METABOLIC BONE DISEASE (MBD)

RECOGNITION AND ASSESSMENT

Definition

- Decreased mineralisation of bones due to deficient phosphate (PO_4), calcium (Ca) or vitamin D in preterm babies
- Also known as osteopenia of prematurity

Causes

- Inadequate postnatal intake or absorption to match intrauterine mineral accretion rate

Risk factors

- <32 weeks' gestation or <1500 g birth weight
- Male gender
- Delay in establishing enteral feeds/enteral feeds with low mineral content/bioavailability [unfortified expressed breast milk (EBM), term formula]
- PO_4/Ca or vitamin D deficiency
- Prolonged parenteral nutrition (PN) (>2 weeks)
- Chronic drug use that increases mineral excretion (diuretics, steroids, sodium bicarbonate)
- Lack of mechanical stimulation e.g. sedation/paralysis
- Chronic lung disease
- Cholestatic jaundice
- Short gut syndrome (malabsorption of vitamin D and Ca)

Signs

- ≤6 weeks – most babies are asymptomatic and normal on examination
- Usually presents aged 6–12 weeks
- Poor weight gain or faltering growth
- Respiratory difficulties: failure to extubate due to increased chest wall compliance
- Fractures with minor or no trauma; may manifest as pain on handling
- Craniotabes (softening of skull bones)

Later clinical consequences

- Marked dolicocephaly (long and narrow skull)
- Reduced linear growth

DIAGNOSIS

Serum biomarkers

- Low serum PO_4 (<1.8 mmol/L) with elevated alkaline phosphatase (ALP) (>900 IU/L) is 100% sensitive and 70% specific for diagnosing low bone mineral density
- Low serum PO_4 concentrations (<1.8 mmol/L) have 96% specificity but only 50% sensitivity. Routine PO_4 supplementation in high-risk babies could lead to secondary hyperparathyroidism, and thus worsen MBD
- Serum Ca levels may remain normal until late in the disease despite bone losses of Ca
- In suspected MBD with elevated ALP and low PO_4, serum parathormone (PTH) measurement will help in establishing if there is underlying Ca or PO_4 deficiency to provide correct supplementation
- Ca deficiency causes increased PTH to maintain normocalcaemia
- in PO_4 deficiency there is no compensatory mechanism – PTH remains normal

Urinary biomarkers:

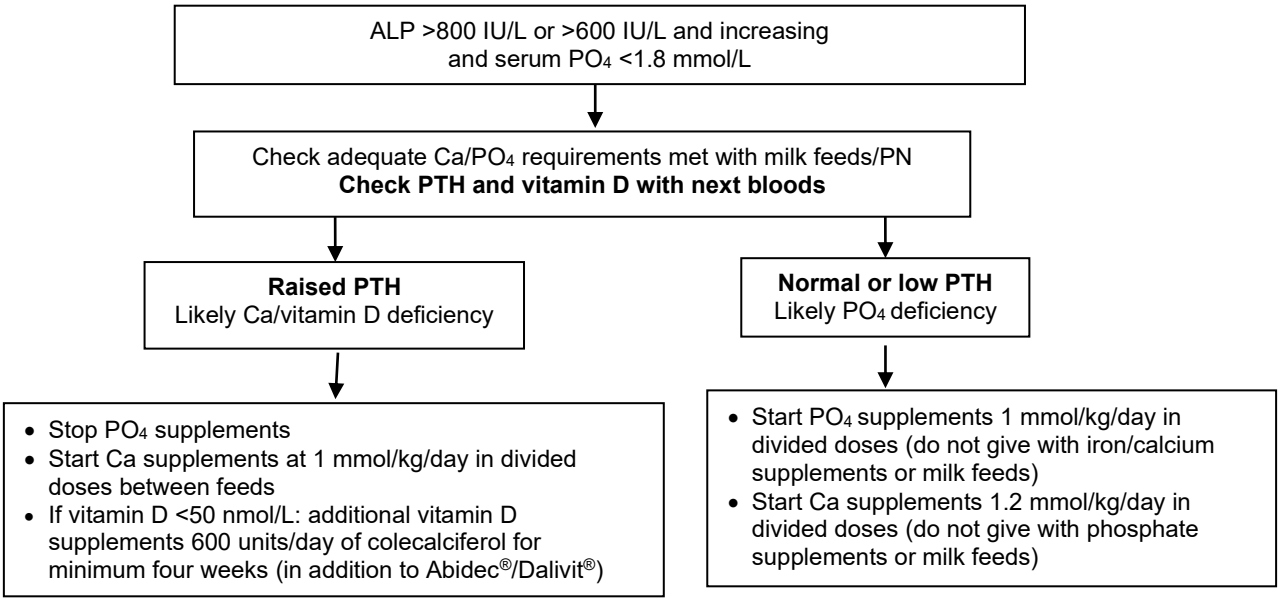
- Urinary excretion of Ca >1.2 mmol/L and PO_4 >0.4 mmol/L signifies slight surplus of supply and correlates with highest bone mineral accretion rate
- phosphaturia can occur due to aminoglycoside, indomethacin and steroid therapy
- calciuria can occur due to diuretics, steroids and theophylline

- Tubular reabsorption percent (TRP) of PO_4 is also a guide to adequacy of PO_4 supplementation. TRP of >95% indicates inadequate supplementation
- TRP (%TRP) = [1 − (urine PO_4/urine creatinine) (plasma creatinine/plasma PO_4)] × 100

Radiological
- Low bone density on X-rays (rachitic changes, cortical thinning, periosteal elevation) or fractures of long bones or ribs
- Dual-energy X-ray absorptiometry/qualitative ultrasound to assess bone mineral density

PREVENTION
- Optimal nutritional intake
  - early PN with optimised Ca and PO_4 content – see **Parenteral nutrition** guideline
  - early enteral feeds
  - optimal ratio of enteral Ca:PO_4 of 1.3:1 – ≤1.4:1 mmol-to-mmol basis should be targeted to avoid secondary hyperparathyroidism
  - adequate Ca (3–5.0 mmol/kg/day) and PO_4 (2.2–3.7 mmol/kg/day) intake by using fortified EBM or preterm formula. ≥140 mL/kg/day fortified EBM or preterm formula is needed to provide this
  - daily intake of ≥400–700 units/kg/day vitamin D
- Ensure appropriate handling and position using deep boundaries to promote active bone loading

INVESTIGATION AND TREATMENT:
For all high risk babies, after ≥1 week of full enteral feeds (≥140 mL/kg/day fortified EBM or preterm formula), measure serum Ca, PO_4 and ALP levels from third week of life and follow this guidance:



- ALP >1000 IU/L: repeat Ca/PO_4/ALP and PTH in 1 week
- ALP 600–1000 IU/L: repeat Ca/PO_4/ALP and PTH in 2 weeks
- ALP <600 IU/L until term: repeat Ca/PO_4/ALP in 2 weeks
- If on additional vitamin D supplementation: check vitamin D levels monthly

NOTE:
- Do not give Ca and PO_4 at the same time as they may precipitate;
- Do not give Ca or PO_4 supplements with feeds
- Ca supplementation can cause intestinal obstruction and hypercalcinosis
- Regular monitoring of urinary Ca/urinary creatinine ratio necessary to detect hypercalciuria (urinary Ca/urinary creatinine) >0.6
- Consider other nutritional deficiencies e.g. zinc, in a baby with faltering growth with evidence of significant bone disease

MONITORING AND FOLLOW-UP

- Stop additional vitamin D when vitamin D and PTH are normal
- Adjust Ca dose based on serum Ca levels and stop only once PTH levels normalise
- Adjust PO_4 dose,based on serum PO_4 levels, and ALP adjusting Ca dose to maintain ratios
- Continue treatment until biochemical indices are normal and radiographic evidence of healing, usually until term corrected gestation