Prematurity and Bone Health

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Abstract
Recent advances in neonatal care significantly increases survival rate in preterm and particularly in extremely low birth weight infants (ELBW infants) and nutrition is becoming one of the most challenging issue to improve short and long term health and developmental outcomes. Nutrition is also relevant for bone development and mineralization reducing the risk of osteopenia and metabolic bone disease (MBD). Osteopenia of prematurity is a multifactorial disease including predominantly nutritional but also biomechanical and environmental factors. At birth, the fetal active mineral transfer is interrupted and the preterm becomes related to the parenteral and enteral mineral supplies. On the other hand, physiological adaptation of bone to extra uterine life leads to an increase in bone resorption. This process occurring earlier in preterm than in term infants can be accompanied by an increased risk of bone fragility and fractures. Early provision of highly bioavailable mineral supplies, correction of vitamin D deficiency and the screening of serum phosphorus concentration combined to urinary mineral excretion appears to be helpful for the prevention of MBD. When available, DEXA is more sensitive than ultrasound for quantifying osteopenia in VLBW infants at the time of discharge. Catch-up of mineralization is rapidly observed during the post term period and osteopenia of prematurity seems to be a self-resolving disease although the potential long-term consequences on the attainment of peak bone mass remains uncertain.

With major advances in life-support measures, nutrition has become one of the most debated issues in the care of very low birth weight (VLBW) infants. So, the goal of nutrition of these preterm infants is to provide postnatal nutrients and retention similar to the intrauterine gain of a normal healthy fetus. Nutrition is also relevant for bone development and mineralization requiring adequate protein and mineral supplies. Non-nutritional factors such intrauterine environment, maternal status, and/or fetal well-being also play a significant role.

Premature infants, particularly those born at <28 weeks’ gestation, are at a significant risk for reduced bone mineral content (BMC) and subsequent bone disease, variably termed metabolic bone disease (MBD), osteomalacia, osteopenia, or neonatal rickets [1–3]. Reduction in BMC and the development of MBD of prematurity are quite common among VLBW infants. The incidence increases with decreasing
gestational age and birth weight but, due to the lack of widely adopted diagnostic criteria, the true incidence is still controversial. The clinical picture can range from abnormal biochemistry to pathological fractures. Early studies showed that fractures in premature infants typically occur several weeks after delivery and prior to the postnatal age of 6 months with an incidence varying between 2.1 and 25% [4, 5]. Rib fractures, the most common type, usually occur silently and are diagnosed only if X-rays are performed. Currently, fracture is becoming an exceptional phenomenon due to improvement of parenteral and enteral mineral supplies, and prospective, systematic skeletal surveys are necessary to evaluate the risk of fractures in VLBW infants.

**Fetal and Neonatal Bone Physiology**

Skeletal development first includes synthesis of the organic bone matrix by the osteoblast. This process is complete by the end of embryonic development at 7–8 weeks and the shapes of all bones are formed during this time. In the second phase, mainly calcium and phosphate are deposited in bones and growth occurs [6]. Most bone mineralization occurs during the third trimester of gestation and accounts for approximately 20 g for calcium (accretion rate of 100–120 mg/kg/day) and 10 g for phosphorus (accretion rate of 50–65 mg/kg/day) [7–10]. This maternofetal transfer is fairly stable and relatively independent of the mother’s nutritional status. The high calcitonin and estrogen environment promotes this hypercalcemic state.

In utero, bone modeling is the main process inducing high net bone formation, with a mineralization higher than necessary from bone growth resulting in a continuous increase in skeletal density. In contrast, after birth, bone metabolism is the result of both modeling and remodeling activities, defined as the continuous succession of bone resorption and formation [6].

These physiological postnatal changes in bone metabolism have been illustrated using Dual EnergyX-Ray Absorptiometry (DEXA) performed at birth and postnatally in preterm and term infants for the evaluation of bone mineral apparent density (BMDA); an estimate of volumetric bone mineral density (in g/cm³) calculated as BMC/BA1.5 [9, 10]. As shown in figure 1, in utero BMAD increases during the last trimester of gestation to reach a maximal value at term, suggesting that bone mineral accretion is higher than that just required from bone growth during that period.

Furthermore, in contrast to fetal life, there is a progressive reduction in BMAD during the first weeks of life in both the preterm and the term infant. Thereafter, the neonatal period is followed by a BMAD stabilization that lasts to the end of the first year of life in term infants and by a relative catch-up of mineralization in preterm infants [9]. Thus, a similar adaptation of bone mineral metabolism occurs in VLBW infants as in term babies but with the difference that it occurs earlier. Mineral retention from birth to theoretical term is far from that observed during fetal life, whereas skeletal growth remains relatively high contributing to
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a reduction in bone density. These postnatal changes, resulting from the limited mineral supplies compared to the materno-fetal transfer correspond to the preterm osteopenia and can be accompanied by increased bone fragility and fracture risk.

Etiology of Bone Disease of Prematurity

MBD is a multifactorial disease included nutritional factors but also biomechanical and environment factors.

Nutritional Factors

Nutritional factors are of major concern in the risk of MBD. Indeed, in preterm infants active fetal mineral transfer is interrupted at birth and becomes related to the parenteral and enteral supplies of mineral. Calcium and phosphorus are deposited in bone as hydroxyapatite with a calcium to phosphorus ratio of 1.66. In addition to bone mineralization, phosphorus retention is also necessary for lean body mass growth accounting for ±10 mg of phosphorus per g protein retention (nitrogen to phosphorus ratio = 16/1) [9]. Due to the bypass of the gastrointestinal tract, enteral and parenteral minerals are not metabolically equivalent and recommended intakes differ quantitatively but also in terms of calcium to phosphorus ratio.

In parenteral nutrition (fig. 2), calcium, phosphorus and amino acids are directly available for metabolism but the limiting factor is the relatively poor solubility of the calcium and phosphorus salts, particularly when inorganic phosphate salts are used.
Fig. 2. Calcium and phosphorus physiology during parenteral and enteral nutrition.
Calcium gluconate in parenteral solution induces a risk of aluminum exposure potentially deleterious in bone formation and neurodevelopment [11–13]. With the use of calcium chloride and Na glycerophosphate, a stable parenteral solution containing 3% of amino acid and 12.5 mmol/l of calcium and phosphorus can be designed with a molar calcium to phosphorus ratio in the range of the recommended value, 1.0–1.3 [14].

In enteral nutrition (fig. 2), the mineral supplies available for bone mineral accretion are diminished due to the immaturity of the gastrointestinal tract. The gastrointestinal absorption rate represents about 50% for calcium and 75–90% for phosphorus. The mineral absorption rate is related to the feeding regimen (human milk or preterm formula), the solubility of the mineral salts, the quantity and quality of fat intake, and the vitamin D status of the preterm infants. Metabolic balance studies in preterm infants fed fortified human milk or formulas have reported that maximal retention values may reach 60–90 mg/kg/day for calcium and 50–75 mg/kg/day for phosphorus. These retention rates are relatively low compared with the fetal accretion rates but appear adequate to reduce the incidence of osteopenia and fracture risk [1, 9–11]. Therefore, the recommendations of the ESPGHAN Committee of Nutrition recently suggested that an intake from 120 to 140 mg/kg/day (110–130 mg/100 kcal) of highly bioavailable calcium salts and from 60 to 90 mg/kg/day (55–80 mg/100 kcal) of phosphate is necessary. In addition, in relation to the high protein intake currently recommended, a sufficient intake of phosphorus is necessary and the recommended molar calcium to phosphorus ratio is 1.1:1.5 [15].

**Vitamin D**

The plasma vitamin D concentration at birth is directly related to the mother's vitamin D status and thus the season, mother’s skin pigmentation, sunlight exposure, and vitamin D supplementation. Vitamin D deficiency is widely observed (50–75%) in the pregnant population and in cord blood at birth [16–18]. Vitamin D improves calcium and phosphorus absorption and mineral deposition. In addition, vitamin D plays a significant role in other health factors such as immune function. Plasma 25(OH)D concentration is a useful index of vitamin D status and needs to be monitored during the first weeks of life in preterm to correct a deficiency in those born to mothers with poor vitamin D status. This monitoring is also necessary to maintain the plasma concentration at over 30 ng/ml (75 nmol/l) even if there is no consensus with regard to the optimal plasma concentration of 25(OH)D for infants and children [16, 19]. Recently, a vitamin D intake of 800–1,000 IU/day (and not per kg) during the first months of life has been recommended by the ESPGHAN CoN [15].

**Physical Activity**

Physical activity plays a significant role in bone mineralization. It is well demonstrated in adults and in children that mechanical strain on bone and joints stimulates bone formation and growth whereas inactivity leads to bone resorption. So, in utero,
regular kicking against the confining uterine wall participates in bone formation and growth. After birth, movements of preterm infants in incubators occur without much resistance. This is aggravated by medications limiting pain and by the reduction in tactile stimulations to reduce stressful events in the NICU. In order to obviate the effects of reduced mechanical stimulation, systematic physical activity programs administered several times a week by nurse, therapist and parents have been evaluated [20]. Recent studies suggest that physical activity improves bone mineralization, and increases bone formation [9, 21].

Additional factors play a significant role in bone mineralization, including genetic polymorphism or the use of various medications such as diuretics, caffeine and steroids that interfere with mineral absorption or retention[10].

**Screening for Metabolic Bone Disease**

Neonatal screening for MBD in preterm infants is still controversial [3].

Plasma calcium concentration carefully regulated by hormonal secretion is not a useful screening tool. However, a low serum phosphorus concentration, below the renal phosphate threshold (<1.8 mmol/l), has been related to insufficient phosphorus intake and to the risk of osteopenia [9, 10].

Urinary excretion of calcium and phosphorus has been proposed as a marker of adequate postnatal mineralization when doses >1.2 mmol/l of Ca and >0.4 mmol/l of inorganic phosphorus are excreted simultaneously. However, these values are more appropriate for estimating the adequacy of the calcium to phosphate ratio in the enteral or parenteral diet than for estimating the mineral accretion [22]. Alkaline phosphatase (ALP) is principally of bone origin (90%) in infants. ALP concentrations usually increase during the first 2–3 weeks of life and may peak further if there are insufficient mineral supplies. Elevated levels have been reported with severe under-mineralization in radiological, speed of sound (SOS) or DEXA studies but this enzyme is probably more sensitive for evaluating fracture risk than for assessing MBD.

Radiological investigations are poorly sensitive to evaluate MBD, detecting only a decrease of >20–40% of bone mineralization [9, 23]. By contrast, DEXA technology is a sensitive, accurate and precise method for evaluating bone mineral density and has been validated in both preterm and term infants [8, 10]. The use of normative data on bone mineral content, projected bone area and bone mineral density allow for determination of changes in bone mineralization postnatally in the preterm baby. In addition, various indices have been proposed for reducing the anthropometric dependency of the various parameters and for facilitating individual comparison.

Quantitative ultrasound has been proposed for the evaluation of bone mineralization in newborn infants [3, 23]. It is a simple, noninvasive, relatively inexpensive bedside procedure. In addition to measuring the SOS and bone transmission time, this procedure provides some information on bone density, cortical thickness, elasticity
and bone microarchitecture. However, changes in SOS values during the last trimester of gestation are relatively small and this technique has a lower sensitivity than DEXA for evaluating MBD in preterm infants [10, 24, 25].

Consequences of Bone Mineral Density

As seen in figure 1, after discharge, catch-up mineralization is rapidly observed in VLBW infants. At 6 months of corrected age, spine and total bone mineral density, corrected for anthropometric values, are in the range of normal term newborn infants. In fact, this catch-up is quite similar to that observed after the initial acceleration of growth during adolescence. Thus, osteopenia of prematurity seems to be a self-resolving disease, although the potential long-term consequences on the attainment of peak bone mass, a strong predictor of later osteoporosis risk, are not clearly evaluated [12].

Conclusions

In summary, after birth, the development of relative osteomalacia or osteopenia is a physiological event resulting from a mismatch of the mineral supply and persistence of a high velocity growth rate on the one hand, and from the stimulation of bone turnover as an adaptation to extrauterine life on the other.

This phenomenon is enhanced in preterm infants born with low mineral stores and immature gastrointestinal tracts and is worsened by the reduced physical activity. These factors might increase the severity of the MBD leading to a risk for fracture. An early optimal parenteral and enteral mineral supply, combined with adequate vitamin D intake to maintain or restore plasma 25(OH)D, contribute to the prevention of MBD. Biological screening of serum phosphorus and ALP concentrations, as well as mineral urinary excretion, appears to be helpful for the prevention of MBD. When available, DEXA is more sensitive than ultrasound for quantifying osteopenia in VLBW infants.

References

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