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EDITORIAL

Metabolic bone disease in the preterm infant: Current state and future directions

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Abstract

Neonatal osteopenia is an important area of interest for neonatologists due to continuing increased survival of preterm infants. It can occur in high-risk infants such as preterm infants, infants on long-term diuretics or corticosteroids, and those with neuromuscular disorders. Complications such as rickets, pathological fractures, impaired respiratory function and poor growth in childhood can develop and may be the first clinical evidence of the condition. It is important for neonatologists managing such high-risk patients to regularly monitor biochemical markers for evidence of abnormal bone turnover and inadequate mineral intake in order to detect the early phases of impaired bone mineralization. Dual-energy X-ray absorptiometry has become an increasingly used research tool for assessing bone mineral density in children and neonates, but more studies are still needed before it can be used as a useful clinical tool. Prevention and early detection of osteopenia are key to the successful management of this condition and oral phosphate supplements should be started as soon as is feasible.

Key words: Premature; Osteopenia; Bone metabolism; Calcium; Alkaline phosphatase; Phosphorus; Nutrition

Core tip: Osteopenia of prematurity remains an important challenge in neonatal medicine due to continuing increased survival of preterm infants. The risk is higher with long-term diuretics or corticosteroids. It is important when managing such infants to regularly monitor biochemical markers for evidence of abnormal bone turnover and inadequate mineral intake. Dual-energy X-ray absorptiometry is increasingly used in research for assessing bone mass density in neonates. Prevention and early detection of osteopenia are key to the successful management of this condition and oral phosphate supplements should be started as soon as it is feasible.

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INTRODUCTION

Neonatal metabolic bone disease (MBD), osteopenia of prematurity (OOP), neonatal rickets or rickets of prematurity, are terms used to describe a reduction in bone mineral content (BMC) of the preterm infant. Although its exact prevalence is difficult to quantify because of the different methods used to screen infants at risk and also because of the difficulty in the interpretation of these results, it has been steadily increasing with the survival of more immature neonates as a result of advances in neonatal care. Born before a term pregnancy and thus deprived of a period of intrauterine supply of minerals, these infants already suffer at birth from suboptimal bone mineralization. The prevalence of MBD is inversely associated with birth weight and gestational age, with up to a third of infants weighing less than one kilogram at birth being osteopenic, more so if they are breastfed[1]. Other factors impeding normal bone mineralization include inadequate postnatal intake of vitamin D, calcium (Ca) and phosphorus (P), extended periods of total parenteral nutrition, lengthy duration of immobilization and as also a side effects of diuretics and corticosteroids prescribed to these infants[2,3]. Depending on the severity of the demineralization, osteopenia can remain clinically silent or develop as rickets, and, if severe, can even result in fractures[4].

As it is an important determinant of skeletal strength structure and density of the skeletal system throughout life, bone mineral density (BMD) in infants is an important topic for neonatologists, pediatricians and also endocrinologists. Guidelines for preventing, screening and treating MBD are not always consistent nor are they universally agreed upon, as still illustrated in a recently published review of this topic[5].

BURDEN OF OOP

Although the burden is not easy to quantify and available data remains conflicting, the known short-term complications are dominated by fractures of the long bones and ribs in the neonatal period. These respond well to therapy and there have no known residual long-term complications. The duration of hospital stay is unaffected by the diagnosis of OOP and preterm infants are routinely given mineral to prevent or treat neonatal rickets[6]. Growth alteration of the skull (dolichocephalic flattening) has been reported in association with poor BMC.

The weight, height, body mass index, lumbar BMC and BMD in 7-year-old children born prematurely and weighing less than 1500 g at birth are lower than those of the reference population[7]. Dual-energy X-ray absorptiometry (DEXA) assessment of areal BMD (aBMD; measured as grams per square centimeter) shows lower values at the level of the radial metaphysis, femoral neck and total hip in ex-preterm girls, but similar values at the radial and femoral diaphysis, with femoral neck aBMD remaining lower 12 mo later[8]. After adjusting for age, weight, height and jump power, prepubertal boys born at term have greater bone size and mass on DEXA scan at the age of at 5.7-8.3 years than those born before 34 wk of gestation[9]. It is still unknown if these changes in BMD in infancy and childhood increase the risk of developing early osteoporosis in adulthood.

PATHOPHYSIOLOGY AND RISK FACTORS

Antenatally

To develop normally, the skeleton of the growing fetus requires considerable active materno-fetal transfer of energy, protein, Ca and P. Serum Ca and *P* levels in the fetus are 20% more elevated than in the mother in the second trimester. Bone mineralization which occurs predominantly during the third trimester, will be inadequate if the fetal increased demands in Ca and P are not met. During pregnancy, augmented maternal intestinal absorption and increased skeletal mobilization increase maternal Ca supply to the fetus. The reduction in the Ca supply by the placenta results in a postnatal increase of parathyroid hormone (PTH) level that continues 48 h after birth when the peak serum Ca and the stabilization of serum Ca and *P* levels are attained[10,11].

Vitamin D also affects BMC and maternal hypovitaminosis D negatively affects the development of the fetal skeleton[12]. It is transferred across the placenta predominantly as 25-hydroxyvitamin D before conversion in the fetal kidney to the active form 1-25-dihydroxy-vitamin D.

Chronic damage to the placenta, with the resulting altered phosphate transport, also contributes to poor bone mineralization and explains the high postnatal incidence of rickets in neonates born with intrauterine growth retardation[13]. Such placental pathologies include pre-eclampsia[14] and also chorioamnionitis and placental infections[15].

Mechanical force patterns, such as fetal movements, including kicking against the wall of the uterus, also stimulate the growth of cortical bone[16]. As a result, preterm infants have a decrease in cortical bone growth leading to a reduction in bone strength. This, added to the reduction in transplacental accretion of Ca and P in the fetus, increases the risk of osteopenia in premature infants.

Postnatally

In infants who are exclusively breast fed, OOP is not

Table 1 Suggested guidelines for the prevention, monitoring and management of neonatal metabolic bone disease

Infants at risk	Prevention	Monitoring	Management
Born with birth weight below 1500 g Born before 28 wk of gestation	Early enteral nutritional intervention Maintain a sufficient supply of Ca and P. Start oral P supplements as soon as its feasible. The P absorption rate is very good in the presence of Ca, with absorption rates exceeding 90% with both human and formula milk. The Ca absorption rate increases from 35 to 60 mg/kg per day when both Ca and P are supplemented and to 90 mg/kg per day when the appropriate dietary Ca/P ratio is attained. High Ca and P retention rates are attained with high-mineral preterm milk formulae or with fortified human milk	Biochemical Monitor weekly serum "bone profile" (Ca, P and ALP): maintain serum Ca concentration between 2.05-2.75 mmol/L and serum P between 1.87-2.91 mmol/L If serum *P* < 1.8 mmol/L and ALP > 500 IU/L, renal TRP should be measured and, if it exceeds 95%, P supplementation should be started If serum P levels fail to increase and if serum ALP levels keep on rising, consider ergocalciferol or alphacalcidol therapy	If the biomarkers of MBD do not normalize, consider either vitamin D supplementation with up to 600 IU/d (although not well supported by evidence) or initiate instead ergocalciferol or alphacalcidol therapy in which case regular monitoring of urinary calcium/creatinine ratio is necessary to detect hypercalciuria
Having received total parenteral nutrition for more than four weeks	Vitamin D supplementation	DEXA	
On long-term diuretics or corticosteroid therapy	Ensure a minimum daily supplement of 400 IU vitamin D. Doses above 400 IU/d do not improve Ca and P absorption	Being increasingly used for assessing BMD in neonates, but not recommended as yet as a clinical tool	
Suffering from neuromuscular disorders	Parenteral nutrition Preparations providing 1.45 to 1.9 mmol/kg per day of Ca and 1.23 to 1.74 mmol/kg per day of P result in Ca and P retention rates of 88%-94% and 83%-97% respectively. The optimal Ca/P ratio in the intravenous solution fluid is between 1.3:1 and 1.7:1.54 If needed, parenteral P delivery can also be enhanced by using special preparations of organic P Exercises Daily exercises such as gentle compression and movements of the limbs Regular review of medications in use Discontinuation of diuretics and steroids when appropriate	Monitor for metabolic acidosis and hypercalciuria which may result from an increase in parenteral mineral delivery during parenteral nutrition	

ALP: Alkaline phosphatase; BMD: Bone mass density; Ca: Calcium; IU: International units; P: Phosphorus; TRP: Tubular reabsorption of phosphate. DEXA: Dual-energy X-ray absorptiometry.

correlated with the degree of the prematurity[17]. Very low birth weight infants (VLBW) whose full enteral feedings have been delayed delayed and who are on long term parenteral nutrition are at increased risk of OOP. Poor bone mineralization is also associated with common neonatal conditions. These include sepsis, broncho-pulmonary dysplasia, cerebral pathology, neuromuscular conditions leading to prolonged immobilisation, acidosis, necrotizing enterocolitis and also cholestasis. Frequently used medications such as diuretics, corticosteroids and methylxanthines also increase the risk of inadequate bone mineralization. Factors associated with increased BMD included higher birth weight, short duration of parenteral nutrition, absence of intraventricular hemorrhage, exclusive feeding of fortified breast milk, and older age at discharge[18].

Candidate genes associated with adult osteoporosis have recently been evaluated in VLBW infants where MBD was found to be associated with a lower number of thymidine-adenine (TA) repeats polymorphism of the estrogen receptor gene, compared to a higher number in those without MBD[19].

SCREENING AND MONITORING

As MBD is usually asymptomatic in most infants, its diagnosis depends essentially on screening. This is based on a set of criteria defined by the presence of clinical manifestations, radiologic findings, biochemical markers and BMC measurements. The recognized clinical-radiological associations include, bone demineralization, periosteal reactions and, in severe cases of osteopenia, rickets and pathological fractures may be present[20]. Infants at high risk of osteopenia, including VLBW infants or neonates on long term diuretic therapy should be regularly monitored for that condition as serious complications can be avoided by early diagnosis with appropriate management. Measuring BMC and BMD relies on a few surrogate markers (Table 1).

Serum biomarkers

As a normal serum Ca level can still be maintained to the detriment of Ca loss from the bone, it should not be used to screen infants at risk. Furthermore, serum Ca may also be affected by unrelated conditions such

as hypophosphataemia[16,21]. Serum P concentration is correlated with BMD, is highly specific but is not sensitive enough to identify infants with ostepenia. While serum P concentration adequately reflects *P* levels in the bone, serum Ca concentration remains maintained at the cost of Ca content in the skeleton.

Serum alkaline phosphatase (ALP) is a marker of bony turnover. Elevated levels indicate increased bone cellular activity and when exceeding 700 to 750 IU/L, they are associated with osteopenia, which is still asymptomatic at that stage[22,23]. The diagnosis of MBD in the preterm infant is usually suggested by the presence of low serum P levels in association with elevated serum ALP levels[1]. The association of serum ALP levels exceeding 900 UI/L with a serum *P* level less than 1.8 mmol/L is 100% sensitive and 70% specific to diagnose OOP[24]. A serum ALP level exceeding five times the upper limit of the normal range in adults is also associated with an increased risk of rickets[25]. The diagnosis of OOP cannot be made however with certainty by elevated serum ALP concentrations, because DEXA scan measurements of BMC did not find an association between ALP levels and OOP in some studies[26] and also because healthy preterm and osteopenic infants have higher serum ALP concentrations than full term infants. Associating multiple measurements of serum ALP with a wrist radiograph, with or without that of the knee, has been suggested for the identification of rickets in VLBW infants if the levels exceed 800 IU/L[27]. Because it is located on osteoblast surfaces, bone-specific ALP is a more specific biomarker of bone turnover, useful to confirm OOP, when high levels of total serum ALP are found[28,29]. Despite its limitations and, despite the absence of a clear cut-off diagnostic level, serum ALP measurement is frequently used to screen high risk infants for MBD. It is a readily available measurement in most laboratories and serial serum levels provide a trend very useful for follow up. Using it in conjunction with serum P levels as a screening tool significantly increases the sensitivity of identifying infants at risk of MBD.

Serum osteocalcin (OC), a non-collagenous protein of the bony matrix, is also a biomarker of osteoblastic activity. It is synthesized by osteoblasts and is partly regulated by 1,25-dihydroxyvitamin D levels. Its serum concentrations are elevated whenever bone turnover is increased, making it a possible useful tool to diagnose OOP[1]. However, despite its specificity, there is no correlation between serum OC levels and BMC in the first four months of age[30].

Urinary biomarkers

Urinary Ca and P excretion have also been used as biomarkers of postnatal skeletal mineralization. Urinary excretion of Ca exceeding 1.2 mmol/L and P exceeding 0.4 mmol/L are strongly associated with high bone mineralization. Infants born between 23 and 25 wk of gestation have a significantly lower renal P excretion threshold than other preterm neonates, resulting in elevated urinary P excretion even when serum *P* levels are low[31]. As, unlike Ca, P is not bound in the plasma, it has been suggested that a better biomarker for OOP is the percentage of renal tubular reabsorption of phosphate (TRP), with TRP > 95% indicating inadequate supplementation, bearing in mind that renal tubular leak of P can also be associated with inadequate Ca intake and increased serum PTH concentration[32]. Similarly urinary Ca or P to creatinine ratios may also be useful as biomarkers for OOP; normal reference ranges in preterm infants have already been established for these ratios[33,34]. However these urinary ratio results need to be carefully interpreted as they are highly dependent on the dietary intake (resulting in uncertainty if the standard reference range) and are also affected by the administration of drug such as furosemide or theophylline[35].

Radiological markers

Old fractures and cortical thinning may be seen on plain radiographs, reflecting poor bone mineralization, but are usually very late signs because they are not usually apparent unless the BMC decreases to 40%[36].

DEXA is currently the most widely used modality to assess BMD. It correlates well with fracture risk and, in both term and preterm infants, it can be used to estimate BMC[37]. Measuring BMD prior to adulthood however is hindered by the "areal" nature of the derived measurement. In addition, the establishment of robust, reliable neonatal, ethnic and gender specific normograms is urgently needed. Barriers to the routine use of DEXA as a screening tool for OOP include its high cost, its limited availability, the dimensions of the equipment used, the lengthy time required for imaging, as well as its sensitivity to movement artifact.

Quantitative Ultra sound (QUS), with already established reference values for both preterm and term infants, is a new inexpensive and portable modality of investigating OOP[38-40]. This simple, non-invasive and inexpensive bedside method measures the broadband ultrasound speed attenuation, and is usually performed on the tibia. Although the measurements it provides correlate well with bone density and structure, the association is a poor with the thickness of the bony cortex[41]. QUS is significantly lower in preterm infants than term infants and a significant correlation of QUS exists with serum ALP, supplementation with Ca, P and vitamin D as well as risk factors for reduced BMD[42]. The combination of longitudinal QUS measurements with serum ALP and *P* levels are helpful to identify infants at increased risk of OOP[43].

Although ultrasound reference values are available for term and preterm infants, there is limited information showing its usefulness.

PREVENTION AND TREATMENT

These are summarized in Table 1. The prevalence and also the severity of OOP can be reduced by early nutritional intervention. Maintaining a sufficient supply of

Ca and P for the growth of VLBW infants' skeleton is challenging because of their relatively high physiological requirements. In addition, although preterm infants are capable of absorbing up to 70% of Ca from human milk, the P content affects the Ca retention rate. Supplementing milk with both Ca and P is more effective: while the Ca absorption rate is 35 mg/kg per day in the presence of P supplementation alone, it increases to 60 mg/kg per day when both Ca and P are supplemented. Ca absorption is also affected by the dietary Ca/P ratio with the retention rate reaching up to 90 mg/kg per day when the appropriate ratio is attained. The neonatal intestinal absorption of P is very good in the presence of Ca, with absorption rates exceeding 90% with both human and formula milk[44]. Ca and P retention rates similar to those observed in utero are attained with high-mineral preterm milk formulae or with fortified human milk[45].

It is imperative to monitor closely serum Ca, P and ALP in such high-risk infants. To prevent OOP, serum Ca concentration should be maintained between 2.05-2.75 mmol/L and serum P between 1.87-2.91 mmol/L. Although VLBW infants are routinely given vitamin D supplementation to increase intestinal absorption of Ca and P, doses above 400 IU/d do not improve their absorption[46].

Parenteral nutrition preparations providing 1.45 to 1.9 mmol/kg per day of Ca and 1.23 to 1.74 mmol/kg per day of P result in Ca and P retention rates of 88%-94% and 83%-97% respectively, equivalent to 60% to 70% of the expected in utero Ca and P accretion rates[47,48]. Ca and P delivery by parenteral nutrition are affected not only by their respective concentrations in the intravenous solution, but also by the ratio of their concentrations. The optimal Ca/P ratio in the intravenous solution fluid is between 1.3:1 and 1.7:1.54[49-51]. The supply of these minerals to infants is limited by the poor solubility of both Ca and P in parenteral nutrition solution, resulting in an increase in the risk of OOP when enteral feeding is not possible for an extended period. Further research is required to improve Ca and P delivery with parenteral nutrition. Vigilance is required during parenteral nutrition as the increase in parenteral mineral delivery may result in metabolic acidosis and hypercalciuria[52]. If needed, parenteral P delivery can also be enhanced by using special preparations of organic P.

Because of the crucial role of mechanical forces on the development of the skeleton, daily exercises such as gentle compression and movements of the limbs are recommended in infants at risk of OOP if greater increase in body weight, forearm bone length, bone area and BMC are to be achieved[53-55].

CURRENT RECOMMENDATIONS

Guidelines for screening and treating infants at risk of OOP have been developed[56]. As summarized in Table 1, it is recommended to monitor all infants for MBD if their birth weight is below 1500 g, or if born before 28 wk of gestation, or if they have received total parenteral nutrition for more than four weeks or in case of diuretic or corticosteroid therapy. Monitoring consists of weekly serum "bone profile" (Ca, P and ALP). If serum P < 1.8 mmol/L and ALP > 500 IU/L, renal TRP should be measured and, if it exceeds 95%, P supplementation should be started. If serum P levels fail to increase and if serum ALP levels keep on rising, ergocalciferol or alphacalcidol therapy should be then considered. The American Academy of Pediatrics recommends that all breast-fed, partially breast-fed and non-breast-fed infants consuming less than 1000 mL of vitamin D fortified milk daily should be supplemented daily with a minimum of 400 IU vitamin D[57]. If the biomarkers of MBD do not normalize, vitamin D supplementation with up to 600 IU/d has been suggested, but without much supporting evidence. In addition, daily passive exercises should be encouraged and the medications in use should be regularly reviewed with discontinuation of diuretics and steroids when appropriate.

CONCLUSION

Preterm infants, those on long-term diuretics or corticosteroids, and those with neuromuscular disorders are at high risk of developing osteopenia. Complications such as rickets and pathological fractures may be the first manifestation of the condition. To detect the early asymptomatic phases of impaired bone mineralization and allow early intervention, all neonates at high risk of MBD appropriate biochemical markers of insufficient intake minerals and of abnormal bone turnover should be regularly monitored. DEXA is being increasingly used for assessing BMD in neonates, but more studies are still needed before it can be used as a useful clinical tool. Prevention and early diagnosis of MBD are key to the successful management of this condition and oral P supplements should be started as soon as is feasible.

Prospective studies of cohorts of preterm infants with OOP are needed with close long-term follow up for later outcomes. More research into urinary Ca and P to creatinine ratios is needed before they can reliably replace direct measurement of BMC. Similarly DEXA needs to be studied further to better define the "areal" nature of the measurement derived for BMD estimation in the newborn and also to establish reliable neonatal, ethnic and sex specific normograms. The possible role of QUS in routine screening for OOP needs also to be studied. As the poor solubility of Ca and P in parenteral nutrition solution hampers the adequacy of their supply to the growing newborn, further research in this area is required to increase their delivery.

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