenia: serum calcium ( $Ca_s$ ), phosphate ( $P_s$ ), and alkaline phosphatase (ALP), urinary calcium ( $Ca_u$ ), phosphate ( $P_u$ ) and creatinine ( $Cr_u$ ). Their measurements are used to state the renal

tubular reabsorption of phosphate ( $TRP=1-(P_u/P_{sp} \cdot Cr_s/Cr_u) \cdot 100$ ) and the  $Ca_u/Cr_u$  ratio (Table 1). Early nutritional intervention is essential in order to promote bone deposition and avoid bone demineralisation. Adequate amounts of calcium and phosphate must be provided with PN, increased during transition to the exclusive enteral feeding, and maybe continued when the infant is on full feeds.

### Calcium and Phosphorus Homeostasis and Intake

Calcium and phosphate are the major inorganic bone constituents. In utero, greater skeletal development occurs during the third trimester; between 24 and 37 weeks of gestation the 80% of the mineral accretion is achieved [4]. During these weeks, 310 mg of calcium and 170 mg of phosphorus are required to allow normal fetal weight gain, of approximately 30 g per day [5].

It has been suggested that placental insufficiency might increase the risk of neonatal rickets and account for early mineral deficiency, as a consequence of the reduced transfer of phosphorus to the fetus [6].

Compared to term infants, preterm babies are thus likely to require higher intake of calcium and phosphorus [7].

Despite modern PN solutions can theoretically match in utero accretion rates, the solubility of calcium and phosphorus in PN might be limited by temperature, amino acids, glucose and lipid concentrations as well as by the pH of the solution.

Current practice recommendations [8], state that at least 12.5 mmol/L (50 mg/dl) up to 15 mmol/L (60 mg/dL) of calcium and 13 mmol (40 mg/dL) up to 15 mmol/L (46 mg/dL) of phosphorus should be administered by parenteral route. When the fluid intake reaches 150 mL/Kg/day, this would give a supply of 75-90 mg/Kg/day of calcium and of 60-70 mg/Kg/day of phosphorus. Such amounts have shown to provide the proper ratio (1:5 to 1.7:1) of calcium and phosphate in order to guarantee bone deposition and to prevent early neonatal hypocalcemia. However, given the sub-optimal mineral retention rates, only the equivalent to 70% of the intrauterine mineralization would be achieved [9].

Currently recommended oral daily intake of calcium and phosphorus varies widely between international committees [10], from a minimum of 120 to a maximum of 220 mg/Kg/day of calcium and from 65 to 140 mg/Kg/day of phosphate. These amounts are higher than those suggested in the previous decades and have changed the current practice of mineral supplementation [3].

As a matter of fact, the introduction of a more aggressive supplementation and the routine use of breast milk fortifiers or preterm high mineral containing formulas has led to a dramatic reduction, by the 50% approximately, in the frequency of the MBDP, especially in ELBW newborns [11].

During weaning from PN phosphate intestinal absorption remains between 80% and 90%, and recommended intake are intended to maintain the optimal calcium to phosphorus ratio suggested for preterm babies [7,12]. In contrast, calcium intestinal absorption is limited to 60% of the dietary intake and is influenced by vitamin D status, solubility of calcium salts and lipid intake. At this rate of assimilation, an infant receiving 120 Kcal/Kg/day would only absorb 25 mg/Kg/day of calcium from human unfortified milk (67 Kcal/dL) given its low calcium content (25 mg/dL).

Providing fortification (80 Kcal/dL), calcium concentration rises to 145 mg/dL accounting for a total amount of calcium of 220 mg/Kg/day that should allow for absorption of 120-130 mg/Kg/day [7] and suit the calcium intake recommended for ELBW infants receiving exclusive enteral nutrition [7,13].

When adequate amounts of calcium and phosphate are provided, the excessive aliquots of both minerals is excreted with urine and a  $Ca_u/Cr_u$  ratio < 0.6, along with a normal urinary phosphate excretion confirmed by a TRP between 80% and 90% is found. If sudden detrimental conditions arise, renal compensation rapidly leads to a complete reabsorption of phosphate from urine, thus increasing the TRP to pathologic values, greater than 90%. Collaterally, despite low values of  $Ca_s$  are potentially found, paradoxical hypercalciuria might be observed ( $Ca_u/Cr_u > 0.6$ ), following the lack of phosphate leading to a reduced calcium deposition in the hydroxyapatite crystals of the bone.

Currently recommended mineral supplementations should allow to maintain normal serum and urinary levels but also mimic *in utero* bone accretion rates for calcium and phosphorus.

For infants with greater mineral requirement, suitable oral solutions are displayed in Table 2.

## Vitamin D Supplementation

It has been suggested that during the first month of life calcium absorption is independent from vitamin D supplementation and occurs passively via a "nonsaturable", non-vitamin D dependent, presumably paracellular process [14]. However, in preterm infants the exact timing and proportion of vitamin D-dependent absorption of calcium and phosphorus is unknown. For preterm infants, a vitamin D intake of 800-1000 IU/day is recommended from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines [15]. However, the American Academy of Pediatrics (AAP) has raised concerns about the potential risks related to such high concentration of vitamin D, especially for ELBW infants for whom the upper tolerable intake is unknown. A randomized controlled trial by Alizadeh et al. demonstrated that 400 IU/day of vitamin D are equally effective as 1000 IU/day in preventing

osteopenia of prematurity [16]. More recently, the same authors have shown equal efficacy of a lower dose of 200 IU/day in preventing biochemical, radiological and clinical presentation of rickets in preterm newborns [17].

Interestingly, Isojima et al. [18], found no statistically significant differences in the height standard deviation score (SDS) at 3 years of age in two groups of VLBW infants with MBDP who did or did not receive standard vitamin D supplementation since birth. Pending further research, for preterm infants the AAP recommendations to provide 200 to 400 IU/day are accepted [19].

Preterm infants are able to hydroxylate the inactive, monohydroxylated vitamin D to its active, dehydroxylated form (calcitriol) since the 24th week of gestation [14]. Supplementing preterm newborns with active dehydroxylated vitamin D is thus not warranted. However, calcitriol suppresses parathyroid hormone (PTH) secretion, minimizing phosphorus wasting while increasing intestinal calcium and phosphorus uptake. Hence, calcitriol administration (0.05 mcg/kg/day up to 0.2 mcg/Kg/day) might be reasonable for those babies receiving exclusive total PN to prevent or treat secondary hyperparathyroidism [20].

## Biochemical Markers for MBDP Management

Monitoring markers of bone metabolism is essential for the management of MBDP. Serum calcium alone is not a good marker since its level is maintained stable at the expense of the bone, as a consequence of PTH secretion. Instead, serum levels of phosphorus and alkaline phosphatase (ALP) are better indicators of disease.

In preterm infants, ALP levels may not peak until 6-12 weeks of age and lack correlation with severity of demineralization [21].

However, ALP levels greater than 500 U/L are suggestive of altered bone homeostasis. ALP levels higher than 900 U/L, associated with serum phosphorus levels persistently lower than 1.8 mmol/L (5.5 mg/dL) have diagnostic sensitivity and specificity of 70% and 100%, respectively [22].

A major concern when managing VLBW patients with increased values of ALP remains the risk for reduced mineralisation and stunted linear growth.

Increasing data suggest an association between prematurity and reduced bone strength in childhood [23], however whether VLBW infants are at increased risk for reduced bone mineral content (BMC) in adulthood is still debated.

Quintala et al. found that preterm infants (28.4 < gestational age < 32) with high ALP levels at birth and at 6 months had lower values of BMC than full term infants during early life, but reached normal values at 6 months of corrected age. Interestingly, the rapid recovery of BMC occurred regardless the type of milk the infants had received [24].

The association between MBDP and stunted growth in VLBW infants has also been investigated.

Isojima et al. documented a negative correlation between peak serum ALP activity levels in early life and height standard deviation score (SDS) at three years of age. Serum phosphorus level was also identified as an independent predicting factor for height SDS. A statistically significant difference of  $P_s$  levels between infants with or without height catch-up growth was found in the analysis restricted to small for gestational age infants, known to be at higher risk for BMDP

compared to VLBW babies with adequate weight for gestational age. This positive correlation between height SDS and serum phosphate levels at peak ALP thus suggests that MBDP, particularly hypophosphatemia, may affect the long-term height prognosis in VLBW infants.

Moreover, no correlation was found between  $Ca_s$  at peak serum ALP and height SDS at three years of age, thus confirming the role of hypophosphatemia in the aetiology and long term outcomes of the MBDP [18].

## Summary and Conclusion

MBDP is frequent in VLBW infants and requires early nutritional intervention.

In order to prevent and treat the disease essential points need to be acknowledged:

1) Identify subjects at higher risk for MBDP:

- Newborns less than 32 weeks g.a. or 1500 g at birth.
- Newborns receiving PN for more than 4 weeks.
- Newborn receiving prolonged therapies with steroids or diuretics.

2) Provide early calcium (12.5 -15 mmol/L) and phosphate (13-15 mmol/L) supplementation in PN and oral vitamin D supplementation (200-400 IU/day).

3) Assess  $Ca_s$ ,  $P_s$ , serum ALP, serum creatinine  $Ca_u$   $P_u$  and urinary creatinine at birth and closely monitor these biomarkers (i.e. every 2 weeks).

4) Assess and monitor  $Ca_u/Cr_u$  and renal TRP [TRP=  $1-(P_u/P_s * Cr_s/Cr_u) * 100$ ].

5) Provide the most appropriate supplementation in the setting of deranged bone metabolism.

- Adjust the amounts of calcium (12.5 -15 mmol/L) and phosphate (13-15 mmol/L) in PN.

- Fortify the human milk and/or provide preterm enriched formula.
- Give additional oral supplementation (Table 2).

6) Measure vitamin D in the setting of persistently altered serum and urinary findings despite aggressive supplementation in provided.

7) Consider calcitriol supplementation (0.05 mcg/kg/day up to 0.2 mcg/Kg/day) for patients on total PN with secondary hyperparathyroidism (PTH > 100 pg/mL).

Markers	Levels of Osteopenia
Alcaline Phosphatase (IU/L)	> 500
Urinary calcium <sup>†</sup> /Urinary creatinine <sup>†</sup>	> 0,6
TRP <sub>s</sub> (%)	> 95
Plasma Phosphate (mg/dL)	< 5,5
<sup>†</sup> spot urine	
<sub>s</sub> renal tubular reabsorption= $1- (Pu/Psp * Crp/Cru) * 100$	

**Table 1:** Main markers of bone metabolism in the preterm newborn with metabolic bone disease.

Solution	Composition	Dosage and notes
<b>Calcium carbonate/ calcium lactate gluconate</b>	1132 mg of calcium lactate gluconate plus 875 mg of calcium carbonate provide 500 mg of ionised calcium	50 mg of ionised calcium given every 12 or 6 hours Administer at distance (at least 2 hours) from phosphate supplements
<b>Sodium phosphate monobasic dehydrate</b>	7.8 g diluted in 50 mL of pure water provide 30 mg of phosphate per mL	1 mL of solution every 12 or 6 hours Administer at distance (at least 2 hours) from calcium supplements

**Table 2:** Available oral solutions providing additional calcium and phosphate supplements.

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