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Original article

Metabolic bone disease of prematurity – a report of five cases

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Abstract

Metabolic bone disease of prematurity (MBDP) is a multifactorial condition characterized by a reduction in bone mineral density, involving chiefly nutritional but also biomechanical and hormonal factors.

This is a relatively common complication among preterm infants, especially in those born before completing 28 weeks of gestation or those with extremely low birth weight (ELBW; < 1,000 g). These infants are prematurely deprived of calcium and phosphorus transplacental transfer, which is maximal during the third trimester of pregnancy and therefore present diminished mineral stores that may be further depleted by increased mineral requirements in the neonatal period.

There are no standard approaches for the investigation and monitoring of MBDP and many cases remain undiagnosed until severe demineralization occurs. This entity is often clinically silent, being detected in laboratory studies or incidentally on radiographies performed for other purposes.

We report five cases of premature infants diagnosed with MBDP in our neonatal intensive care unit (NICU) and discuss early prevention and detection of this disease.

The primary prevention and treatment approach is based on early and adequate nutritional intervention by providing sufficient calcium and phosphorus intakes and vitamin D supplementation. Motor physiotherapy is also recommended.

Despite these preventive strategies, some infants may still develop MBDP and require further supplementation.

Considering the potential complications of MBDP, screening should target infants at high risk, including those with very low birth weight (VLBW, < 1,500 g), namely those born before 28 weeks of gestation, on total parenteral nutrition (TPN) for longer than 4 weeks, unable to reach full fortified feeds or exposed to drugs with deleterious effects on bone health.

Keywords

Metabolic bone disease, preterm, calcium, phosphorus, alkaline phosphatase, nutrition.

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Introduction

Metabolic bone disease of prematurity (MBDP), otherwise referred to as osteopenia of prematurity or neonatal rickets [1], is a multifactorial condition characterized by a reduction in bone mineral density (BMD) [2], involving chiefly nutritional but also biomechanical and hormonal factors [3]. The frequency of MBDP is inversely correlated with gestational age and birth weight [2, 4, 5].

The development of the skeletal system comprises a delicate balance between osteoblastic activity, responsible for the synthesis of the organic bone matrix (osteoid) – onto which mainly calcium and phosphate salts are deposited in a process known as bone mineralization –, and osteoclastic activity, responsible for bone reabsorption and remodeling [6].

Low BMD may result from a disorder of the normal physiological process of mineralization, leading to a reduction in bone mineral content (BMC) – osteomalacia –, and/or from either insufficient deposition or increased resorption of organic bone matrix – osteopenia. The mineralization defect may also affect the growth plate cartilage, resulting in rachitic abnormalities.

In literature, the term "osteopenia" is commonly used to describe a reduction in BMD regardless of the cause, which might be confusing. Thereby, the term "MBDP" is the most accurate designation for this entity, involving different pathophysiological conditions: osteomalacia, osteopenia and rickets [7]. In addition, the term "osteoporosis" has been used to describe the radiological finding of bone rarefaction in premature infants.

In both term and preterm infants, the physiological adaptation of skeleton to the extra-uterine environment leads to an increase in bone resorption, which sharply contrasts with the predominant modeling activity that occurs *in utero*. As a result, infants' long bone mineral density decreases approximately 20-30% during the first 6 months of life [6, 7].

Preterm neonates, especially those born before completing 28 weeks of gestation [8] or those with extremely low birth weight (ELBW; < 1,000 g) [9], are particularly susceptible to further decreases in bone density, as they are prematurely deprived of calcium and phosphorus transplacental transfer, which is maximal during the 3rd trimester of pregnancy (accretion rates of 100-120 mg/kg/day for calcium and 50-65 mg/kg/day for phosphorus) [3].

Chronic damage to placenta observed in cases of intrauterine growth restriction, pre-eclampsia and chorioamnionitis may also interfere with the mineral transport, contributing to bone demineralization [1, 8, 10, 11].

Furthermore, it is difficult to match the transplacental mineral accretion in the postnatal period using unfortified breast milk or standard formula, and supplementation of both calcium and phosphorus has turned out to be challenging, principally in infants who do not tolerate enteral feeding and require prolonged total parenteral nutrition (TPN) [2, 12, 13]. In addition to the limited solubility of minerals in parenteral solutions (particularly when fluid restriction is needed), the use of calcium gluconate induces a risk of aluminum contamination, which is potentially deleterious for bone formation and neurodevelopment [1, 3, 14].

Other risk factors include chronic comorbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis and TPN-associated cholestasis, as well as the administration of specific drugs in the neonatal intensive care unit (NICU) like methylxanthines, diuretics (e.g., furosemide) and steroids [4, 15].

Additionally, evidence indicates that mechanical forces exerted upon the bones and joints stimulate bone formation and growth, whereas immobilization leads to bone resorption and urinary calcium excretion [3, 16]. Bone loading occurs mainly in the last trimester of pregnancy through active fetal movements against resistance of the uterine wall, and largely contrast with the prolonged periods of immobilization in the NICU [17, 18]. Similarly, sepsis, central nervous system pathology, muscular disorders and paralysis may contribute to the lack of mechanical stimulation [15, 19].

Vitamin D deficiency is not the primary cause of MBDP [18, 20]. Although the plasma concentration of this hormone at birth depends on the mother's vitamin D status [12], the pathways of vitamin

D absorption and metabolism are fully operative in babies born before 28 weeks of gestation [6] and, with adequated vitamin D supplementation, even very low birth weight (VLBW, < 1,500 g) newborns can synthesize sufficient levels of 1,25-dihydroxyvitamin D3 [21].

MBDP has become a relevant concern in neonatology, as the continuous advances in neonatal intensive care have significantly improved survival rates in preterm neonates [22].

The incidence of this disease in premature infants who have not received fortified breast milk or high mineral containing formulas is reported to be approximately 23% in VLBW and 55% in ELBW [23]. The prevalence in breastfed preterm infants is estimated at 40%, compared to 16% in those fed with preterm formula supplemented with calcium and phosphorus [11, 24]. However, this remains a controversial topic due to the lack of standardized approaches for the investigation and monitoring of MBDP.

In this article, we report five cases of premature infants diagnosed with MBDP in our NICU and discuss early prevention and detection of this disease.

Case 1

A male preterm infant was delivered in March 2001 by cesarean section at 28^{+6} weeks of gestation due to maternal pre-eclampsia, weighing 880 g. Apgar scores were 6 and 7 at 1st and 5th minutes, respectively.

The patient was admitted to the NICU on his 1st day of life and required ventilatory support during his entire hospitalization (186 days).

TPN was required during 90 days, followed by a combination of parenteral and orogastric feeding until enteral feeding was tolerated. He received expressed breast milk whenever possible and semi-elemental formula or preterm formula supplemented with maltodextrin and medium chain triglyceride (MCT) oil. While on completely enteral feeding, oral multivitamin supplementation was given, including vitamin D3 (667 IU/day).

Other clinical characteristics, comorbidities and management are reported in **Tab. 1**.

During his 14th week of life, a pathological fracture of the left femur occurred as a consequence of osteomyelitis. Antibiotic therapy was administered and satisfactory consolidation of the fracture was achieved by cast immobilization of the affected limb.

Other radiographic findings at this time included considerable osteopenia, costochondral widening and multiple rib fractures. Craniotabes and "rachitic rosary" were also shown on physical examination. A week later, the serum alkaline phosphatase (ALP) was 1,421 IU/L, serum phosphorus was 4.08 mg/dl (1.351 mmol/L) and serum calcium was 4.76 mEq/L (2.380 mmol/L).

In addition, a wrist radiography performed during the 19th week of life showed widening of the metaphyses of radius and ulna bones, as well as marked osteopenia. At this time, the serum ALP was 775 IU/L, serum phosphorus was 34 mg/dl (1.095 mmol/L) and the serum calcium was 4.0 mEq/L (2.000 mmol/L).

Low ionized calcium (0.940 mmol/L) was detected a week later and persisted until his last week of life. During this period, treatment with calcitriol was given (0.10 mcg on alternated days).

The infant's clinical status progressively deteriorated, resulting in fatal cardiorespiratory arrest at 6 months of age. Necropsy was not authorized by his parents.

Case 2

This male preterm infant was delivered in September 2001 by cesarean section at 26^{+0} weeks of gestation due to fetal bradycardia, weighing 940 g. The mother had been declared brain-dead one month earlier as a result of a malignant glioma and life support measures were maintained in order to achieve fetal pulmonary maturation. Apgar scores were 7 and 9 at 1st and 5th minutes, respectively.

This newborn was admitted to the NICU on his first day of life and required ventilatory support during his entire hospitalization (70 days).

TPN was required during 62 days, followed by a combination of parenteral and orogastric feeding with semi-elemental formula.

Other clinical characteristics, comorbidities and management are reported in **Tab. 1**.

During the 7th week of life, laboratory studies showed an increase in serum ALP (475 IU/L). The serum phosphorus was 3.80 mg/dl (1.225 mmol/L), serum calcium was 3.6 mEq/L (1.800 mmol/L) and ionized calcium was 1.03 mmol/L. Two weeks later, marked osteopenia was detected on a radiography of the lower limbs.

The infant's clinical status was critical, resulting in fatal cardiorespiratory arrest at 10 weeks postnatal age. Necropsy was not authorized by his father.

Table 1. Clinical characteristics and morbidity of the five patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Year of birth	2001	2001	2003	2005	2010
Gestational age (weeks)	28^{+6}	26^{+0}	30^{+4}	36^{+3}	27^{+3}
Birth weight (g)	880	940	1,030	3,136	520
Gender	Male	Male	Female	Female	Female
PDA	Yes	Yes	Yes	Yes	Not reported
PDA management	1 course of indomethacin	2 courses of indomethacin	3 courses of indomethacin + surgery	2 courses of indomethacin	-
Anemia	Yes	Yes	Yes	Yes	Yes
Red blood cell transfusions (n)	16	15	10	8	18
Thrombocytopenia	Yes	Yes	Yes	No	No
Platelet transfusions (n)	11	25	11	-	-
Phototherapy for hyperbilirubinemia (days)	6	5	6	3	5
Culture-proven sepsis	Yes	Yes	Yes	Yes	Yes
Osteomyelitis	Yes	No	No	No	Yes
Necrotizing enterocolitis (management)	No	Yes (Medical)	No	No	Yes (Surgical)
Seizures	No	Yes	Yes	No	Yes
Anticonvulsants	-	Phenytoin Phenobarbital	Phenobarbital	-	Phenobarbital Levetiracetam Clonazepam
IVH (grade ≥ III)	No	Yes	No	No	Yes
ROP (grade ≥ II)	No	No	No	No	Yes
BPD	Yes	Yes	Yes	Yes	Yes
TPN (days)	90	62	57	89	75
Furosemide (days)	15	10	56	52	16
Hydrochlorothiazide + spironolactone (days)	43	-	57	-	-
Steroids (days)	12	4	15	12	12
Caffeine citrate (days)	20	18	11	-	24
Antibiotic therapy (days)	94	57	73	73	115
Kinesiotherapy	Yes	Yes	Yes	Yes	Yes
Mechanical ventilation (days)	186	70	148	89	78
Hospitalization (days)	186	70	148	121	154
Outcome at discharge	Death	Death	Death	Death	Discharge

PDA: patent ductus arteriosus; IVH: intra-ventricular hemorrhage; ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia; TPN: total parenteral nutrition.

Case 3

A female preterm infant with a prenatal diagnosis of omphalocele was delivered in March 2003 by cesarean section at 30^{+4} weeks of gestation, with a birth weight of 1,030 g. Apgar scores were 5 and 8 at 1st and 5th minutes, respectively.

The patient was admitted to the NICU and underwent surgery for omphalocele repair on her first day of life. She experienced subsequent hypotensive periods, requiring fluid, inotropic and vasopressor support during the 1st week of life.

Ventilatory support was necessary during her entire hospital stay (148 days).

The patient required TPN during 57 days, followed by a combination of parenteral and orogastric feeding until enteral feeding was tolerated. She received expressed breast milk whenever possible and semi-elemental formula or preterm formula supplemented with maltodextrin and MCT oil. While on completely enteral feeding, oral multivitamin supplementation was given, including vitamin D3 (667 IU/day).

Other clinical characteristics, comorbidities and management are reported in **Tab. 1**.

During the 16th week of life, an increased serum ALP level of 795 IU/L was detected in laboratory studies. The serum phosphorus was 4.45 mg/dl (1.440 mmol/L), serum calcium was 4.8 mEq/L (2.4 mmol/L) and ionized calcium was 1.080 mmol/L. Urinary calcium concentration was 2.1 mmol/L and urinary phosphorus concentration was 0.315 mmol/L.

Considerable osteopenia was shown on radiographic studies performed during the same week. Calcium supplementation in the milk was initiated (1 ml of calcium gluconate 10% in each bottle) and vitamin D3 intake was increased to 1,334 IU/L. Three weeks later, urinary calcium and phosphorus increased to 5.95 mmol/L and 1.84 mmol/L, respectively.

The patient suffered a fatal cardiorespiratory arrest at postnatal age of 21 weeks. Necropsy was not authorized by her parents.

Case 4

This is a case of a female infant with a prenatal diagnosis of diaphragmatic hernia, delivered in October 2005 by cesarean section at 36^{+3} weeks of gestation, with a birth weight of 3,136 g. Apgar scores were 7 and 9 at 1st and 5th minutes, respectively.

She was admitted to the NICU on her 1st day of life and required inotropic and ventilation support until the 9th and the 12th postnatal weeks, respectively.

An echocardiography was performed on her 2nd day of life, showing severe pulmonary hypertension and right ventricular dilatation. She received treatment with nitric oxide (122 days) and sildenafil (53 days).

The patient underwent surgery for correction of the diaphragmatic hernia on the 6th postnatal week with no complications reported. Three weeks later, her clinical status deteriorated, resulting in cardiorespiratory arrest, which was successfully reversed.

The patient required TPN during 89 days followed by a combination of parenteral and orogastric feeding with semi-elemental formula supplemented with maltodextrin and MCT oil.

Other clinical characteristics, comorbidities and management are reported in **Tab. 1**.

During her 10th week of life, thoracoabdominal and lower limbs radiographies were performed, which detected the presence of diffuse osteopenia and rarefaction of the metaphyses of tibia and fibula bones. The serum ALP was 345 IU/L, serum phosphorus was 4.05 mg/dl (1.305 mmol/L), serum calcium was 4.70 mEq/L (2.350 mmol/L) and ionized calcium was 0.800 mmol/L. At this time, oral vitamin D3 supplementation was initiated (667 IU/day). The serum ALP level continued to increase, reaching 542 IU/L during the 17th week of life.

The patient suffered fatal cardiorespiratory arrest at postnatal age of 17 weeks. Necropsy was not authorized by her parents.

Case 5

A female preterm infant with severe intrauterine growth restriction was born in January 2010 by cesarean section at 27^{+3} weeks of gestation, with a birth weight of 520 g. Apgar scores were 8 at both 1st and 5th minutes.

The patient was admitted to the NICU on her 1st day of life and required ventilation support until the 11th postnatal week.

The patient's clinical status deteriorated during the 3rd week of life due to necrotizing enterocolitis, requiring fluid and inotropic support. Surgical treatment of necrotizing enterocolitis was performed during her 4th postnatal week with excision of the necrotic tissue and ileostomy. Ileostomy reversal was performed 10 weeks later.

She required several periods of TPN (75 days total) intercalated with a combination of parenteral and orogastric feeding with semi-elemental formula until enteral feeding was tolerated. Then, she received preterm formula supplemented with maltodextrin or fortified breastmilk whenever possible. While on total enteral feeding, oral multivitamin supplementation was given, including vitamin D3 (667 IU/day).

Other clinical characteristics, comorbidities and management are reported in **Tab. 1**.

During the 9th week of life, it was noticed that the patient had a red and tender tumor on her left thigh, associated with pain on handling. The ultrasound findings were suggestive of left femur fractures in both proximal and distal diaphysis.

At this time, the serum ALP was 1,783 IU/L, serum phosphorus was 3.03 mg/dl (0.975 mmol/L), serum calcium was 4.9 mEq/L (2.450 mmol/L) and ionized calcium was 0.970 mmol/L. Parathyroid hormone (PTH) was increased (133.9 pg/ml) and 25-hydroxyvitamin D concentration was within the normal range (27 ng/ml).

Antibiotic therapy was administered and satisfactory consolidation of the fractures was achieved by cast immobilization of the affected limb. In addition, calcium supplementation in the milk was initiated (1.2 ml of calcium gluconate 10% in each bottle) and vitamin D3 intake was increased to 1,334 IU/L.

A skeletal X-ray study performed on the 14th week of life revealed marked diffuse osteopenia, periosteal reaction of the diaphysis of all long bones and multiple fractures of the left inferior limb, confirming the diagnosis of MBDP.

The patient was discharged on the 22nd postnatal week, weighing 2,390 g. Preterm formula (8 x 45 ml) and oral multivitamin supplementation including vitamin D3 (667 IU/day) were prescribed.

Discussion

We discuss five patients diagnosed with MBDP in our NICU, all of which had common risk factors for this disease and several other comorbidities (**Tab. 1**). The different clinical approaches seen reflect not only the lack of standardized screening criteria for this entity, but also the difficult management of prematurity-related complications.

MBDP usually occurs between the 6th and 16th postnatal weeks [25] and is often clinically silent, being detected in laboratory studies or incidentally on radiographies performed for other purposes [22].

Findings at physical examination suggesting MBDP were only reported for patient 1.

Measurements of serum total ALP, serum phosphorus and serum calcium concentrations have been previously used to detect the development of MBDP but these biochemical parameters correlate poorly with bone mineralization and no clear cut-off values have been established so far [2, 11].

ALP is predominantly produced by bone tissue in infants (90%) and physiologically increases over the first 3 weeks of life [1], achieving a plateau around 5-6 weeks [26]. A rise in ALP beyond 6 weeks typically represents insufficient mineral supplies [10] and may precede radiographic changes by 2-6 weeks. These changes are more frequently associated with higher ALP levels (> 800 IU/L) but can also be present at lower levels (< 600 IU/L) [2, 10], as shown in cases 2 and 4. Several studies have suggested that ALP levels higher than 500 IU/L indicate the presence of osteopenia [4, 23, 27, 28].

The wide range of ALP levels between preterm infants, also seen in these reported cases (345-1,783 IU/L), limits its diagnostic value but individual serial measurements for each patient may increase its usefulness.

In addition, elevated ALP is usually associated with hypophosphatemia, which is the principal nutritional deficiency in MBDP [29, 30]. The assessment of serum phosphorus associated with ALP measurements can significantly increase the sensitivity of the screening [1, 24].

All patients presented serum phosphorus concentrations below 1.8 mmol/L, normal serum calcium (total) but low ionized calcium (**Tab. 2**). However, serum calcium is not a useful screening test since its levels usually remain within normal limits despite inadequate intake or stores, as a result of the regulatory effect by PTH or due to hypophosphatemia [1, 13].

Other biochemical studies may help identify the underlying mineral deficiency and provide some guidance on supplementation requirements.

The renal response to hypophosphatemia consists in optimizing phosphate reabsorption, and so a percent tubular reabsorption of phosphate

$$[\mathrm{TRP} = (1 - \frac{Urinary\ phosphate \times Serum\ creatinine}{Urinary\ creatinine \times Serum\ phosphate}) \times 100]$$

[1, 10] higher than 95% indicates insufficient intake of phosphorus [10, 31]. At the same time, phosphorus deficiency prevents the formation of apatite crystals, leading to calcium release and hypercalciuria [32]. Therefore, phosphorus supplementation should be initiated in the setting of hypophosphatemia associated with high TRP [1, 10].

In case 5, the patient developed secondary hyperparathyroidism and presented 25-hydroxy-vitamin D concentration within normal range. Although PTH improves renal and intestinal calcium absorption, it may worsen osteopathy by stimulating resorption of calcium and phosphate from already osteopenic bones and by increasing urinary phosphate excretion [10, 30]. In cases of low TRP associated with high PTH levels, calcium supplementation should be considered [10].

Considering that calcium supplementation is sometimes challenging, calcitriol administered enterally or intravenously (0.05-0.2 mcg/kg/day) may be a plausible choice for this subset of patients, even in the absence of vitamin D deficiency. Calcitriol may increase intestinal calcium and phosphorus absorption and seems to directly suppress PTH secretion, improving

Table 2. Biochemical and radiographic findings.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age of biochemical findings (weeks)	15	7	16	10	9
Age of X-ray diagnosis (weeks)	14	9	16	10	14
Biochemical parameters					
ALP (IU/L)	1,421	475	795	345	1,783
Phosphorus (mmol/L)	1.351	1.225	1.440	1.305	0.975
Calcium (mmol/L)	2.380	1.800	2.400	2.350	2.450
Ionized calcium (mmol/L)	0.940	1.030	1.080	0.800	0.970
PTH (pg/ml)	Not reported	Not reported	Not reported	Not reported	133.9
25-hydroxyvitamin D (ng/ml)	Not reported	Not reported	Not reported	Not reported	27
Radiographic findings	Osteopenia, femur and multiple rib fractures, widening of costochondral junctions, widening of the metaphyses of radius and ulna	Osteopenia	Osteopenia	Osteopenia, rarefaction of the metaphyses of tibia and fibula	Osteopenia, periosteal reaction of the diaphysis of all long bones and multiple fractures of the left inferior limb

ALP: alkaline phosphatase; PTH: parathyroid hormone.
Reference values: ALP: 150-420 IU/L; phosphorus: 1.45-2.16 mmol/L; calcium (total): 1.6-2.8 mmol/L; ionized calcium: 1.20-1.38 mmol/L; PTH: 10-65 pg/ml; 25-hydroxyvitamin D: ≥ 20 ng/ml [48].

urinary phosphate wasting and serum phosphorus [33].

PTH and 25-hydroxyvitamin D concentrations were not routinely measured in any other patient.

However, PTH seems to be a promising early biomarker for MBDP, showing higher sensitivity than ALP [34] and possibly indicating both severity and response to treatment [30].

On the other hand, 25-hydroxyvitamin D levels may be reserved for specific cases [10, 35], as well as bone-specific ALP measurements [35].

In case 3, urinary calcium and phosphorus concentrations were measured in order to monitor supplementation, as the simultaneous presence of calcium (4.8 mg/dl or 1.2 mmol/L) and phosphorus (1.2 mg/dl or 0.4 mmol/L) in spot urine samples suggests that both are provided in sufficient amounts [1, 18].

Urinary calcium or phosphorus to creatinine ratios have also been used for this purpose, on the basis that mineral to creatinine ratios correct for volume-induced changes in concentration. However, most preterm infants receive a constant daily fluid intake and no circadian variation in the urinary concentrations of these minerals was demonstrated [32, 36].

These urinary measurements need to be cautiously interpreted, as they are highly variable depending on the type of nutritional intake, renal function and medications such as loop diuretics and methylxanthines [31, 32, 37].

The diagnosis may be confirmed by radiographic findings of MBDP [3]. Although bone anomalies may remain unseen in conventional radiographies until bone mineralization is seriously decreased (20-40%) [3], this technique is relatively safe, easily used in clinical practice and available in most NICUs, providing generalizable results [20, 34].

All patients reported had radiographic signs of marked osteopenia (**Tab. 2**). Bone fractures in patients 1 and 5 occurred as a consequence of osteomyelitis of the osteopenic bone.

The diagnosis can be made more accurately by performing objective bone mineralization measurements using Dual Energy X-ray Absorptiometry (DEXA) or Quantitative Ultrasound (QUS), but these techniques are used essentially for research purposes [34, 35, 38, 39] and were not performed in our NICU.

The primary prevention and treatment approach for MBDP is based on early and adequate nutritional intervention by providing sufficient calcium and phosphorus intakes and vitamin D supplementation [8]. Whenever possible, risk factors should be minimized, for instance, by limiting the prolonged

courses of unnecessary therapy with diuretics, methylxanthines and steroids [1, 10].

While on parenteral nutrition, administration of 1.45-1.9 mmol/kg/day of calcium and 1.23-1.74 mmol/kg/day of phosphorus results in 60-70% of the expected intrauterine accretion rates [31]. The optimal calcium to phosphorus ratio in the parenteral solutions is 1.7:1 [10].

All efforts should be made to accelerate the transition of premature infants receiving TPN to enteral feedings, using formulas designed for preterm infants or fortified human milk.

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) suggests that an intake of 120-140 mg/kg/day (110-130 mg/100 kcal) of highly bioavailable calcium salts and of 65-90 mg/kg/day (55-80 mg/100 kcal) of phosphate, with a calcium to phosphorus ratio of 1.5-2.0, is necessary [40]. The American Academy of Pediatrics (AAP), however, recommends daily intake values for enteral feeding of infants with VLBW of 150-220 mg/kg for calcium and 75-140 mg/kg for phosphorus [35]. Regarding vitamin D supplementation, the ESPGHAN recommends an intake of 800-1,000 IU/day [40], whereas the AAP guidelines propose 200-400 IU/day [35]. In a recent clinical trial, Alizadeh Taheri et al. have shown that a low dose of vitamin D supplement for premature newborns, 200 IU/day, has the same value regarding BMC as 400 IU/day [41].

Our patients' nutritional protocol was based on the parenteral and enteral nutrition consensus determined by the Portuguese Neonatology Society [42, 43].

In addition to nutritional support, motor physiotherapy with passive range of motion exercise and gentle compression at the end of the flexion/extension range for 5-15 minutes per day is recommended [17, 19].

Even with these preventive strategies, some infants may still develop MBDP and require higher amounts of human milk fortifier and/or feeding volume of preterm formula. In infants not responding to these measures or if no further increases in these can be made, elemental calcium and phosphorus can be provided, usually beginning at 20 mg/kg/day of elemental calcium and 10-20 mg/kg/day of elemental phosphorus and increasing, as tolerated, usually to a maximum of 70-80 mg/kg/day of elemental calcium and 40-50 mg/kg/day of elemental phosphorus [35].

Despite the implementation of evidence-based protocols regarding nutritional requirements for preterm infants, the actual delivery of minerals and energy is limited by several difficulties in clinical practice, such as feeding intolerance, fluid restriction and overall neonatal health [2].

Infants who develop MBDP are often those with more prematurity-related complications, resulting in significantly longer hospital stay and higher mortality [25, 27, 34]. In addition, these infants may not tolerate the procedures and relatively large amounts of study specimens required for MBDP screening and monitoring [25].

It is not yet clear whether MBDP is a self-resolving condition or a disease with long-term consequences [17]. In the short-term, the defective bone development may cause fractures, impaired respiratory status and skeletal deformities like dolichocephalic skulls, resulting in frog eyes and myopia of prematurity [30, 32, 44, 45]. While a rapid catch-up growth during the first 2 years of life has been demonstrated in preterm infants [35], other studies have suggested that MBDP disease may be associated with subnormal growth throughout childhood [22, 29, 46].

Despite these inconsistencies, it should be kept in mind that these infants may not achieve a peak bone mass comparable to term infants, being at greater risk of osteoporosis and subsequent bone fractures in the adult life [25].

Conclusion and final recommendations

MBDP is a relatively common complication of prematurity, becoming relevant as neonatal intensive care has significantly improved survival rates in preterm neonates. Early and adequate nutritional intervention is needed in order to reduce the incidence and severity of this disease. As there are no standard approaches for MBDP, many cases remain undiagnosed until severe demineralization occurs.

The screening for MBDP should target infants at high risk, including those with VLBW (< 1,500 g), namely those born before 28 weeks of gestation, on TPN dependence for longer than 4 weeks, unable to reach full fortified feeds or exposed to drugs with deleterious effects on bone health [1, 8, 47], as we show in **Fig. 1**.

Serum calcium, phosphorus and ALP should be measured at 4-6 weeks of life, and then weekly or biweekly [25, 35]. If any of these results are suggestive of MBDP, for instance, if phosphorus is lower than 1.8 mmol/L and ALP higher than 500 IU/L [1, 31], other screening tests like TRP and PTH should be performed.

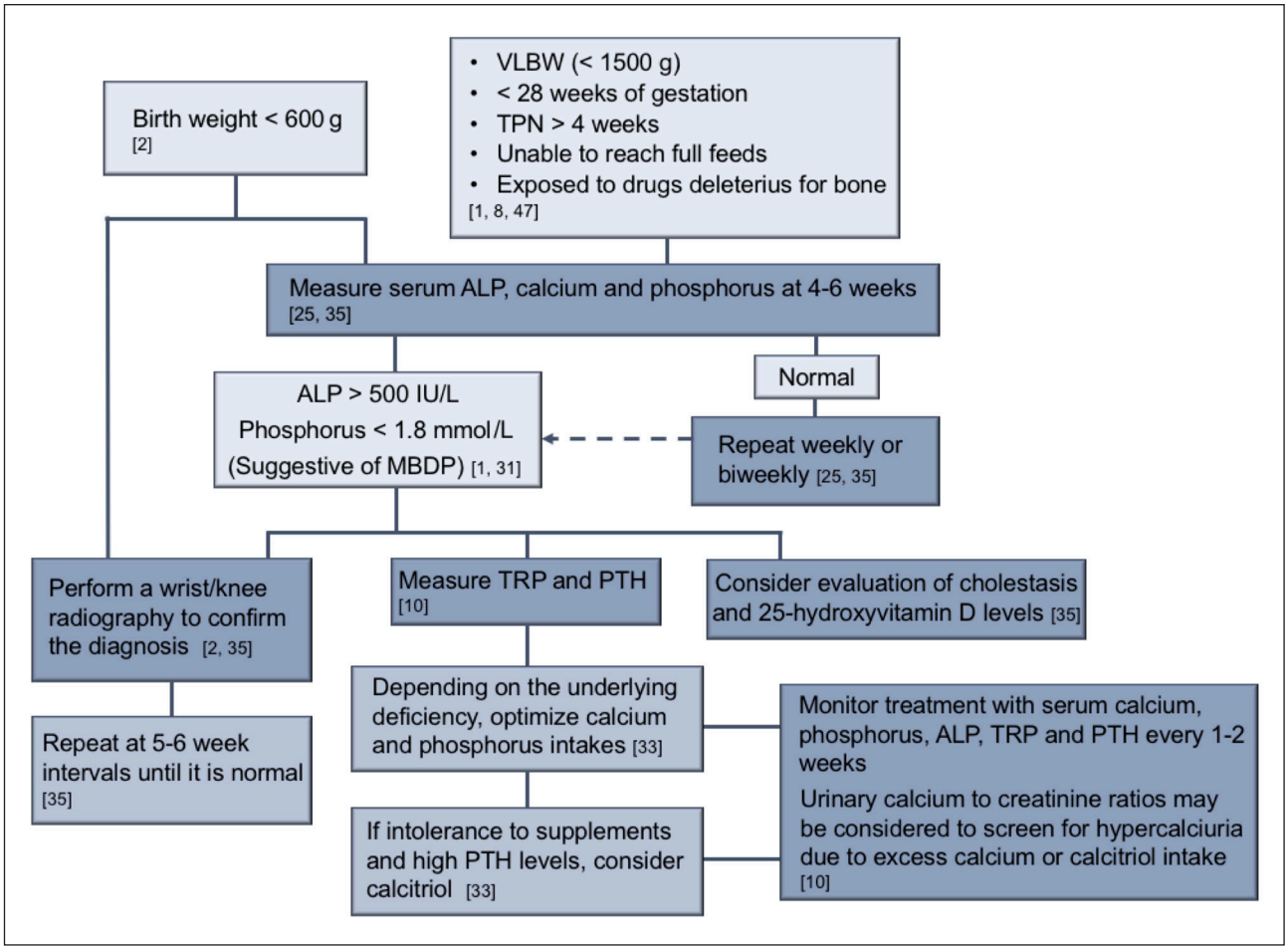

Figure 1. Algorithm for screening and management of metabolic bone disease of prematurity (MBDP).
VLBW: very low birth weight; TPN: total parenteral nutrition; ALP: alkaline phosphatase; MBDP: metabolic bone disease of prematurity; TRP: tubular reabsorption of phosphate; PTH: parathyroid hormone.

A low TRP in the setting of secondary hyperparathyroidism indicates a possible calcium deficiency, whereas a high TRP (> 95%) associated with low or normal PTH levels suggests phosphorus deficiency [10]. Depending on the underlying deficiency, calcium and phosphorus intakes must be optimized as described earlier. In cases of intolerance to supplements and high PTH levels, calcitriol may be an alternative choice [33].

Evaluation of cholestasis and 25-hydroxyvitamin D levels can also be performed, targeting serum 25-hydroxyvitamin D concentration higher than 20 ng/ml.

The AAP recommends carrying out a long-bone (wrist or knee) radiography to confirm the diagnosis of MBDP, and to repeat these studies at 5-6 week intervals until these study results are normal [35].

Additionally, it has been suggested that a radiograph of the wrist or knee should be performed in all infants with a birth weight lower than 600 g, at around 6 weeks of life or when on full enteral feeds [2].

Treatment goals can be monitored by assessing serum calcium, phosphorus, ALP, TRP and PTH every 1-2 weeks. Urinary calcium to creatinine ratios may be considered to screen for hypercalciuria due to excess calcium or calcitriol intake [10].

Considering the potential complications of MBDP, further knowledge concerning screening, prevention and treatment is required.

Ethical approval

The study was approved by the ethics committee of Hospital São João.

Declaration of interest

The Authors declare that there is no conflict of interest.

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