Approach to Metabolic Bone Disease of Prematurity

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Abstract :

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 various methods used for screening of infants who are 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. Pathological conditions which impair placental macro and micronutrients transfer, such as preeclampsia, intrauterine growth restriction, and chorioamnionitis are associated with an increased risk of MBD in preterm infants. There are no specific diagnostic methods for MBD of prematurity. The clinical findings appear late and sometimes the diagnosis is not carried out. Indeed, it is necessary to screen the subjects who are at risk to develop MBD. 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. 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.

Key words: Osteopenia, Rickets, Vitamin D, Phosphorous, Demineralisation.

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 various methods used for screening of infants who are 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]

Risk factors for MBD of prematurity

The most of placental transfer of calcium and phosphate occurs in the third trimester of gestation with a peak at 34 weeks. Pathological conditions which impair placental macro and micronutrients transfer, such as preeclampsia, intrauterine growth restriction, and chorioamnionitis are associated with an increased risk of MBD in preterm infants.[6]

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Data from animal models and observational studies in humans have demonstrated that calcitriol is not required to regulate serum mineral levels during the fetal life, as severe vitamin D deficiency and absence of vitamin D receptor or 1α-hydroxylase do not impair serum calcium and phosphate concentrations. However, clinical trials have shown that vitamin D supplementation of pregnant women reduces the risk for preeclampsia and gestational diabetes which represent risk factors for MBD. Male gender and polymorphisms of vitamin D receptor, estrogen receptor, and collagen alpha 1 genes have also been indicated as risk factors for MBD in preterm infants.[7]

After birth, the role of mineral intake of calcium, phosphate and vitamin D in the etiology of MBD of prematurity is still debated. Some studies reported that ELBW infants <30 weeks of gestation who had lower weekly intake of calcium, phosphate, vitamin D, and proteins during the first 8 weeks of life, developed MBD , whereas other studies have not found this correlation in the same cohort of subjects , and in infants <1,500 gr recruited independently from gestational age.[8]

It has been demonstrated that newborns are fed exclusively with breast milk showed lower levels of phosphate than those receiving special formulas or mineral supplementation. In addition, preterm infants fed with unfortified human milk present rickets in 40% of the cases, compared to the 16% of those fed with special formulas. It has also been demonstrated that phosphate supplementation improves the biochemical markers of MBD in a cohort of preterm infants with low gestational age and birth weight more than in a cohort of preterm newborns with higher gestational age and birth weight. A less effective intake of calcium and phosphate occurs in infants with poor tolerance to enteral nutrition and who require total parenteral nutrition (TPN) >4 weeks.[9] The adverse effects related to prolonged TPN include the possibility of aluminum contamination and the risk of mineral precipitation in the solution due to the small volumes.

Common neonatal morbidities, like sepsis, chronic lung disease (CLD) , acidosis, necrotizing enterocolitis, cholestatic jaundice, and long-term treatments with diuretics and glucocorticoids can impair bone remodeling by reducing osteoblast proliferation, stimulating osteoclast activity, decreasing calcium absorption, and increasing calcium renal excretion . An impaired osteoblast activity due to bilirubin and bile acids has been reported in experimental studies. Moreover, the lack of mechanical stimuli due to fetal movements against the uterine wall, as in presence of muscular disorders and paralysis, may contribute to decrease the bone formation.[10]

Diagnosis

There are no specific diagnostic methods for MBD of prematurity. The clinical findings appear late and sometimes the diagnosis is not carried out. Indeed, it is necessary to screen the subjects who are at risk to develop MBD.

Serum Biochemical Markers

The assessment of serum biochemical markers is useful for early detection of mineral deficiency (third week of life). However, none of the bone metabolism markers, such as calcium, phosphate, alkaline phosphatase (ALP), PTH, and vitamin D alone can be considered specific of MBD of prematurity.

1 – Calcium

The assessment of serum calcium levels is not a reliable screening tool because newborns can maintain normal calcium values despite a bone calcium loss. Furthermore, serum calcium levels may also be affected by other disorders such as phosphate depletion and hypophosphatasemia.

2 – Phosphate

Hypophosphatemia is the earliest marker of disrupted mineral metabolism, occurring 7–14 days after birth. Serum phosphate levels lower than 3.6 mg/dl (1.16 mmol/L) in newborns exclusively maternal breastfed suggest the depletion of the mineral content and indicate a greater risk for MBD development. Serum phosphate levels <5.6 mg/dl (<1.8 mmol/L) have been strongly associated with the presence of radiological evident rickets in preterm infants with a mean gestational age of 30.3 weeks (range 24.7–33.0 weeks) & a mean birth weight of 1,490 g (range 735–2,250 g).[11]

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3 – ALP

ALP is a bone marker which physiologically increases over the first 3 weeks of life and reaches a peak at 6–12 weeks of age . There are at least four ALP isoenzymes, encoded by four genes: 3 tissue non-specific alkaline phosphatase (TNSAP) (intestinal, placental, and germ cell), and the ubiquitous TNSALP especially abundant in the liver, bone and kidney, but also expressed in the brain, particularly in the cortical sensory areas. ALP levels >500 IU/L are suggestive of impaired bone homeostasis and values >700 IU/L are associated with bone demineralization, despite the absence of clinical signs.[13, 14] ALP levels higher than 900 IU/L in preterm infants <33 weeks of gestational age, associated with serum phosphate levels persistently lower than 5.6 mg/dL (<1.8 mmol/L), have a diagnostic sensitivity and specificity of 70 and 100%, respectively.[12] An X-ray of the wrist and/or knee has been suggested in VLBW infants when 2 values of ALP measured at least 1 week apart exceed 800 IU/L . Viswanathan et al. have shown that ALP level >500 IU/L in ELBW infants <30 weeks of gestation is associated with MBD . Of the 230 infants included in the study, 71 (30.9%) developed radiological evidence of MBD of which 24/71 (33.8%) showed spontaneous fractures. The differences of the cut-off between the above studies could depend on the selection of patients who were VLBW with higher gestational age in the studies from Backstrom and Chan, differently from those selected by Viswanathan who were an omogenous population of ELBW <30 weeks of gestation. The assessment of serum phosphate and ALP has been recommended weekly or biweekly.[15, 16]

4-Other Biomarkers

Serum PTH levels >100 pg/ml may suggest ELBW neonates at risk for MBD (17). A high PTH level indicates not only a secondary hyperparathyroidism but, in association with the kidney tubular reabsorption of phosphate (TRP), can discriminate the underlying cause of hypophosphatemia. A low TRP with a high PTH would suggest a calcium deficiency, while a high TRP with low or normal PTH would indicate phosphate deficiency . Serum osteocalcin (OC), a protein of the bone matrix, is a marker of osteoblastic activity, partially regulated by 1,25-dihydroxyvitamin D levels. In presence of high bone turnover, OC levels are increased. However, despite its specificity, there is no a clear relationship between serum OC levels and bone mineral content in the first 4 months of life. It has been demonstrated that serum PTH levels might predict a reduction of bone mineral content in preterm infants who have reached the at term age, while urinary phosphate excretion and OC might be useful markers to predict a low bone mineralization at 3 months of corrected age.[18]

Urinary Biomarkers

Urinary calcium and phosphate excretion have also been indicated as biomarkers of postnatal skeletal mineralization. Hypophosphatemia, the most common biochemical alteration associated with MBD of prematurity, causes reduced PTH release which increases renal tubular phosphate reabsorption. Decreased phosphate also directly stimulates renal tubular synthesis of vitamin D which increases intestinal calcium absorption. Thus, phosphate deficiency interferes with calcium balance, leading to hypercalcemia, hypercalciuria, and nephrocalcinosis. Infants born <28 weeks of gestation have a lower phosphate threshold value compared to other preterm newborns, resulting in elevated urinary phosphate excretion even in the presence of low phosphate levels. The normal range of TRP is 78–91% and a value above 95% is a significant marker of insufficient phosphate supplementation.14 Tubular phosphorus reabsorption is calculated according to the following formula:

[1-(urinary phosphorus/urinary creatinine × serum creatinine/serum phosphorus)] × 100.

Likewise, urinary calcium or phosphate to creatinine ratios may also be useful as biomarkers for MBD, although these ratios are highly dependent on the dietary intake and are also affected by the administration of drugs such as furosemide or theophylline.[14]

Radiological Markers

The instrumental diagnosis of bone impairment in preterm infants remains a difficult challenge.

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X-rays are not reliable at early stage of bone disease due to the absence of significant demineralization or fractures. Bone mineralization must be reduced by 20–40% to be identifiable and usually it occurs later in life.[15]

The Koo's score describes the radiological alterations:[17]

- Grade 1: presence of bone rarefaction;
- Grade 2: presence of bone rarefaction associated with metaphyseal alterations, shadow, and subperiosteal bone formations;
- Grade 3: associated with the presence of spontaneous fractures.

Dual energy X-ray absorptiometry (DEXA) is the gold standard technique to assess bone mineral density (BMD), adaptable to preterm infants. DXA expresses the bone calcium content as grams of hydroxyapatite per centimeter squared. The method implies the use of low ionizing radiation (effective dose, 0.001 mSv; <0.1 mrem), and the preferred target regions in neonates are the lumbar spine, the forearm and the calcaneus. A BMD >0.068 g/cm^2, evaluated in a cohort of preterm infants <31 weeks (birth weight <1,500) at discharge, has been associated to a low probability of developing MBD of prematurity. However, the instrumental dimensions, the time employed for imaging and movement artifacts limit the widespread use of this technology in preterm and at term infants. Backstrom et al. found that the association of ALP serum levels >900 IU/L and phosphate <1.8 mmol/L indicates a low BMD with sensitivity and specificity of 100% and 70%, respectively, compared to DXA measurements, in VLBW and ELBW infants <33 weeks of gestation and mean birth weight of 1,490 g. This correlation was not found in a prospective study performed in a cohort of infant <32 weeks with a mean birth weight of 1,129 g.[18] In these subjects ALP and phosphate were measured weekly from 1 week of age until 37 weeks of gestational age, and no associations were observed between either ALP or serum phosphate and bone mineralization at term.

Fig 1: X ray showing spontaneous fracture of humerus due to MBD of prematurity.

Prevention & Management

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. Ca and P retention rates similar to those observed in utero are attained with high-mineral preterm milk formulae or with fortified human milk.

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.

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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. 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. 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. 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.[19]

References:

1. Koo WW, Sherman R, Succop P, Krug-Wispe S, Tsang RC, Steichen JJ, Crawford AH, Oestreich AE. Fractures and rickets in very low birth weight infants: conservative management and outcome. J Pediatr Orthop. 1989;9:326–330.
2. Callenbach JC, Sheehan MB, Abramson SJ, Hall RT. Etiologic factors in rickets of very low-birth-weight infants. J Pediatr. 1981;98:800–805.
3. Dokos C, Tsakalidis C, Tragiannidis A, Rallis D. Inside the "fragile" infant: pathophysiology, molecular background, risk factors and investigation of neonatal osteopenia. Clin Cases Miner Bone Metab. 2013;10:86–90.
4. Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. J Pediatr. 2001;139:509–515.
5. Rustico SE, Calabria AC, Garber SJ. Metabolic bone disease of prematurity. Journal of Clinical & Translational Endocrinology. 2014;1:85–91.
6. Rustico SE, Calabria AC, Garber SJ. Metabolic bone disease of prematurity. J Clin Transl Endocrinol. (2014) 1:85–91. 10.1016/j.jcte.2014.06.004.
7. Funke S, Morava E, Czak ó M, Vida G, Ertl T, Kosztolányi G. Influence of genetic poymorphisms on bone disease of preterm infants. Ped Res. (2006) 60:607–12. 10.1203/01.pdr.0000242340.45676.5d.
8. Christmann V, Gradussen CJ, Körnmann MN, Roeleveld N, van Goudoever JB, van Heijst AF. Changes in biochemical parameters of the calcium-phosphorus homeostasis in relation to nutritional intake in very-low-birth-weight infants. Nutrients. (2016) 29:8 10.3390/nu8120764.
9. Mimouni FB, Mandel D, Lubetzky R, Senterre T. Calcium, phosphorus, magnesium and vitamin D requirements of the preterm infant. World Rev Nutr Diet. (2014) 110:140–51. 10.1159/000358463.
10. Yeh JK, Liu CC, Aloia JF. Effects of exercise and immobilization on bone formation and resorption in young rats. Am J Physiol. (1993) 264:E182–9. 10.1152/ajpendo.1993.264.2.E182.
11. Backström MC, Kouri T, Kuusela AL, Sievänen H, Koivisto AM, Ikonen RS, et al. . Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. Acta Paediatr. (2000) 89:867e73.
12. Hung YL, Chen PC, Jeng SF, Hsieh CJ, Peng SS, Yen RF, et al. . Serial measurements of serum alkaline phosphatase for early prediction of osteopaenia in preterm infants. J Paediatr Child Health. (2011) 47:134–9.10.1111/j.1440-1754.2010.01901.x.
13. Tsakalidis C, Dokos C, Tragiannidis A, Rallis D, Nikolaidis N. Gestational age, body weight and bone metabolism markers in premature infants: a single institution experience of Northern Greece. Acta Paediatr. (2010) 99:99.

14. Pohlandt F, Mihatsch WA. Reference values for urinary calcium and phosphorus to prevent osteopenia of prematurity. Pediatr Nephrol. (2004) 19:1192–3. 10.1007/s00467-004-1651-5.
15. Rehman MU, Narchi H. Metabolic bone disease in the preterm infant: current state and future directions. World J Methodol. (2015) 5:115–21. 10.5662/wjm.v5.i3.115.
16. Moreira A, February M, Geary C. Parathyroid hormone levels in neonates with suspected osteopenia. J Paediatr Child Health. (2013) 49:E12e6. 10.1111/jpc.12052.
17. Koo WW, Gupta JM, Nayanar VV, Wilkinson M, Posen S. Skeletal changes in preterm infants. Arch Dis Child. (1982) 57:447–52. 10.1136/adc.57.6.447.
18. Faerk J, Peitersen B, Petersen S, Michaelsen KF. Bone mineralisation in premature infants cannot e predicted from serum alkaline phosphatase or serum phosphate. Arch Dis Child Fetal Neonatal. (2002) 87:F133–6. 10.1136/fn.87.2.F133.
19. Moghis Ur Rehman and Hassib Narchi. Metabolic bone disease in the preterm infant: Current state and future directions . World J Methodol. 2015 Sep 26; 5(3): 115–121.