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REVIEW ARTICLE

Osteopenia of prematurity: a national survey and review of practice

CM Harrison (catherine.harrison@leedsth.nhs.uk)[1], K Johnson[2], E McKechnie[2]

1.Department of Neonatology, Leeds Teaching Hospitals Trust, Leeds, UK
2.Peter Congdon Neonatal Unit, Leeds General Infirmary, Belmont Grove, Leeds, UK



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Correspondence
Dr. C Harrison, Peter Congdon Neonatal Unit, Leeds General Infirmary, Belmont Grove, Leeds LS2 9NS, UK.
Tel: 0113-3928537 |
Fax: 0113-3926093 |
Email: catherine.harrison@leedsth.nhs.uk

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Abstract

Premature infants are at significant risk of reduced bone mineral content (BMC) and subsequent osteopenia. There are currently no standard practices regarding screening, investigation or treatment of this condition. We present a case report and findings of a national survey of 36 level 2 and 3 neonatal units (72% response rate). The findings showed widely disparate practice regarding screening, prevention and treatment. We summarize the tests currently available for osteopenia and suggest guidelines for management of the at risk group.

Conclusion: Our survey confirms inconsistent practices regarding management of infants at risk of osteopenia of prematurity. Investigations and treatments available are summarized together with a guideline for management of this susceptible group of infants.

INTRODUCTION

Premature infants are at significant risk of reduced bone mineral content (BMC) and subsequent bone disease, variably termed metabolic bone disease of prematurity, osteopenia of prematurity or neonatal rickets. It is an important issue that we need to consider in neonatology. There are a variety of ways to screen with an aim to prevent this problem, but there is no universal consensus as to which is the best method.

In this paper, we describe a typical case of an extremely preterm infant who developed metabolic bone disease with fractures. We also present results from a postal survey of many neonatal units in the United Kingdom designed to assess the current vogue of monitoring babies at risk. The various methods available to monitor for osteopenia are reviewed along with different treatment modalities. Finally we present a protocol on how to manage this complex problem.

Abbreviations
ALP, alkaline phosphatase; BMC, bone mineral content; Ca, calcium; CPAP, continuous positive airways pressure; DEXA, dual energy X-ray absorbitometry; P, phosphate; PN, parenteral nutrition; SOS, speed of sound; TRP, tubular reabsorption of phosphate; USS, ultrasound scan.

BACKGROUND

The clinical onset of osteopenia of prematurity is usually between 6 and 12 weeks postnatally. In the acute neonatal phase, this reduced BMC can lead to fractures, which have been described in up to 10% of low-birthweight infants (1). Bone mineralization can take a significant time to reach normal levels. In low-birthweight infants at term equivalent, BMC is significantly reduced compared to that of normal term infants (2) and may not then approach normal values until after the first year of life (3).

In the short-term, osteopenia has been implicated in myopia of prematurity (4), impaired respiratory function (5) and, in the longer-term, with poor growth during childhood (6).

There are several biochemical investigations, such as serum calcium and alkaline phosphatase (ALP) that have been used to act as markers, but these correlate poorly with bone mineralization. It can therefore be difficult to screen for and diagnose osteopenia of prematurity.

CASE REPORT

A male infant was born to a 25-year-old woman in her third pregnancy. The mother consumed 35 U of alcohol/week but

was otherwise fit and well. There was an obstetric history of one early miscarriage and a second pregnancy that resulted in delivery of a full-term male infant with gastroschisis who had a stormy, protracted postnatal course. In this pregnancy an ultrasound scan (USS) at 24 weeks revealed a small but normal infant with absent uterine artery end-diastolic flow. Follow-up USS at 26 weeks showed an abnormal foetal biophysical profile. A single dose of betamethasone was administered to the mother and a male infant, weighing 570 g (2nd centile), was delivered by caesarean section 4 h later.

He had an initial stormy course on the neonatal unit, with a pulmonary haemorrhage on day 3, hyperglycaemia needing insulin up to day 5 and hypotension requiring dopamine and dobutamine for 48 h and steroids for 12 h. His chest X-ray on day 14 was consistent with bronchopulmonary dysplasia and an echocardiogram confirmed a patent ductus arteriosus, and diuretics were started. He required ventilatory support until day 124, and a course of dexamethasone to aid weaning from full ventilation to continuous positive airways (CPAP). There was a further course of low-dose dexamethasone to aid weaning to low-flow oxygen. He had several episodes of suspected sepsis requiring courses of antibiotics. His diuretics were continued until 38 weeks corrected age. Cranial USSs remained normal throughout.

Parenteral nutrition (PN) was started on day 4 and expressed breast milk was commenced on day 11 after intermittent episodes of abdominal distension. PN was continued until day 42 when he was established on full enteral preterm formula feeds. He received a maximum of 2.0 mmol/kg/day calcium and 2.5 mmol/kg/day phosphate in his PN.

For the first 10 weeks of life, he had maintained a normal calcium level. His phosphate had remained low (less than 2 mmol/L) despite increasing amounts in his PN/oral supplements. He required a maximum of 2.5 mmol/kg/day. By 7 weeks of age, he had a normal serum phosphate level (1.98 mmol/L). Oral phosphate supplements were introduced when full enteral feeds were tolerated. He was started on 1.5 mmol/kg/day. His ALP had increased suddenly from normal <500 to 1300 IU/L at the same time. By week 11, regular monitoring showed low calcium (1.75 mmol/L) and raised phosphate (2.75 mmol/L) with a persistently raised ALP (>1000 IU/L). Alfacalcidol and calcium supplements were therefore commenced. On day 79, he was noted to have decreased movement of his left leg. X-ray revealed a fractured femur and a subsequent skeletal survey also showed fractures of his right tibia and both distal radii. These fractures healed well without intervention. (See Figures S1 and S2 in Supplementary Material online for his calcium, phosphate and ALP levels.)

He was discharged on day 165 (10 weeks post term) in air, fully bottle fed on oral calcium and phosphate supplements that continued for 6 months. His discharge weight was 4.06 kg (0.4th centile). At the time of writing this report he remained small (2nd centile), but following this centile. Regular neonatal follow-up continues.

RISK FACTORS

Risk factors for reduced BMC are commonly encountered in the preterm infant. The majority of bone mineralization, along with calcium and phosphate accretion occurs during the third trimester of pregnancy. Infants born before this time therefore have depleted stores of these minerals.

From 24 weeks onwards, foetal weight gain is approximately 30 g per day, which requires 310 mg calcium and 170 mg phosphorus per day (7).

There is evidence that the placenta has a role in BMC. Vitamin D is converted to 1,25-dihydrocholecalciferol in the placenta which is important in the transfer of phosphate across the placenta to the foetus (8). Holland et al. (9) describe a higher incidence of postnatal rickets in babies with intrauterine growth restriction, suggesting that chronic damage to the placenta may alter phosphate transport. There is an association between neonatal rickets and pre-eclampsia (10) and demineralization can be seen in the bones of stillborn babies. Severe demineralization has also been described in infants born to mothers with chorioamnionitis and placental infection (11). Some preterm babies are therefore born phosphate deficient and this, compounded with poor postnatal intake, increases the risk of osteopenia.

The baby described in the case report was symmetrically small suggesting chronic placental insufficiency.

Bone strength has been shown to decrease after birth, and this is associated with biochemical evidence of new bone formation during the first 2 months of postnatal life in very low-birthweight infants. The decrease in bone strength and the poor mineral supply contribute to the development of osteopenia (12) in the newborn premature infant.

There are added factors that compound the risk of reduced bone mineralization following premature delivery. The most important one appears to be an inadequate supply of calcium and phosphorus for the needs of the infant. One study found evidence of rickets in 40% of premature infants fed with human breast milk compared with 16% of those fed with formula supplemented with calcium and phosphorus (13). Enteral absorption of phosphorus is extremely efficient and oral supplementation should therefore be started when enteral feed is tolerated. However, protracted feed intolerance may lead to the prolonged use of PN. The provision of minerals in PN is limited by their solubility increasing the risk of reduced BMC further and this may be compounded by the need for fluid restriction; for example phosphate supplementation in PN is commonly linked to PN sodium supplementation. Aluminium contamination of PN has been reported and this may further affect bone formation and mineralization adversely (14). Medications frequently used in the nursery, such as steroids, methylxanthines and diuretics, can increase the risk of inadequate bone mineralization (15–17). The case in our report had multiple courses of steroids and a protracted course of diuretics.

Common neonatal conditions such as sepsis, cerebral pathology, muscular disorders and paralysis may result in prolonged periods of immobility, well recognized as a risk factor for poor bone mineralization. Bone growth and

strength is stimulated by activity, when skeletal stability is needed. In utero, osteoblasts increase in activity in response to mechanical loading. Without stimulation bone resorption and urinary calcium losses increase and bone mass is reduced. This has been confirmed using ultrasound (18).

INVESTIGATIONS

Serum biochemical markers

Alkaline phosphatase

Bone is constantly being remodelled by a process involving resorption by osteoclasts and formation by osteoblasts. ALP is a glycoprotein enzyme produced by a variety of tissues including bone, liver, kidney and intestine. Tissue nonspecific ALP is generally measured; however, 90% of ALP in infants is of bone origin and is thought to reflect bone turnover. ALP rises in all newborns in the first 2–3 weeks of life and increases further if there is insufficient mineral supply. Appropriate mineral supplementation of preterm infants may lead to smaller rises in ALP (19). Potentially, a biochemical marker that reflects an abnormal rise in bone activity due to either rapid growth or lack of minerals may help detect osteopenia in infants. There is conflicting evidence as to whether ALP is such a marker. Kovar et al. have suggested that an ALP of greater than five times the upper adult limit of normal is an indicator of the risk of rickets (20). Other data have shown that ALP positively correlates with the rate of bone mineral accretion, and could therefore be a surrogate marker for bone mineralization. C-terminal propeptide of type 1 collagen (PICP) has also been shown to be a good marker (21). Studies using dual energy X-ray absorbitometry (DEXA) scan as a screening tool conclude that there is no association between BMC and ALP(22).

Despite this controversy, ALP is a readily available measurement and provides a trend that can be easily followed. It therefore remains a frequently used screening tool for metabolic bone disease.

Other minerals can affect serum ALP levels. Copper deficiency causes raised levels associated with neutropenia and hypoalbuminaemia (23). Zinc deficiency is associated with decreased ALP levels (24). It is therefore important that in infants on long-term PN, all trace elements are closely monitored.

Calcium

Serum calcium is not a useful screening test as infants can maintain a normal calcium level at the expense of a loss of bone calcium. The level can also increase with phosphorus depletion and hypophosphataemia.

Phosphate

Preterm infants with low serum inorganic phosphate (<2 mmol/L) are at risk of osteopenia, and levels less than 1.8 mmol/L have been strongly associated with the presence of radiographically evident rickets (25).

Data have confirmed that although phosphate concentration is related to bone mineral density, it is not sensitive enough to identify infants with bone mineral deficits. It is however highly specific. The use of serum phosphate levels in combination with ALP levels can significantly increase the sensitivity of the screening and identification of infants at risk of metabolic bone disease (26).

Radiological investigations

X-ray

Osteopenia can be discovered as an incidental finding on a plain radiograph, showing 'thin bones' or healing fractures. Bone mineralization, however, needs to be decreased by at least 20–40% for these changes to be visible (27,28).

DEXA

DEXA is now the gold standard for bone mass measurements in adults and results correlate well with risk of fracture (29). It is becoming more widely used in infants but availability is limited. Two beams of relatively high and low energy levels are used to estimate total body or regional BMC. Body mass remains the major predictor of bone mineral status throughout infancy, and thus reference values for DEXA data, that is total body BMC, area and bone mineral density are bodyweight dependent. DEXA scans are sensitive in detecting small changes in BMC and density, and can predict risks of fractures (30). Use is now validated in preterm and term infants (31).

Quantitative ultrasound

Ultrasound gives measurements that are related to bone mineral density and structure. It is simple, noninvasive, and a relatively cheap bedside test (32). Some machines have been developed to measure broadband ultrasound attenuation or the speed of sound (SOS), commonly on the tibia. Reference values are available for both term and preterm infants (33). It has been shown that SOS lies within the normal reference range in the first week of life in preterm infants, presumably demonstrating that these infants had undergone adequate skeletal development until the onset of preterm birth. On subsequent scans the SOS fell in all infants, especially those under 26 weeks of gestation. This fall was seen despite adequate nutrition leading to sustained weight gain, and also occurred in infants with a normal ALP (34).

Urine analysis

Urinary excretion of calcium and phosphorus

Studies using this measure as a marker of postnatal mineralization found that infants who simultaneously excreted calcium >1.2 mmol/L and inorganic phosphorus at >0.4 mmol/L showed the highest bone mineral accretion (35). Infants between 26 and 31 weeks were found to have a renal phosphate threshold in the range of normal serum phosphate values (2 mmol/L). Data have shown that extremely preterm infants had a much lower renal phosphate threshold, leading to urinary phosphate excretion even in the presence of low phosphate levels (36). Phosphate is not bound in the plasma like calcium and so the percent tubular reabsorption of phosphate (TRP) is the best guide to adequacy of phosphate supplementation. A percent tubular reabsorption of >95% shows inadequate supplementation.

However, this must be taken in relation to plasma calcium; inadequate calcium intake will lead to hyperparathyroidism and hence tubular leak of phosphate. Similarly, if phosphate intake is low, there is breakdown of bone and hence release of calcium. This leads to hypercalcaemia and calcium leaking into the urine.

On a practical note, urinary electrolyte levels are the same cost as blood tests such as calcium, phosphate and ALP.

TRP can be calculated (37) using the formula:

$$\text{TRP}\,(\%\,\text{TRP}) = 1 - \frac{\text{Urine phosphate}}{\text{Urine creatinine}} \times \frac{\text{Plasma creatinine}}{\text{Plasma phosphate}} \times 100.$$

Urinary calcium and phosphate creatinine ratios

That urinary calcium and phosphate concentrations may vary is well recognized, and simultaneous measurement of creatinine may allow correction for changes in urine volume. Use of urinary mineral to creatinine ratios may therefore be appropriate. Reference ranges for these ratios in preterm infants have been reported (38). The 95th centile for urinary calcium: creatinine ratio is 3.8 mmol/mmol and decreases with increasing postnatal age while the 95th centile for urinary phosphate creatinine ratio is 26.7 mmol/mmol and remains stable with increasing postnatal age. Although treatment with both frusemide and theophylline may lead to a significant increase in the urinary calcium creatinine ratio, no effect has been demonstrated on the excretion of phosphate. Dexamethasone also has no effect on phosphate excretion (39).

There are very specific patterns of urinary calcium and phosphate levels depending on whether babies are formula-fed or breast-fed. Formula-fed infants show very low urinary calcium concentrations but a high urinary phosphate, attributed to a low absorption rate of calcium from preterm formulas. Breast milk contains insufficient phosphate for the needs of preterm infants and therefore infants maximize renal phosphate reabsorption. As urinary ratios depend heavily on type of feed, standard reference ranges are less useful. In addition, it has still not been proven that urinary ratios are a reliable substitute for direct measurement of BMC, and more research is needed in this area (see Table S1 in Supplementary Material online).

TREATMENT

Prevention of bone disease of prematurity should be the aim rather than treatment of the disease. Known risk factors as described earlier should be minimized where possible, for example regular review of infant's medication to avoid prolonged courses of unnecessary therapy.

Adequate supply of calcium and phosphate from an early stage is paramount. Modern parenteral solutions can theoretically match in utero accretion rates. Recommended oral daily intake of calcium varies between international committees from 140–160 mg calcium/100 kcal (American Academy of Pediatrics [AAP]) to 70–140 mg/100 kcal (European Society of Paediatric Gastroenterology and Nutrition[ESPGAN]). A recent review by Rigo (40) suggested 100–160 mg/kg/day of calcium. Similarly, recommendations for phosphate intake vary from 95 to 108 mg phosphate/100 kcal (AAP) to 50–87 mg P/100 kcal (ESPGAN). Rigo recommends 60–75 mg/kg/day. There are several phosphate formulations on the market, combining phosphate with salts, for example potassium acid phosphate, sodium phosphate and Joulie's phosphate (41). The obligatory combination of phosphate with another mineral can limit the level of supplementation.

Most preterm infants who are enterally fed with human milk have fortifier added to the milk to achieve a more nutritionally appropriate diet. The timing of introduction of fortifier is variable. A Cochrane systematic review (42) shows short-term benefit in linear and head growth with fortifier use although the effect on long-term BMC is not clear. However, in the absence of adverse effects the addition of fortifier is recommended once the infant is on more that 90 mL/kg/day of enteral feeds.

Monitoring serum phosphate, calcium, ALP and urinary tubular reabsorption will guide the requirement for additional phosphate supplementation in enterally fed infants.

Current recommended daily intake of vitamin D for preterm infants is 400 IU. Vitamin D is present in human milk fortifier and preterm formulae but can also be provided in multivitamin drops. Some infants may need additional vitamin D. There are many different formulations of vitamin D and the evidence regarding which formulation is best in this population is confusing. We currently recommend the use of Ergocalciferol (Eli-Lilly & Company, Indianapolis, IN, USA).

There is evidence to support a daily passive exercise regime for preterm infants at risk of bone disease. BMC, bone length and bone area are all improved in infants with a passive exercise programme compared to controls (43) although systematic review suggests more research is needed.

POSTAL SURVEY

Background

Infants born at 32 weeks gestation or less are at risk of developing metabolic bone disease. Consensus on screening, diagnosis and treatment of the disorder has not been achieved. The aim of this survey was to assess the criteria used for screening, diagnosis and treatment of metabolic bone disease in the United Kingdom.

Methods

A one-page questionnaire (for questionnaire see Appendix S1 in the Supplementary Material online) was sent to 50 neonatal units across England that provided either level 2 or level 3 care (British Association of Perinatal Medicine definitions) and were thus familiar with the care of infants less than 32 weeks of gestation. The questionnaire was sent with a covering letter to a named consultant and a reply paid envelope was included. The questionnaire asked whether the unit screened for bone disease and if so who

was screened and how. The frequency of screening was requested, as were treatment criteria.

Results

Out of 50 questionnaires sent, 36 (72%) replies were received. All units monitored infants for bone disease of prematurity. The gestation at which units monitor was variable (Figure S3 in Supplementary Material online).

Screening

(a) *Biochemical tests*: All units monitored infants with readily available biochemical tests; serum calcium, phosphate and ALP. In addition, two units used urinary calcium: creatinine ratios and a further two units used urinary calcium and phosphate indices. One unit calculated tubular phosphate resorption.
(b) *Radiology*: Several units occasionally used X-ray appearances to aid the diagnosis; one unit routinely X-rayed the wrist at 6 weeks.
(c) *Frequency of screening*: Monitoring of bone biochemistry was weekly in 32 (89%) units and fortnightly in 4 (11%).

Supplementation

For infants at risk of metabolic bone disease, vitamin D or multivitamin solutions, human milk fortifier or preterm formula was used (Figure S4 in Supplementary Material online). Five units also added additional phosphate. One unit did not use prophylaxis while all other units used at least one of the agents, with some using a combination dependent on the individual infant.

Treatment

Treatment was begun in three units (8%) guided by the infant's birthweight (2 units started all infants born at <1500 g, one at <1800 g). Three units (8%) started treatment once an infant thought to be at high risk, was tolerating full enteral feeds. The remaining 30 units (83%) began treatment on the basis of biochemical levels. The levels used were widely variable. Seven units (19%) were guided by serum phosphate levels and 23 units (64%) used serum ALP (Figure S5 in Supplementary Material online)

For treatment, 34 units (94%) used phosphate supplements and occasionally vitamin D. One unit used only calcium sandoz and one Joulie's Phosphate, in double the prophylactic doses in both cases.

Treatment was stopped at discharge in four units (11%), on biochemistry results in 20 units (56%; all different levels), when the infant is >1.8 kg in two units (5%) and on the basis of an individual consultant decision in the remaining 10 (28%).

DISCUSSION

There are no current figures for the incidence of metabolic bone disease in the preterm population. With advances in infant nutrition, it is to be expected that the incidence will have dropped in recent years. However, as the results of our survey indicate, opinion is extremely varied as to diagnosis and treatment.

The most popular screening tools are serum calcium, phosphate and ALP. More sensitive urinary measures are rarely used, nor are more invasive testing, such as X-rays and bone densitometry. Screening occurs at least fortnightly, usually weekly.

Supplementation of feeds for preterm infants is essentially routine across all units, using preterm formula, human milk fortifier and multivitamin solutions either alone or in combination. Most units will begin such treatment on the basis of the results of biochemical tests, most commonly ALP. Some will routinely add supplements for infants most at risk. Most units use phosphate supplements as first line treatment, with vitamin D if required. Opinion on stopping treatment is divided – units use weight, discharge from hospital, biochemistry or clinical judgment to discontinue treatment.

No units in our survey are currently using a daily exercise regime for preterm infants at risk of bone disease as a method of prevention.

Metabolic bone disease carries a significant morbidity for the preterm population. Improvements in nutrition have helped reduce the incidence. However, as we have shown, opinion remains divided on which infants should be monitored and on the best means of monitoring and treating them. Following our survey results and review of literature, we have developed the following guideline for screening and monitoring for osteopenia of prematurity.

Guideline for screening and treatment for babies at risk of osteopenia of prematurity

All babies should be monitored for bone disease if

- <1500 g,
- ≤28 weeks,
- Total PN for >4 weeks and
- Course of diuretics/steroids.

Monitor with

- Weekly bone profile bloods (Ca, P and ALP)

If phosphate <1.8 mmol/L and ALP >500 IU/L, check urinary tubular phosphate reabsorption. If TRP >95%, start phosphate supplementation. If no increase in phosphate levels and ALP continues to rise, consider ergo/alphacalcidol. Encourage the use of daily passive exercises. Review medications and if appropriate stop diuretics/steroids.

CONCLUSION

Infants born prematurely may have an inherent predisposition to osteopenia that may be compounded further by neonatal nursery intervention. Regular screening will identify infants developing neonatal rickets enabling neonatologists to minimize risk factors and optimize nutrition and mineral supplementation.

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Supplementary material

The following supplementary material is available for this article:

Figure S1 Calcium and phosphate over time
Figure S2 Alkaline phosphatase over time
Figure S3 Upper limit of gestational age of infants monitored for bone disease
Figure S4 Methods of prophylaxis of infants at risk of bone disease of prematurity
Figure S5 Serum alkaline phosphatase level at which treatment is commenced
Table S1 Summary of investigations for bone disease of prematurity
Appendix S1 Bone disease of prematurity questionnaire

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