Metabolic bone disease

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Introduction

The fetus accrues approximately 80% of bone mineral content between 24 weeks gestation and term. During the third trimester, the estimated average daily fetal accretion of calcium is approximately 2.302.98 mmol (92120 mg)/kg/d and phosphorous is 1.902.39 mmol (6075 mg)/kg/d [1]. Infants born very preterm are at risk of missing this period of maximal mineral accretion, particularly through inadequate dietary intake of minerals (calcium and phosphorous), with bone mineralization and mineral excretion also adversely affected by use of diuretics and corticosteroids [1]. Human milk has insufficient calcium and phosphorous for normal bone mineral accretion in preterm infants. Infants fed unfortified human milk have progressive decreases in serum phosphorous, and increases in serum calcium and alkaline phosphatase compared to infants fed formula [2]. In many infants, this metabolic bone disease (MBD) is a self resolving process. However, MBD may be associated with significant clinical effects including fractures, marked dolichocephaly and reduced linear growth [3, 4]. The long term consequences of MBD in preterm infants on peak bone mass later in life are unclear. This guideline will focus on prevention of MBD through optimising enteral nutrition, and the evidence for screening high risk infants who have failed to tolerate full enteral nutrition and human milk fortification.

Incidence and risk factors

Metabolic bone disease predominately affects very low birth weight or preterm infants, particularly infants fed unfortified human milk. The following risk factors have been reported:

- **Fetal:** The strongest predictor for the development of biochemical and radiological MBD is premature or low birth weight delivery [5]. Fetal growth restriction has been reported not to be associated with the development of MBD independent of birth weight and length or height [6, 7]. Although infant vitamin D deficiency, largely secondary to maternal vitamin D deficiency, has been reported to a re-emerging problem in Australia [8], most infants with biochemical evidence of MBD have normal or increased levels of vitamin D metabolites [9]. Male gender and genetic polymorphisms of vitamin D receptor, estrogen receptor, and collagen Ialpha1 genes have also been reported as a risk factor for MBD in preterm infants [5].

- **Infant:** Risk factors for MBD in the newborn include [1]:
  - Decreased mineral intake:
    - Preterm delivery <32 weeks gestation,
    - Very low birth weight osteopenia incidence up to 30% in infants <1500g (75% in infants <800g),
    - Prolonged total parenteral nutrition,
    - Delayed enteral nutrition,
    - Failure to provide multicomponent of mineral fortification of human milk feeds,
    - Bronchopulmonary dysplasia.
  - Increased mineral excretion [10]:
    - Frusemide increases urinary calcium excretion,
    - Methylxanthines both caffeine and theophylline increase urinary calcium excretion [11], and
    - Possibly infants on dexamethasone.

Consequences

Metabolic bone disease usually appears between the 6th and 12th postnatal week in high risk infants and is clinically apparent only in a minority of cases [1]. Consequences of MBD include:

Short term:

- **Biochemical:** In human milk fed infants, who are relatively phosphate deficient, the typical features are normal serum calcium concentrations, low serum phosphate and high serum alkaline phosphatase. Urinary phosphate excretion is very low or absent, while urinary calcium excretion increases as serum phosphate concentration decreases [1, 9]. In most infants the vitamin D status (as indicated by serum 25-OH D concentrations) is normal, and serum 1,25-$(OH)_2$ D levels and free 1,25-$(OH)_2$ D index higher, suggesting the primary issue is phosphate deficiency [9]. Parathyroid hormone concentrations are generally in the normal range [12].
- **Radiological:** Standard x-ray films may reveal osteopenia, rickets-like changes including widening of the metaphases, and fractures (frequently rib).
- **Clinical:** Prior to widespread use of high mineral preterm formulas, fractures were detected in about 24% of VLBW infants [13, 14], with the fractures occurring concurrent with the period of increased enteral intakes and physical growth. Dolichocephaly has also been partially attributed to MBD [15], and the same author has suggested the myopia may also be contributed to by the postnatal ellipsoid deformation of the globe secondary to dolichocephaly [16].

Longer term: The clinical, biochemical and radiological features of MBD resolve over the first months beyond the infants due date. However, MBD has been reported to be associated with significant effects on linear growth [3, 4]. Lucas reported the deficit in body length associated with peak neonatal plasma alkaline phosphatase activity ≥ 1200 IU/l was 1.6 cm At 18 months after adjusting for confounding factors [3]. The height discrepancies in infants with an alkaline phosphatase ≥ 1200 IU/l persisted to 8 years [4]. The long term consequences of MBD in preterm infants on peak bone mass later in life are unclear. In twins, adult bone mass has been associated with birth weight and also by intra-pair differences in birth weight. However, a substantial part of this related to skeletal size at birth as predicted by height [17]. Low birth weight has not been proven to be a risk factor for fractures in adults [18].

Diagnosis

Prevention: The goal of management is prevention of MBD through the provision of adequate mineral intake in at risk infants. There have been insufficient trials to determine the place of diagnostic testing in the management of MBD. If an infant reaches full enteral feeds within the first 2 weeks, and tolerates optimal enteral nutrition (EBM 180 ml/kg/day with Breast Milk Fortifier BMF 25 cal/30 ml), then screening

for MBD is not indicated.

Who to screen:

HIGH RISK = infants <28 weeks gestation and/or <1000g, ***AND any one of the following:***

- Substantial delay (≥ 4 weeks) in reaching full enteral feeds / prolonged TPN, **OR**
- Inability to supplement human milk feeds with multicomponent fortifier 2 failed attempts, **OR**
- Chronic lung disease requiring diuretics, **OR**
- Postnatal growth failure this is particularly related to failure in growth in length. However, as length is difficult to measure accurately and growth in weight is well correlated to growth in length, use failure to gain wait as an indicator for screening.

How to screen:

Consider performing serum tests from ***6 weeks of age every 2 weeks:***

- Serum calcium and phosphate normal or high calcium, low phosphate typical of human milk fed infants with MBD,
- Serum total alkaline phosphatase bone isoenzyme usually contributes a small proportion of total alkaline phosphatase by 6 weeks, so has little added value in infants with suspected MBD.
- Urinary calcium and phosphate (with or without creatinine) - low levels indicate nutritional deficiency. Low phosphate typical of human milk fed infants.
- If the serum calcium is low, then measurement of vitamin 25 OH-D and PTH in mother and infant should be considered.

High alkaline phosphatase >900iU/L and hypophosphataemia <1.8mmol/L predictive of low bone mineral content at 3 months corrected age [19]. Alkaline phosphatase ≥ 1200IU/L associated with reduced linear growth at 18 months and 8 years [3, 4].

Radiological screening: This is rarely indicated. Standard x-ray films may reveal osteopenia, rickets-like changes including widening of the metaphases, and fractures. However, the bone mineral density must be reduced by at least 30% before reductions in bone mineral content can be detected. The current gold standard for measurement of bone mineral content is dual-energy x-ray absorptiometry (DXA) [1]. New techniques using ultrasound speed through bone are currently being evaluated [20]. These techniques at not easily available for infants in RPA Newborn Care.

Interventions

Prevention:

For infants born < 32 weeks and / or <1500g (see Infant feeding guideline):

The nutritional goal is to grade the infant up to 180ml/kg/day EBM supplemented with 25 cal/30ml breast milk fortifier (feeding guideline). This provides mineral intakes (calcium 4.5 mmol/kg/day and phosphate 3.5 mmol/kg/day) substantially in excess of that accrued in-utero (See: Nutritional content of feeds for enterally fed infants at RPA Newborn Care).

The goal of management is prevention of MBD through the provision of adequate mineral intake in at risk infants and includes:

- Early minimal enteric feeds with human milk may increase bone mineral content in preterm infants [21], although clinical benefits are not conclusive [22, 23];
- Provision of early TPN with optimised calcium and phosphate content - prolonged periods of TPN

have been associated with osteopenia and rickets. However, with solutions containing 15 mmol/l of calcium, 15 mmol/l of phosphate and 3 mmol/l of magnesium, stable serum indices of mineral homeostasis have been obtained [1]. Preterm TPN for infants in RPA Newborn Care is supplements with 12 mmol/l of calcium and 12 mmol/l of phosphate;
- Grading of breast milk feeds at optimal rate determined by clinical trials (up to 35 ml/kg/day) results in reduced time to full enteral feeds [24] and allows for early introduction of human milk fortifier;
- Multicomponent fortification of human milk when tolerating full enteral nutrition - supplementation of human milk with multicomponent fortifiers is associated with short term increases in weight gain, linear and head growth. There was heterogeneity in trials outcomes for an effect on alkaline phosphatase, and a significant increase in bone mineral content in trials comparing multicomponent fortification to no fortification or mineral supplementation. Use of multicomponent fortifiers does not appear to be associated with adverse effects [25],
- For infants with recurrent feed intolerance:
    - Either repeated attempts to reintroduce multicomponent fortifier, or
    - Optimal calcium and phosphate supplementation of human milk feeds.
- In infants for whom human milk is not available (mothers or donor), use of a preterm infant formula with adequate mineral content.
- In high risk infants, continuing multicomponent fortification of human milk beyond the period of maximal osteopenia [26].

Recommended intakes of calcium and phosphorous (See Table for actual amounts): Recommended intakes of calcium and phosphorous in preterm infants are usually based on demands for matching intrauterine bone mineral accretion rates [27-29]. A recent review, however, has suggested that in view of a calcium retention level ranging from 60 to 90 mg/kg/day assures appropriate mineralization, and decreases the risk of fracture and diminishes the clinical symptoms of osteopenia. To achieve this, an intake of 100 to 160 mg/kg/day (2.5-4.0 mmol/kg/day) of highly bioavailable calcium salts, 60 to 90 mg/kg/day (1.9-2.9 mmol/kg/day) of phosphorus and 800 to 1000 IU of vitamin D per day was recommended [30].

Total parenteral nutrition: Prolonged periods of parenteral nutrition have often been associated with osteopenia and rickets. However, with solutions containing 15 mmol/l calcium, 15 mmol/l phosphate and 3 mmol/l magnesium, stable serum indices of mineral homeostasis have been obtained [1]. Recommended parenteral intakes have been calcium 12.515 mmol/l, phosphate 12.914.5 mmol/l, magnesium 2.03.0 mmol/l and vitamin D 160 - 400 IU/kg/d [31]. Greater amounts may be needed in the extremely premature infant, although solubility is a limiting factor. Maximal mineral accretion rates have been reported with Ca/P ratio 1.7:1 [32, 33]. Calcium solubility is increased by using calcium glycerophosphate, which is more soluble than calcium gluconate. TPN at RPA Newborn Care has 12 mmol/L Ca and 12 mmol/L PO_4 (= 1.8 mmol/kg/day Ca and PO_4 at 150 ml/kg/day).

Infants not tolerating multicomponent fortification of human milk:

High risk infants who fail to tolerate the addition of Breast Milk Fortifier should have minerals added to their feeds as for infants being treated for MBD (see below).

Treatment of infants with biochemical or clinical MBD:

Goal of treatment: For infants with biochemical features of MBD, aim for the upper end of the recommended range to prevent fractures and clinical symptoms of osteopenia [30]. To achieve this, an intake of 4.0 mmol/kg/day of calcium and 2.9 mmol/kg/day of phosphorus is recommended.

For infants on 150 ml/kg/day EBM (calcium 1.3 mmol/kg/day phosphate 0.7 mmol/kg/day):

Prescription:

Prevention or 1st week treatment MBD: Starting 50% dose: Prescribe elemental calcium

1.35mmol/kg/day and elemental phosphate 1.1mmol/kg/day;

So:

Calcium 1.35mmol/kg/day = calcium gluconate 10% 6.0ml/kg/day in 2 or 3 divided doses according to feeding regimen, alternating with:

Phosphate 1.1mmol/kg/day = NaH2PO4 (1mmol/ml) 1.1ml/kg/day in 2 or 3 divided doses according to feed regimen

From 2nd week treatment MBD only: 100% dose:

Prescribe elemental calcium 2.7mmol/kg/day and elemental phosphate 2.2mmol/kg/day;

So:

Calcium 2.7 mmol/kg/day = calcium gluconate 10% 12.0ml/kg/day in 4 or 6 divided doses according to feeding regimen, alternating with:

Phosphate 2.2 mmol/kg/day = NaH2PO4 (1mmol/ml) 2.2ml/kg/day in 4 or 6 divided doses according to feed regimen

Optimising mineral supplementation: The method described to optimise mineral intake is to supplement calcium and phosphate with the goal of achieving a slight surplus of supply (SSS) [34]. In infants not on diuretics or methylxanthines, this is achieved by regular adjustments to mineral intake with a goal of achieving a slight excess of urinary mineral excretion:

- Urinary calcium ≥ 1.2mmol/L and phosphate ≥ 0.4 mmol/L [1, 34, 35].

Administration:

Do not administer calcium and sodium dihydrogen phosphate supplements in the same feed. Must be ordered by the registrar on the medication chart and given at alternative feeds.

Side effects of treatment:

- Intestinal obstruction has been associated with calcium supplementation of enteral feeds [36].
- Increased urinary excretion of calcium and phosphate have been associated with nephrocalcinosis in preterm infants [37-41]. Urinary calcium excretion is directly related to calcium intake and increased by furosemide, theophylline and dexamethasone, with furosemide also increases phosphate excretion. Mineral intakes should be targeted to avoid hypercalciuria using the strategy of a slight supply excess.

How long to supplement?

In low risk infants: who had no biochemical or clinical evidence of MBD, there is little evidence on which to base this question but consider changing preterm to standard formula and stopping adding BMF to EBM when babies reach 2000 grams in weight, or more than 50% of enteral feeds are sucking feeds.

In high risk infants: who had biochemical evidence of MBD, fortification of human milk should continue up until biochemical evidence of MBD has resolved and the infant is near term (36 40 weeks).

Summary of Policy

Who is at risk of MBD?

- Immature (< 28 weeks and <1000 g)
- Prolonged TPN

- Breast Fed (mineral deficient but particularly PO_4)

Prevention of MBD

- Early enteral feeds
- BMF

Screening infants at risk of MBD

- Who? = **HIGH RISK** = infants <28 weeks gestation and/or <1000g, ***AND any one of the following:***
  - ≥ 4 weeks to reaching full enteral feeds, OR
  - Inability to supplement with BMF, OR
  - CLD requiring diuretics, OR
  - Postnatal growth failure
- How? = from 6 weeks of age every 2 weeks:
  - Serum Ca / PO_4
  - Serum total alkaline phosphatase
  - Urinary calcium and phosphate

Treatment

- Who? = infants with biochemical, radiological or clinical features of MBD
- How? = optimising mineral intake:
  - Aim for an intake of 4.0 mmol/kg/day of calcium and 2.9 mmol/kg/day of phosphorus (link to table above)

Key Points

Key points	Level of evidence
Human milk feeds in preterm infants are relatively mineral deficient, particularly in phosphate	Cohort (2b) 9, 42
Biochemical features of human milk fed infants with MBD do not accurately predict bone mineral content, but include: • Normal or high serum calcium and low serum phosphate • Increased urinary calcium and decreased phosphate • Increased alkaline phosphatase	Cohort (1b) 43 Cohort (2b) 6, 10 Cohort (1b) 19, 43
The following interventions have been associated with improved mineral accretion or reduced indices of MBD: • Early minimal enteric feeds may increase bone mineral content in preterm infants • Multicomponent fortification of human milk feeds for preterm infants • Avoidance of diuretics (particularly furosemide)	RCT (1b) 21 RCT (1b) 44 RCT (1b) 45
It is unclear whether the target of mineral supplementation in preterm infants should be: • to achieve rates of mineral accretion occurring in the fetus at equivalent gestations, or • to minimize the risk of osteopenia and fractures	Cohorts (2b) 10, 35

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