

Metabolic bone disease of prematurity: causes, recognition, prevention, treatment and long-term consequences

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ABSTRACT

Metabolic bone disease of prematurity (MBDP) is characterised by skeletal demineralisation, and in severe cases it can result in fragility fractures of long bones and ribs during routine handling. MBDP arises from prenatal and postnatal factors. Infants who are born preterm are deprived of fetal mineral accumulation, 80% of which occurs in the third trimester. Postnatally, it is difficult to maintain a comparable intake of minerals, and medications, such as corticosteroids and diuretic therapy, lead to bone resorption. With improvements in neonatal care and nutrition, the incidence of MBDP in preterm infants appears to have decreased, although the recent practice of administering phosphate supplements alone will result in secondary hyperparathyroidism and associated bone loss, worsening MBDP. Postnatal immobilisation and loss of placental supply of oestrogen also contribute to skeletal demineralisation. There is no single diagnostic or screening test for MBDP, with pitfalls existing for most radiological and biochemical investigations. By reviewing the pathophysiology of calcium and phosphate homeostasis, one can establish that plasma parathyroid hormone is important in determining the aetiology of MBDP – primarily calcipenia or phosphopaenia. This will then direct treatment with the appropriate supplements while considering optimal physiological calcium to phosphate ratios.

INTRODUCTION

In this review, we will discuss the aetiology and risk factors of metabolic bone disease of prematurity (MBDP) and the current evidence surrounding diagnosis, treatment and prevention. In recent years, we have noted an increase in the number of cases of MBDP associated with skeletal demineralisation due to secondary hyperparathyroidism resulting in pathological fractures. All of these infants were treated with phosphate supplements alone, following diagnosis of MBDP based on elevated serum alkaline phosphatase (ALP) and low serum phosphate. By reviewing the underlying bone mineral homeostasis, we will discuss why such an approach may be inappropriate.

Definition

MBDP is characterised by undermineralisation of the skeleton of preterm infants arising from multiple factors. This undermineralisation of the bone can range from mild to severe and may, ultimately, be associated with fractures that can occur during

What is already known on this topic?

- ▶ Metabolic bone disease of prematurity is the undermineralisation of the preterm infant's skeleton arising from inadequate calcium and phosphate mineral, both prenatally and postnatally.
- ▶ Although usually clinically asymptomatic and identified through biochemical screening or incidentally on radiographs, severe metabolic bone disease of prematurity can result in fragility fractures.
- ▶ Providing at-risk infants with adequate calcium and phosphate through breast milk fortification or specific preterm formulae helps prevent metabolic bone disease of prematurity.

What this study adds?

- ▶ Measurement of parathyroid hormone helps in establishing underlying calcium or phosphate deficiency as a cause for metabolic bone disease of prematurity.
- ▶ Phosphate supplementation alone can reduce serum ionised calcium triggering secondary hyperparathyroidism and worsening metabolic bone disease of prematurity.
- ▶ Treatment of metabolic bone disease of prematurity with oral supplementation should maintain the optimal calcium to phosphate intake ratio to avoid phosphate-driven secondary hyperparathyroidism.

normal handling. MBDP is variably referred to in the literature as rickets of prematurity and osteopaenia of prematurity. However, these latter two terms should be avoided as both generally coexist.

Incidence

The incidence of MBDP is difficult to quantify exactly from the literature, in part due to differences in terminology and in part due to differences in diagnostic criteria. The incidence, when examining for radiological evidence of rickets in preterm infants with a birth weight less than 1000 g, has decreased from approximately 50% in 1987¹ to approximately 15% in 2009.² This decrease is likely to be secondary to general improvements in the care of preterm infants, especially with fortification



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Table 1 Risk factors for metabolic bone disease of prematurity and their underlying causative mechanisms^{3 8–13 66 67}

Risk factor	Underlying mechanism(s)
Prematurity	▶ Loss of maximal in utero mineralisation.
Low birth weight	▶ Associated with prematurity. ▶ Associated with placental insufficiency resulting in reduced active placental transport of minerals in utero.
Loss of maternal oestrogen	▶ Increased osteoclast formation and bone resorption.
Reduced physical activity	▶ Increased bone resorption from reduced mechanical stimulation and deformation.
Parenteral nutrition	▶ Limitations in calcium and phosphate content due to precipitation.
Glucocorticoids	▶ Reduce gut absorption of minerals. ▶ Direct effect on bone (increased bone resorption and reduced bone formation).
Antacids	▶ Reduced gut absorption of calcium (neutralisation of stomach acid).
Loop diuretics	▶ Increased renal calcium loss (inhibition of calcium reabsorption).
Chronic lung disease/ bronchopulmonary dysplasia	▶ Higher energy requirements compromising mineral supply to the bones. ▶ Increased use of glucocorticoids and loop diuretics.
Necrotising enterocolitis	▶ Prolonged periods of parenteral nutrition. ▶ Poor gut function and therefore poor mineral absorption.
Excessive phosphate supplementation	▶ Imbalance in calcium to phosphate ratio resulting in secondary hyperparathyroidism and bone resorption.

of breast milk and use of specific preterm formulae providing extra calcium and phosphate mineral.^{3 4}

Aetiology and risk factors

MBDP is characterised by skeletal demineralisation that arises from inadequate provision of calcium and phosphate minerals necessary for skeletal mineralisation in utero and increased bone resorption after birth. During fetal life, bone mineral accretion is maximal during the third trimester (specifically 32–36 weeks' gestation), with calcium accretion occurring at a rate of 100–130 mg/kg of fetal body weight per day and phosphate accretion occurring at a rate of 60–70 mg/kg of fetal body weight per day to account for a period of rapid bone growth in the developing skeleton.^{5 6} The third trimester thus accounts for approximately 80% of fetal bone mineral accretion and infants who are born preterm will be deprived of this mineral accumulation.⁷ Postnatally, it is difficult to maintain a comparable intake of minerals. Furthermore, medications such as glucocorticoids and diuretic therapy lead to bone resorption. Postnatal immobilisation and loss of placental supply of oestrogen contribute to skeletal demineralisation.^{8 9} Along with gestational age, birth weight has been identified as the strongest independent risk factor for MBDP.^{10–12} Therefore, recommendations suggest that all infants less than 27 weeks' gestation or with a birth weight of less than 1000 g are at high-risk of MBDP, although all infants with a birth weight less than 1500 g should be screened for MBDP.³

Parenteral nutrition is a common risk factor for MBDP.^{11 12} The risk of calcium and phosphate precipitation limits the content of these minerals in parenteral nutrition. A systematic review has demonstrated that a longer duration of parenteral nutrition (greater than 4 weeks) reduces the bone mineral content in

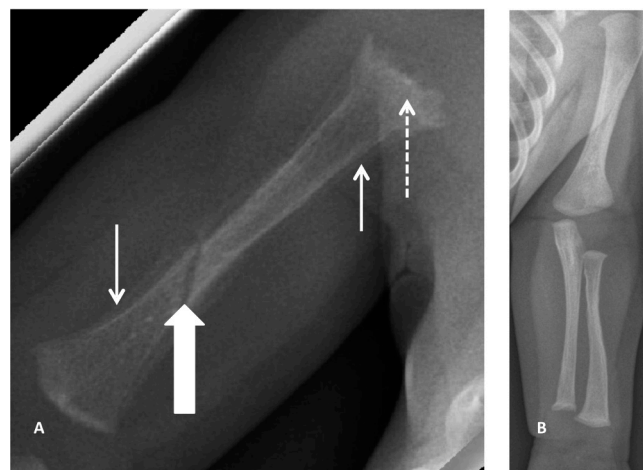


Figure 1 Radiographs of case. (A) Right humerus at 3 months of age, demonstrating fragility fracture (block arrow), diffuse osteopaenia, periosteal reaction (solid arrows) in keeping with hyperparathyroidism and metaphyseal widening and fraying (dotted arrow) in keeping with rickets. (B) Left arm at 5 months of age, within 2 months of adequate treatment for dietary calcium and vitamin D deficiency. This demonstrates almost complete healing of rickets and osteopaenia, with no periosteal reaction evident.

preterm individuals and that calcium and phosphate content also have an affect.¹³ Adequate protein content is required to modulate the solubility and pH of the parenteral nutrition solution and thus allow optimal calcium and phosphate content.¹⁴

Risk factors for MBDP, and their mechanisms of action, are summarised in [table 1](#).

Clinical features

Infants with MBDP demonstrate few symptoms or signs until late into the disease process. Usually, initial suggestions are biochemical, with elevated serum ALP noted on regular neonatal screening regimes. Radiological features are noted later and include osteopaenia (a 'washed out' appearance and thin cortices on radiographs) and eventually pathological fractures if left untreated. The classical features of rickets are rarely encountered with adequate recognition and treatment these days. If fractures occur, they may manifest with pain on handling and swelling, tenderness and deformity at fracture site. However, often they may be noted incidentally on radiographs performed for other indications.¹⁵ Thus, the true fracture incidence is currently unknown but is estimated to be 17%–34%.^{1 15–17} Typically, the fractures occur in the long bones or the ribs.¹⁵ Radiologically apparent rib fractures were only present in 7% of extremely low birth weight infants (less than 1000 g) receiving contemporary neonatal care.¹⁸ Severe MBDP may also lead to respiratory difficulties due to excessive chest wall compliance.

Long-term consequences

The long-term consequences of MBDP itself are difficult to study, partly because of the difficulties in defining a diagnosis of MBDP, and partly because it is challenging to control for all the other inter-related factors that may confound the findings such as gestational age, birth weight, comorbidities, nutrition and later diet and medications.

Lucas and colleagues¹⁹ longitudinally followed up over 700 preterm infants, demonstrating that elevated ALP was independently correlated to reduced lengths at 9 months and 18

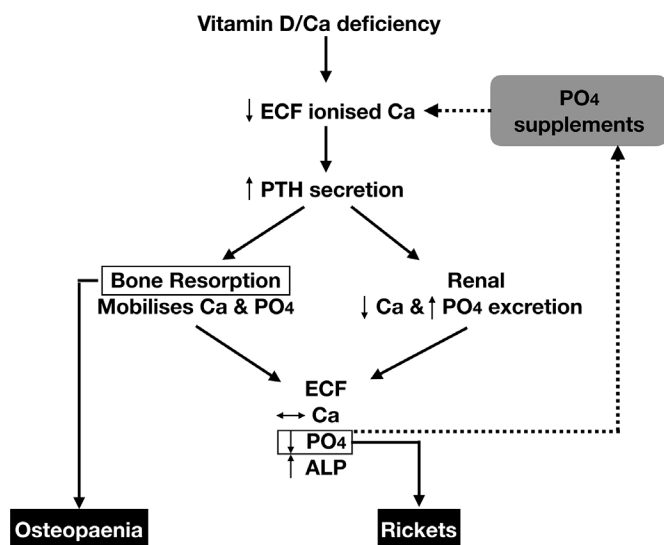


Figure 2 Pathophysiology of calcipenic metabolic bone disease of prematurity, demonstrating how resultant hyperparathyroidism leads to bone resorption, hypophosphataemia and rickets, as well as how treatment with phosphate supplements alone further drives this secondary hyperparathyroidism (dotted arrows). ALP, alkaline phosphatase; Ca, calcium; ECF, extracellular fluid; PTH, parathyroid hormone; PO₄, phosphate.

months of age. A similar correlation was observed in this cohort on longer term follow-up also of 9–12 years.²⁰ This suggests an association between MBDP and childhood growth, although with elevated ALP used as marker.

Dual-energy X-ray absorptiometry (DXA) is useful for assessment of bone mineral content and density, and some studies have used this to investigate bone health in preterm infants. Most studies show that bone mineral content of preterm infants at term is significantly lower than term controls,^{21–23} which persists at 6 months.^{24–25} Others, however, have shown evidence of later catch-up mineralisation.^{15–21–23} Similarly, comparative studies in prepubertal children and young adults (at an age of peak bone mass) have shown differing results.^{26–37}

In summary, the long-term impact of prematurity on bone mineralisation has not been truly established. Furthermore, even if there is a long-term impact on bone mineralisation, the clinical impact of this in terms of fracture incidence in childhood and adulthood has not been established. It is important to note that these studies have examined the effect of prematurity (rather than MBDP) on later bone mineralisation.

Current practices

There is wide variability in screening, diagnostic and treatment practices for MBDP, as demonstrated by surveys performed in the UK³⁸ and the USA.³⁹ Screening has traditionally involved measurement of serum calcium, phosphate and ALP, with MBDP diagnosed in the presence of raised ALP and low phosphate. Treatment in the literature has supported mineral supplementation, taking into consideration that both calcium and/or phosphate deficiency needs addressing. However, current practices in the UK seem to focus almost exclusively on phosphate supplementation alone or in combination with active analogues of vitamin D such as alfacalcidol.³⁸ The following describes a typical case that we commonly see that demonstrates the flaws to such screening and treatment approaches.

Case

A male infant was born at 26 weeks' gestation, weighing 700 g. He suffered from chronic lung disease, as well as a prolonged period of poor enteral nutrition (including 2 weeks of exclusive parenteral nutrition). Once enterally fed, he was on unfortified expressed breast milk, before switching to a preterm formula due to decline in maternal milk supply.

At 3 months of age, 'bone biochemistry' revealed: corrected calcium (cCa) 2.54 mmol/L (normal range: 2.2–2.7), phosphate 0.98 mmol/L (normal range: 1.2–2.2), ALP 923 U/L (90–540). Based on this biochemistry, phosphate supplements (1 mmol/kg/day) were initiated by the neonatal team. He was already on multivitamin supplements providing 400 IU of ergocalciferol. Repeat bone biochemistry demonstrated: cCa 2.49 mmol/L, phosphate 1.06 mmol/L, ALP 1220 U/L, parathyroid hormone (PTH) 72.3 pmol/L (normal range 1.6–6.9), 25-hydroxy-vitamin D 46.2 nmol/L, 1,25-dihydroxy-vitamin D:380 pmol/L (normal adult range: 43–144). One week later, he was noted to have a swollen left thigh, with a radiograph demonstrating fracture of his left femur. A skeletal survey in addition demonstrated a right humeral fracture, with periosteal reaction along diaphysis of long bones (in keeping with hyperparathyroidism), as well as radiological changes of rickets (figure 1A). At this point, he was referred to our service. We discontinued phosphate supplements, provided oral calcium supplements (4 mmol/kg/day) and additional colecalciferol (3000 IU daily for 4 weeks).

Within 2 months, his bone biochemistry had normalised: cCa 2.82 mmol/L, phosphate 2.13 mmol/L, ALP 483 U/L and PTH 5.2 pmol/L. His calcium supplements were discontinued, and he remained only on multivitamin supplements and formula milk feeds appropriate for his age. Follow-up radiographs showed healing of rickets and improvement in mineralisation (figure 1B).

Calcium and phosphate homeostasis underlying MBDP

In order to understand the pathophysiology of MBDP in the case above, a review of calcium and phosphate homeostasis is required. Calcium and phosphate are required for a multitude of important cellular processes and bones provide a storehouse for these minerals. Calcium is predominantly an extracellular ion, and its concentration is tightly maintained between 2.2 mmol/L and 2.7 mmol/L so that important biological processes are sustained.

Phosphate, however, is predominantly an intracellular ion,⁴⁰ which may reflect its increased requirement for intracellular processes during childhood. While a robust mechanism exists for maintaining serum calcium within the normal range, such a mechanism does not exist for phosphate.

PTH plays an important role in calcium and phosphate homeostasis. It facilitates conversion of 25-hydroxy-vitamin D to 1,25-dihydroxy-vitamin D (the active metabolite of vitamin D), which helps in calcium and phosphate absorption from the diet. In a state of vitamin D deficiency and/or inadequate dietary absorption/intake of calcium (calcipenia), PTH mobilises calcium and phosphate from the bones and actively excretes phosphate in the urine (figure 2). Paradoxically therefore in mild to moderate calcipenia, serum calcium concentration is maintained, while that of phosphate is reduced. The increased bone turnover from the resorptive action of PTH on bones leads to elevated ALP.

However, low dietary intake of phosphate or increased urinary phosphate leak (phosphopaenia), as seen in renal tubular disorders, will reduce serum phosphate concentration. In such a scenario, there is unfortunately no compensatory mechanism to

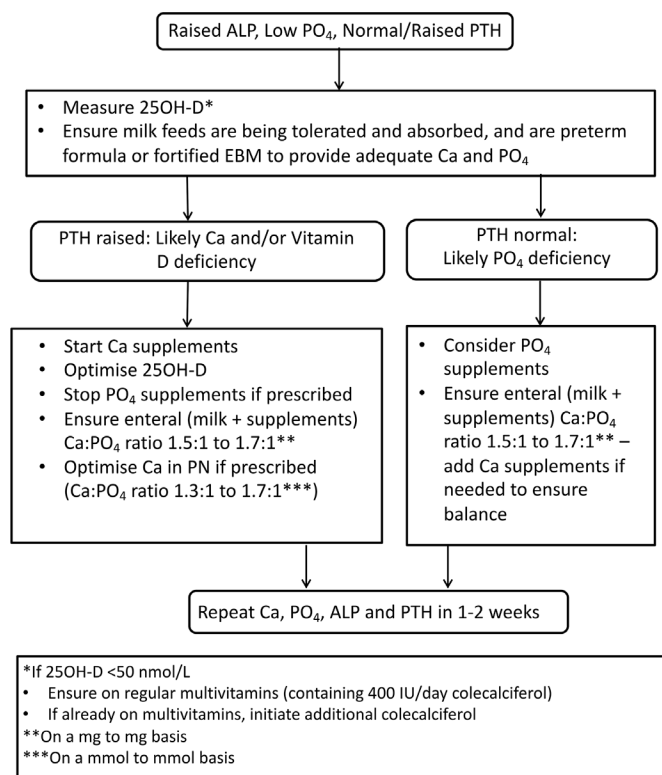


Figure 3 Flow chart of suggested management approach to biochemical evidence of metabolic bone disease of prematurity, based on plasma parathyroid hormone level. 25OH-D, 25-hydroxy-vitamin D; ALP, alkaline phosphatase; Ca, calcium; EBM, expressed breast milk; PN, parenteral nutrition; PO₄, phosphate; PTH, parathyroid hormone;

mobilise phosphate from the bones, and therefore, PTH concentration is maintained within the normal range.

Low serum phosphate concentration reduces apoptosis of terminally differentiated hypertrophic chondrocytes in the growth plates causing failure of mineralisation and is thus the end point causing rickets in both calcaemic and phosphopaenic states.⁴¹ In the calcaemic state, elevated PTH in addition leads to bone resorption, which radiologically manifests as osteopaenia, superiosteal bone resorption, periosteal reaction along the diaphysis and brown tumours. Skeletal demineralisation resulting from secondary hyperparathyroidism significantly reduces bone strength resulting in pathological long bone and rib fractures on minimal or routine handling. Thus, in the calcaemic state, elevated PTH worsens the rickets.

In the calcaemic state, treatment with high dose calcium and vitamin D supplementation provides additional calcium for bone mineralisation and increases serum ionised calcium which reduces PTH concentration, thereby reversing hypophosphataemia as well as bone resorption and facilitating healing of rickets. Treatment with oral phosphate may appear logical in such a scenario as serum phosphate concentration is low. However, this will bind to ionised calcium to form a calcium-phosphate product, causing a further reduction of ionised calcium, which will trigger further elevation of PTH, thereby worsening rickets (figure 2). In the above case, treatment with phosphate supplements without concurrent calcium supplementation to address the calcaemia resulted in secondary hyperparathyroidism and worsening of bone demineralisation. By simply providing adequate calcium supplementation, the secondary hyperparathyroidism and rickets resolved.

Prevention of MBDP

Preterm infants have a much higher requirement of minerals compared with term infants. Recommendations for preterm and low birthweight infants from nutritional consensus guidelines are to provide 120–200 mg/kg/day of calcium and 60–140 mg/kg/day of phosphorous through enteral feeds.^{3 4 42} For optimal absorption and retention, it is crucial to maintain the enteral calcium to phosphate intake ratio at 1.5:1 to 1.7:1 on mg-to-mg basis.³ A higher requirement of calcium is likely because the efficiency of calcium absorption by preterm infants is around 50%–60%,^{43 44} while that of phosphorous is 80%–90%.^{45 46} Human milk fortifier, added to the breast milk, and preterm formulae are designed to provide increased mineral requirements for preterm infants.

For parental nutrition, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended calcium 1.3–3.0 mmol/kg/day and phosphate 1.0–2.3 mmol/kg/day, with a molar calcium to phosphate ratio in the range 1.3:1 to 1.7:1,⁴⁷ and this was supported by the American Society for Parenteral and Enteral Nutrition Board.¹³ However, there are reports of hypercalcaemia and hypophosphataemia in the first week of life with this formulation.⁴⁸ Recent ESPGHAN guidelines therefore have suggested molar calcium to phosphate ratio between 0.8:1 and 1:1 in early days followed by 1.3:1 in a growing preterm infant.⁴⁹

While importance of vitamin D on skeletal health is well recognised, its role in dietary calcium and phosphate absorption specifically in preterm infants is not clear. In the absence of good quality evidence, it is recommended to supplement preterm infants with vitamin D to maintain 25-hydroxy-vitamin D concentrations above 50 nmol/L (20 ng/mL).⁵⁰ American Academy of Pediatrics' committee on nutrition recommends oral 400 IU/day of vitamin D supplementation in preterm infant weighing less than 1500g and 200–400 IU/day in preterm infants weighing greater than 1500g.³ This recommendation is in addition to the vitamin D present in fortified breast milk and preterm formula feeds.

Calcium and phosphorous homeostasis is influenced by multiple factors in sick preterm infants, which therefore increases the risk of metabolic bone disease. It is therefore important that the nutrition of each infant is individualised, keeping in mind optimal enteral and parenteral calcium to phosphate ratios. Mineral requirements should be reviewed by regular biochemical monitoring. Since MBDP typically develops between 3 weeks and 12 weeks, biochemical monitoring should commence from 2 weeks to 3 weeks of age. This should include serum ALP, phosphate and adjusted calcium and plasma PTH. Although there is no literature surrounding the frequency of biochemical monitoring, we would recommend 1–2 weekly depending on the degree of risk based on risk factors present.

There is no evidence in the medical literature to routinely supplement oral phosphate to preterm infants, therefore we *do not recommend routine supplementation of oral phosphate in premature infants for prevention of MBDP*. On the contrary, oral phosphate increases the risk of secondary hyperparathyroidism (by reducing serum ionised calcium) and in fact may promote or worsen MBDP.

Investigations for MBDP

There is not a single precise biochemical marker, which can be used for the diagnosis of MBDP.⁵¹ ALP has been widely used as a marker for MBDP, although there are no agreed cut-off values^{10 52 53} and in isolation it is not a useful indicator of disease.⁵⁴

Table 2 Authors' summary recommendations for prevention, investigation and treatment of metabolic bone disease of prematurity in at-risk groups based on pathophysiology and evidence

At-risk groups	<ul style="list-style-type: none"> ▶ Preterm: gestational age less than 28 weeks. ▶ Low birth weight: less than 1500 g. ▶ Parenteral nutrition for over 2 weeks. ▶ Chronic lung disease/bronchopulmonary dysplasia. ▶ Necrotising enterocolitis. ▶ Prolonged prescribing of glucocorticoids, antacids or loop diuretics.
Prevention	<ul style="list-style-type: none"> ▶ Fortified breast milk or preterm formula. ▶ Maintain serum 25OH-D concentration above 50 nmol/L, with additional vitamin D supplementation if necessary. ▶ Ensure optimal enteral and parenteral calcium to phosphate ratios.
Investigations	<p><i>When?</i></p> <ul style="list-style-type: none"> ▶ From 2–3 weeks of age. ▶ 1–2 weekly depending on degree of risk. <p><i>What?</i></p> <ul style="list-style-type: none"> ▶ Bone profile: serum ALP, phosphate and adjusted calcium. ▶ Plasma PTH. <p><i>If metabolic bone disease of prematurity suspected biochemically (↑ALP, ↓phosphate, ↑PTH)?</i></p> <ul style="list-style-type: none"> ▶ Measure serum 25OH-D and supplement if less than 50 nmol/L. ▶ Review causative medications that can be discontinued. ▶ Radiograph of wrist and knee for evidence of osteopaenia or rickets. <p><i>Calcipenic state (suggested by ↑PTH)</i></p> <ul style="list-style-type: none"> ▶ Start oral calcium supplements. ▶ Ensure total enteral calcium to phosphate intake ratio 1.5:1 to 1.7:1 on a mg-to-mg basis. ▶ Optimise calcium supply from parenteral nutrition, if applicable, with molar calcium to phosphate ratio 1.3:1 to 1.7:1. ▶ Monitoring 1–2 weekly with plasma PTH and serum ALP, adjusting calcium dose and calcium to phosphate ratios based on PTH. <p><i>Phosphopaenic state (suggested by normal PTH)</i></p> <ul style="list-style-type: none"> ▶ Consider starting oral phosphate supplements, ensuring that total enteral calcium to phosphate intake ratio remains 1.5:1 to 1.7:1 on a mg-to-mg basis (oral calcium supplements may need to be started concurrently). ▶ Optimise phosphate supply from parenteral nutrition, if applicable, while keeping molar calcium to phosphate ratio 1.3:1 to 1.7:1. ▶ Monitoring 1–2 weekly with plasma PTH and serum ALP, adjusting phosphate (and calcium dose if applicable) and calcium to phosphate ratios based on PTH and ALP.
Treatment	<p><i>Calcipenic state (suggested by ↑PTH)</i></p> <ul style="list-style-type: none"> ▶ Start oral calcium supplements. ▶ Ensure total enteral calcium to phosphate intake ratio 1.5:1 to 1.7:1 on a mg-to-mg basis. ▶ Optimise calcium supply from parenteral nutrition, if applicable, with molar calcium to phosphate ratio 1.3:1 to 1.7:1. ▶ Monitoring 1–2 weekly with plasma PTH and serum ALP, adjusting calcium dose and calcium to phosphate ratios based on PTH. <p><i>Phosphopaenic state (suggested by normal PTH)</i></p> <ul style="list-style-type: none"> ▶ Consider starting oral phosphate supplements, ensuring that total enteral calcium to phosphate intake ratio remains 1.5:1 to 1.7:1 on a mg-to-mg basis (oral calcium supplements may need to be started concurrently). ▶ Optimise phosphate supply from parenteral nutrition, if applicable, while keeping molar calcium to phosphate ratio 1.3:1 to 1.7:1. ▶ Monitoring 1–2 weekly with plasma PTH and serum ALP, adjusting phosphate (and calcium dose if applicable) and calcium to phosphate ratios based on PTH and ALP.

25OH-D, 25-hydroxy-vitamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone.

Based on pathophysiology of MBDP described above, it is surprising that the crucial role of PTH in MBDP has received limited attention. This may be in view of the fact that the majority of the research concerning MBDP occurred in the 1980s and 1990s, when a reliable PTH assay was not readily available. Moreira *et al*⁵⁵ demonstrated that elevated PTH was more sensitive (71% vs 29%) and roughly as specific (88% vs 93%) as ALP as a marker for severe MBDP. When combined with low serum phosphate, an elevated PTH was 100% sensitive and 94% specific in identifying MBDP. In 160 preterm infants, Czech-Kowalska *et al*⁵⁶ found only PTH to be a predictor of low bone mineral content at term age using DXA scan. Considering the pathophysiology, one would expect that plasma PTH would become elevated earlier than changes in ALP or phosphate. Therefore, in our view, measurement of plasma PTH both for screening and diagnosis is crucially important. The reference

range of plasma PTH in neonates is not well established. However, a recent study of 20 healthy preterm neonates (birth weight of 1000–1500 g, gestational age of 27–31 weeks) using third-generation chemiluminescence immunoassay demonstrated that the physiological range for PTH in neonates was close to the reference limits for adults (1–7 pmol/L; 9.4–66 pg/mL).⁵⁷ It is important to note that the trend in plasma PTH values is just as important as the absolute value, both for screening and monitoring.

Urinary calcium and phosphate excretion studies have shown variable results and are significantly affected by medications such as diuretics. On their own, they cannot be used for diagnosis of MBDP or making decisions on calcium and/or phosphate supplementation.⁵⁸

Osteopaenia, with or without rickets, and signs of secondary hyperparathyroidism may be noted incidentally on radiographs, for example a chest radiograph performed for clinical reasons. Wrist and knee radiographs can help in confirming the diagnosis and could be undertaken in those showing biochemical features of MBD. They are, however, subjective, and radiologically apparent osteopaenia only becomes reproducibly apparent when 30%–40% of mineral is lost.⁵⁹ Therefore, there is no consensus on the role and type of radiographs in assisting diagnosis of MBDP. If fractures are detected, then a limited skeletal survey may be necessary to identify other fractures.¹⁵ In medico-legal cases, a skeletal survey in accordance with guidance from The Royal College of Radiologists will be required.⁶⁰

DXA and quantitative ultrasonography are research tools, and it is not possible to undertake them in routine clinical practice in neonatal units to predict, confirm, diagnose or monitor MBDP.⁶¹

Treatment of MBDP

Once diagnosis of MBDP is confirmed, the approach of management is summarised in [figure 3](#).

Management should be guided by biochemical parameters pointing either towards relative calcipenia or phosphopaenia. Measurement of PTH is therefore of paramount importance as elevated PTH is seen in calcium deficiency, while it is low or normal in phosphate deficiency.⁶²

In children with elevated PTH suggesting calcium deficiency, oral calcium supplementation helps in normalising plasma PTH, serum phosphate and ALP and healing of rickets. ALP takes longer to completely normalise as improvement in growth after healing of rickets reflects increased bone formation. Moreira *et al* were able to normalise plasma PTH in 44 preterm infants (mean gestational age was 25±1.4 weeks and mean birth weight was 688±121.6 g) with MBDP by supplementing additional calcium through feeds.⁵⁵

The recommendation for calcium supplementation is initiation at a dose of 0.5 mmol/kg/day, which can be increased as tolerated to 1–1.25 mmol/kg/day in 2–3 divided doses.³ Higher doses may be required in those with severe MBDP with very high plasma PTH and serum ALP concentrations. The dose can be adjusted by 1–2 weekly monitoring of PTH, calcium, phosphate and ALP. The dose can be reduced if serum calcium is above the normal range but should not be discontinued until plasma PTH levels have normalised. High serum calcium poses a risk for nephrocalcinosis, but in the presence of normal or elevated PTH, the risk is negligible as PTH facilitates active tubular reabsorption of calcium from the glomerular filtrate.

Elevated PTH in MBDP converts 25-hydroxy-vitamin D into 1,25-dihydroxy-vitamin D and can cause depletion of 25-hydroxy-vitamin D. Therefore, vitamin D supplementation should be continued, and high-dose supplementation would be required in cases of deficiency/insufficiency (<50 nmol/L).

Historically, active vitamin D analogues such as alfacalcidol and calcitriol were given to preterm infants with MBDP on the assumption of immaturity of 25-hydroxylation. However, this has been demonstrated not to be the case.⁶³ Therefore, these active vitamin D analogues have no role in the routine management of MBDP. They are only indicated in the presence of kidney disease, liver failure and genetic defects in vitamin D pathways.

In contrast, in dietary phosphate deficiency and/or urinary phosphate loss, PTH levels are not elevated,⁶⁴ and phosphate supplements may be used to treat the MBDP. However, even in presumed phosphate deficiency, phosphate supplementation must be used carefully to ensure that the ratio of total enteral calcium to phosphate is not altered in favour of phosphate, otherwise a relative excess of phosphate will result in reduced serum ionised calcium and resultant hyperparathyroidism (and further urinary phosphate loss) in response. Evidence suggests that phosphate retention and calcium absorption is optimised when the ratio of calcium to phosphate intake is 1.5:1 to 1.7:1 on mg-to-mg basis.³ This must be considered before initiating phosphate supplementation, taking into account calcium and phosphate in nutrition also and due consideration given to starting concurrent calcium supplements to maintain this ratio.

Caution must be observed in administration of calcium and phosphate supplements. The two must not be provided simultaneously as they precipitate and are not absorbed. Calcium supplements administered simultaneously with feeds will precipitate with phosphate in the feeds and can reduce serum phosphate levels. Similarly, oral phosphate supplements administered with feeds can reduce calcium absorption.

Finally, although physical activity programmes have been investigated, a Cochrane review only demonstrated short-term benefits in weight gain and bone mineralisation, with inadequate data to assess long-term benefit.⁶⁵

Our recommended prevention, investigation and treatment strategies for MBDP are summarised in table 2.

CONCLUSION

MBDP continues to be a problem in preterm infants, though its incidence has decreased with improvements in neonatal care with nutritional practices focusing on increased calcium and phosphate provision. Biochemical investigations should include plasma PTH, as well as calcium, phosphate and ALP. Treatment is based on identifying whether the MBDP is due to calcipenia or phosphopaenia, with supplements provided while maintaining optimal calcium to phosphate intake ratios.

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