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Osteopenia in Neonates: A Review

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Abstract Neonatal osteopenia is a well-known condition that predisposes to pathological fractures in newborn infants. Mineral deficiency leading to abnormal bone formation is the commonest cause of neonatal osteopenia and preterm infants are at increased risk of developing this condition. Other risk factors of neonatal osteopenia such as prolonged parenteral nutrition, chronic diseases such as bronchopulmonary dysplasia and short bowel syndrome have also been implicated. Early detection of this condition by monitoring markers of bone metabolism is, therefore, important in these high-risk populations. In this review, we will examine the literature with regard to identification of high-risk infants and methods that will help minimise the development of this condition.

Key words Bone mineral density; Calcium; Neonates; Osteomalacia; Osteopenia; Phosphate

Introduction

The study of bone mineral density (BMD) is of interest not only to adult physicians, but also neonatologists[1-3] and paediatricians.[4,5] Important determinants of skeletal strength and, therefore, risk of pathological fractures include size, structure and density of the bone. Low BMD (osteopenia) is an important fracture risk. In neonates, especially those born prematurely or of very low birth weight (VLBW), osteopenia is a common cause of pathological fractures. Decreased BMD can be a result of either decreased bone mineralisation or increased bone resorption. Many factors contribute to the increased risk of osteopenia in neonates, such as reduced opportunity for transplacental mineral delivery in premature infants, poor nutritional intake in vulnerable VLBW infants and excessive mineral loss after birth. The incidence of neonatal osteopenia is inversely associated with gestational age and body weight. As many as 30% of infants born with a birth weight less than 1000 g was reported to be osteopenic.[2] Other risk factors of neonatal osteopenia include chronic diseases, such as bronchopulmonary dysplasia and necrotising enterocolitis, and nutritional problems, such as delay in establishing full enteral feeding and prolonged parenteral nutrition.[6]

Pathophysiology

Development of the fetal skeleton requires large amounts of energy, protein and minerals. Minerals, such as calcium and phosphorus, are actively acquired by the fetus from the mother. By the second trimester of pregnancy, fetal serum calcium and phosphate concentrations are approximately 20% higher than maternal serum concentrations.[7] Bone mineralisation occurs predominantly during the third trimester. If the increased fetal demand in minerals is not met, then inadequate fetal bone mineralisation may result. There is evidence that mothers increase calcium supply during pregnancy, e.g., by increased intestinal absorption of calcium[8] and increased

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skeletal mineral mobilisation. The importance of maternal calcium consumption is suggested by the improvement of adverse effects of severe maternal dietary restriction by calcium supplementation.[7,9] Vitamin D is transferred transplacentally predominantly as 25-hydroxyvitamin D[10] and subsequently converted to 1,25-dihydroxyvitamin D in the fetal kidney.[11] Although the exact role of 1,25-dihydroxyvitamin D in fetal bone mineralisation is unclear, it has been shown that chronic maternal vitamin D deficiency can adversely affect fetal skeletal development.[7,9]

As the postnatal growth of an infant's bone marrow cavity is faster than the increase in the cross-sectional area of the bony cortex, over the first 6 months of life, the long bone density can decrease by 30%.[12] It is thought that these changes may reflect differences between postnatal and prenatal hormonal profiles and patterns of mechanical forces exerted through the skeleton. For example, fetal movements such as kicking against the uterine wall stimulate cortical bone growth. It means that preterm infants have less opportunity for cortical growth with a consequent decrease in bone strength.[13] These mechanical factors accompanied with decreased opportunity for transplacental mineral accretion place premature infants at high risk for neonatal osteopenia.

Risk Factors

Our increased understanding of the pathophysiology of neonatal osteopenia has raised awareness of the need for early monitoring, prevention and treatment of this condition in high-risk infants.

As already described, prematurity is a very important risk factor for neonatal osteopenia because transplacental calcium and phosphorus delivery is greatest after 24 weeks of gestation with as much as two-thirds of the fetal accretion of calcium occurring during this time.[14] As a result, premature infants have bone mineral stores at birth that may not be adequate for the rapid bony growth that occurs during the postnatal period.

Preterm infants are also prone to neonatal osteopenia due to mechanical factors. Skeletal development is strongly influenced by forces that are exerted upon the bones. It has been shown in an *in vitro* study[15] that osteoblastic activity increases with mechanical loading. Furthermore, it has been shown that a lack of mechanical stimulation leads to increased bone resorption, decreased bone mass and increased urinary calcium loss.[16] The skeletal structure remodels according to the prevalent forces, leading to increased bone strength at areas where this is most needed.[17] Lack of mechanical stimulation in preterm infants places them at increased risk of osteopenia. Mechanical factors are also thought to contribute to inadequate bony growth in infants born with hypotonic muscular disorders.[18] The association between decreased bone mineral density and reduced spontaneous movements has also been demonstrated in a study using quantitative ultrasound measurement in subjects with cerebral pathology.[19] Infants with decreased levels of physical activities and movements against resistance, such as preterm infants are at high risk of developing osteopenia.[20]

Use of various medications for neonatal diseases increases the risk of osteopenia in newborn infants. For example in preterm infants, the use of long-term methylxanthines and diuretics such as frusemide can increase urinary loss of minerals required for bony growth.[21] Also, use of high-dose systemic corticosteroids has been demonstrated to impair bony growth. An *in vitro* study showed inhibition of osteoblast function and DNA synthesis with high-dose systemic steroids,[22] while a clinical study showed a reversible reduction in serum bone-specific alkaline phosphatase and osteocalcin after a 3 week course of systemic dexamethasone.[23] VLBW infants with bronchopulmonary dysplasia are frequently exposed to such medications, further increasing their risk of developing osteopenia. This problem is compounded by fluid restriction and relatively high energy requirements, limiting the supply of minerals and energy available for skeletal development.

Despite a lack of change in bony biomarkers during infection,[24] it has been shown that neonatal osteopenia is associated with infection.[25] It is thought that this is related to the infant's catabolic state during infection.

Investigation and Monitoring

Severe neonatal osteopenia can lead to serious complications, such as rickets and pathological fractures. Often, the earliest clinical features of osteopenia in neonates are these complications. High-risk infants, such as VLBW infants or neonates on long-term medications such as diuretics should be regularly monitored for the possibility of osteopenia. This would allow the condition to be detected as early as possible so that appropriate management may avert the development of serious complications. Several modalities and surrogate markers for the measurement of bone mineral content (BMC) and BMD have been developed.

Radiological Investigations

Plain radiographs can sometimes show evidence of osteopenia such as previous fractures and cortical thinning (due to hypo-mineralisation). These changes are often very late signs as a decrease in BMC of less than 30 to 40 percent is unlikely to be apparent on conventional radiographs.[26]

The most widely used modality to assess BMD in the adult literature is currently dual-energy X-ray absorptiometry (DXA). DXA utilises two X-ray beams of different energy levels to scan the subject. The differential absorption of the X-ray energy by different tissues can be detected and analysed to reflect the amount of different tissues in a given area of projection (Ap). After calibration with materials of known density, the scanner may be used to detect fatty tissue, lean mass (fat-free mass), and BMC. BMD is defined as BMC/Ap. DXA has been shown to be superior to other methods of absorptiometry such as single photon absorptiometry, which although has been shown to correlate with BMC in infants,[27] does not appear to correlate well with rickets or fracture risk.[28] DXA, on the other hand, has been shown to correlate well with fracture risk.[29] Although DXA has been widely used as a measure of bone mineral density in adults, its use in paediatric patients in general and neonates in particular, is still limited. A study by Rigo *et al* has shown that DXA can be used to estimate BMC in both preterm and term infants.[1] One of the main problems with the use of DXA to measure BMD in non-adult patients is the "areal" nature of the measurement derived. As defined, the BMD measured by DXA is BMC/Ap which is a two-dimensional measurement. The true density is a three-dimensional measure and should correctly be BMC divided by the volumetric measurement. The areal approximation is reasonable in adult patients, but introduces systematic over estimation of BMD in larger patients.[30,31] This can be to some extent corrected by mathematical conversions based on assumptions of the skeletal structures of different bony regions.[31] However, further study is required to establish reliable neonatal, ethnic and sex specific normograms.

Although DXA exposes the subject to less ionising radiation than a chest radiograph,[30] it is nevertheless desirable to develop even less invasive methods of bone assessment. A portable and inexpensive method is the quantitative ultrasound (QUS). The speed of sound is analysed to derive parameters that is correlated with BMD. It has been shown that QUS measurements are associated with bone density and structure,[32] but not the thickness of the bony cortex.[33] It has been shown that QUS parameters are associated with fracture risk in adult subjects independently of BMD,[34] and QUS has been suggested to be a practical method of assessing for osteopenia in premature infants.[35,36]

Biomarkers

Plasma or serum biochemical markers such as calcium, phosphate, alkaline phosphatase and osteocalcin have been used to detect the development of neonatal osteopenia in premature infants.[3] There are several limitations to the use of these biomarkers. For example, while serum phosphate concentration reflect of bony phosphorus levels well[37] (persistently depressed concentrations reflect inadequate phosphorus levels and increased risk of osteopenia), serum calcium concentration is stringently controlled at the expense of bone calcium content. Further, serum calcium is affected by conditions that may not be related to neonatal osteopenia, such as hypophosphataemia.[38]

Serum total alkaline phosphatase concentration has been used as a marker of bony turnover.[39] Concentrations are elevated with increased bone cellular activity. It has been shown that concentrations above 750 IU/L, are associated with severe neonatal osteopenia and may precede clinical features of osteopenia of prematurity.[40] The literature regarding total alkaline phosphatase is conflicting, with poor associations reported in other studies.[41,42] Bone-specific alkaline phosphatase, a more specific biomarker that is located on osteoblast surfaces may present a more accurate picture of bone turnover,[23,43] and may be considered in cases with high levels of total alkaline phosphatase to increase diagnostic value.

Another biomarker of osteoblastic activity is osteocalcin, a non-collagenous protein of the bony matrix.[23,44] Circulating concentrations of osteocalcin are elevated during periods of increased bone turnover.[45] Despite its specificity, no correlation between serum osteocalcin and BMC was found during the first 4 months of age.[42]

Treatment and Preventative Measures

Maintaining an adequate supply of minerals for bony growth to VLBW infants has been difficult in view of the relatively high requirements and multiple limitations as previously described. It is, therefore, important to closely monitor circulating calcium and phosphate concentrations in high-risk infants, such as VLBW infants, maintaining calcium and phosphate concentrations between 2.05-2.75 mmol/L and 1.87-2.91 mmol/L, respectively to prevent osteopenia. However, both enteral and parenteral delivery

of calcium and phosphorus are fraught with difficulties. A comprehensive review of dietary intake and long-term medications should be undertaken in osteopenic infants and it may be necessary to increase enteral calcium and phosphorus intake. Additionally, it is possible to use special preparations of organic phosphorus to enhance parenteral phosphorus delivery. Vitamin D supplementation is routinely given to VLBW infants and serves to increase gastrointestinal absorption of calcium and phosphorus. However, increasing vitamin D dose above 400 IU/day has not been shown to improve calcium and phosphorus absorption.[46] Doses above 800 IU/day may increase risk of hypervitaminosis D and its associated complications. In essence, osteopenic infants should be monitored closely, using biomarkers such as serum phosphate and alkaline phosphatase concentrations to guide mineral supplementation. As pathological fractures may occur easily, these infants should be handled with extra care and vigorous physiotherapy avoided.

In view of the difficulty of treating neonatal osteopenia, monitoring calcium homeostasis and mineral stores of high-risk infants with a view to preventing development of complications is the preferred strategy. The poor solubility of calcium and phosphate in parenteral nutrition fluid often limits the supply of these minerals to infants, thus increasing the risk of osteopenia in cases which cannot be fed for long periods of time. The problem is worsened in VLBW infants or other sick infants who may also be fluid restricted. Current parenteral nutrition preparations may not be able to meet the metabolic needs of these infants.[47]

Neonates have different requirements during different periods of postnatal life. Initially, over the first few days of life, parenteral nutrition with approximately 1 mmol/kg/day of elemental calcium has been shown to be sufficient to maintain calcium homeostasis and prevent neonatal hypocalcaemia.[48] After this period, a larger mineral supply is required for rapid growth and bone mineralisation. It has been demonstrated in a randomised controlled trial that by increasing parenteral nutritional supplementation of calcium and phosphorus from 0.68 to1.25 mmol/kg/day and 0.61 to 1.20 mmol/kg/day, respectively, preterm infants exhibited higher plasma phosphate concentrations, lower plasma alkaline phosphatase activity, and less radiological features of rickets.[49] Other studies show that parenteral nutrition preparations that provide calcium and phosphorus at 1.45 to 1.9 mmol/kg/day and 1.23 to 1.74 mmol/kg/day respectively could achieve calcium and phosphorus retention rates of 88% to 94% and 83% to 97% respectively, approximately 60 to 70 percent of expected *in utero* mineral accretion rates.[50-52] Higher mineral retention rates that match *in utero* accretion rates are difficult to achieve due to the poor solubility of calcium and phosphate in parenteral nutrition fluids.[53] Further research in this area is required to increase calcium and phosphorus delivery via this route. For example, using monobasic potassium phosphate salt rather than the usual mixture of monobasic and dibasic salts can improve the solubility of calcium and phosphorus leading to a doubling in the amount of both elements that could be added to preparation. The increase in mineral delivery was shown to be at the cost of metabolic acidosis and increasing calciuria.[51]

Calcium and phosphorus delivery by parenteral nutrition has been shown to be affected not only by their concentrations, but also their concentrations relative to each other. Studies have been performed to determine the optimal ratio between calcium and phosphorus content in parenteral nutrition fluid.[54,55] In a study varying the calcium to phosphorus ratio from 4:1 to 1:8 by weight, it was suggested that calcium and phosphorus retention was optimised with a ratio of between 1.3:1 to 1.7:1.[54] Also, it has been shown that a ratio below 1:1 could result in hypocalcaemia and hyperphosphataemia.[55]

As the concentrations of calcium and phosphate in parenteral nutrition fluid are limited by the solubility product, infusions of calcium and phosphate separately and alternately have been considered. Studies using this method report lower retention rates of between 42 and 63%[56,57] compared with the 83 to 97% achieved with conventional simultaneous infusions.[50,51] Further, separate infusions are associated with complications such as hypercalcaemia and hyperphosphataemia,[56] and elevated urinary cyclic adenosine monophosphate concentrations during phosphate infusion, reflecting increased parathyroid response.[55]

As VLBW infants often suffer from feed intolerance and have high energy and mineral requirements, enteral supply of calcium and phosphorus is often limited. The inadequacy of the mineral supply has been reflected in raised circulating alkaline phosphatase[58] and 1,25 dihydroxyvitamin D[59] concentrations, development of radiological features of rickets,[60] and decreased BMC.[61] Preterm infants are normally able to absorb between 60 and 70% of calcium from human milk. However, phosphorus content will affect the calcium retention rate. Supplementation of milk with both calcium and phosphorus is more effective, with calcium absorption rates of 35 mg/kg/day with phosphorus alone, compared with 60 mg/kg/day with both calcium and phosphorus. Using different calcium/phosphorus salts also affect calcium absorption, with retention rates of 90 mg/kg/day achieved

with highly soluble calcium glycerophosphate.[62] In contrast, the gastrointestinal absorption of phosphorus by neonates is normally very good in the presence of calcium with absorption rates greater than 90% from both human milk and formula milk.[63] Studies have shown that calcium and phosphorus retention rates approximating *in utero* conditions can be achieved with high-mineral preterm milk formulae or human milk with fortification that provide a calcium and phosphorus intakes of 3.7-5.8 mmol/kg/day and 2.5-4.1 mmol/kg/day, respectively in a calcium: phosphorus ratio of between 1.8:1 and 2:1 (by weight).[64, 65] A randomised controlled study investigating the use of oral phosphate supplementation demonstrated that 50 mg/day was sufficient to prevent VLBW infants from developing radiological evidence of rickets.[66]

As previously discussed, mechanical forces exerted on the developing skeleton play an important part in its development. Some investigators have studied the effects of daily exercises, comprising gentle compression and movements of the limbs, on bony parameters. It was found that such a regular exercise regime was associated with greater increases in body weight, forearm bone length, bone area, bone mineral content and fat-free tissue mass.[67] Another study showed beneficial effects of a similar exercise regime on BMD as measured by QUS.[68]

Conclusions

Neonatal osteopenia 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 and pathological fractures can develop and may be the first clinical evidence of the condition. It is important for neonatalogists 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 mineralisation. DXA has become an increasingly used research tool for assessing BMD in paediatrics and even neonatal subjects, but requires more study before it can make a useful clinical tool. Treatment of established severe osteopenia is difficult as effective treatment such as bisphosphonates for adult osteopenia is lacking. Prevention and early detection of osteopenia is, therefore, the key to the successful management of this condition in neonates. Such infants should be commenced on oral phosphate supplements as soon as is practicable.

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