

# METABOLIC BONE DISEASE OF PREMATURITY

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## Abstract

The survival rate of premature infants has significantly increased during the last few decades. As a consequence, new disorders such as osteopenia of prematurity have been emerging.

Osteopenia (metabolic bone disease - MBD) is common among extremely low birth weight infants (ELBW, <1000 g birth weight) despite current practices of vitamin and mineral supplementation. (9)The diagnosis of osteopenia of prematurity is based evidence for less bone mineral density compared to fetuses or infants at the same gestational age in the absence of laboratory parameters and/or clinical signs for rachitis or other metabolic bone disease. The incidence of osteopenia among infants born before 28 weeks of gestational age are high.

The aim of this paper is to review the information regarding the prevention and treatment of osteopenia of prematurity. The latter is essential for the prevention of osteoporosis in adulthood, a significant problem of public health.

**Keywords:** osteopenia, prematurity, metabolic bone disease

## Introduction

The survival rate of premature babies has increased significantly in recent decades through the continuous progress made in intensive care units in hospitals where resuscitation equipment is available respiratory. Among the common conditions of morbidity due to the prematurity a growing interest is focusing now on the metabolic bone disease of the prematurity, also called osteopenia of prematurity.(5)

Osteopenia, a condition characterised by a reduction in bone mineral content, is a common disease of preterm babies. Prematurely born infants are deprived of the intrauterine supply of minerals affecting bone mineralization. The aetiology is multifactorial: inadequate nutritional intake (or poor absorption) of Ca and P, insufficient intake of vitamin D, insufficient intake of protein, limitation of physical activity.

Identification of risk factors is essential for monitoring of osteopenia. Some of the risk factors include low birth weight, prematurity, chronic placental lesions, prolonged parenteral nutrition, prolonged immobilization, long term administration of drugs such as corticosteroids, methylxanthines, furosemide, abnormalities in vitamin D metabolism, inadequate maternal intake of Ca, P.

Neonatologists, pediatricians and endocrinologists should investigate premature, low birth weight infants that have high serum alkaline phosphatase and have at least one risk factor.

## *Bone physiology*

Amounts of minerals necessary for normal development of the skeleton are very different depending on the age of the child.

During intrauterine life, and especially in the last trimester of pregnancy occurs skeletal development. Significantly increases bone volume with gestational age and bone formation activity is due to the modeling process, an increase in trabecular thickness (trabecular thickening rate being about 240 times higher in fetal than in children). The mineralization process is determined by synthesis of the organic bone matrix by osteoblasts (osteoid) onto which calcium and phosphate salts are deposited. This process increases exponentially between 24 and 37 weeks of gestation, reaching the 80% of mineral accretion in the third trimester.(1)

At term the newborn skeleton has a high physical density (expressed as bone mass divided by bone volume). Fetal accumulation of calcium and phosphorus in the last three months of gestation is about 20 g to 10 g, which represents the storage rate of 100-120 mg/kg/day of calcium and 50-65 mg/kg/day to phosphorus. A very important role in the formation of the fetal skeleton is played by the placenta. Calcium transfer from mother to fetus through the placenta occurs through active transport of basement membrane calcium pump. Moreover, the placenta is able to convert vitamin D to 1,25-dihydrocholecalciferol which is fundamental for transferring phosphate to the foetus. The foetus is maintained hypercalcemic in a high calcitonin and estrogen environment which promotes the modelling/remodelling ratio in favour of modelling and thus increasing the endocortical bone. Such premature babies will be deprived of the intrauterine supply of calcium and phosphorus that cause bone mineralization.

Chronic impairment of the placenta may alter phosphate transport, explaining why children with intrauterine growth retardation may have osteopenia. Demineralization is observed in children born to mother chorioamnionitis and placental infection.

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After birth, bone density decreases term newborns by 30% in the first 6 months of life. This is largely due to an expansion of the size of the marrow cavity, which occurs more rapidly than the increase in cross-sectional area of the bone cortex.

There are significant changes in the hormones: estrogen reducing maternal and postnatal growth of PTH levels due to a reduction in the supply of calcium from the placenta.(2)

As the serum calcium levels falls in the first day of life, PTH secretion is stimulated. During this transition the response of the parathyroid gland to falling levels of ionised calcium is blunted. This finally results in a physiological nadir in neonatal serum calcium levels within the first 48 hours of life. Of note, PTH level is still within the normal range for term babies or adult, but represents a decrease from foetal levels.

Many factors play a role in the absorption of calcium: maternal vitamin D status, the solubility and bioavailability of calcium salts, calcium quality and quantity, the amount and type of lipid and bowel function. Calcium absorption from the intestine occurs by both passive and active transport dependent on vitamin D. In a newborn preterm low mineral content of human milk associated with poor absorption from the gut determine a net reduction of calcium and phosphorus supply. Phosphorus absorption occurs in the jejunum and depends on food intake. The phosphorus supply regulates calcium absorption and retention: the higher is the phosphorus content of the diet, the higher is the calcium retention. However, an excessive amount of one decreases the absorption of the other.

Among the other pathogenic factors, also problems related to inadequate supply of calcium to babies, which require parenteral nutrition and interference of several drugs, may contribute to determine preterm osteopenia with an increasing risk of bones fractures.

#### Risk factors of osteopenia

##### a.Prematurity

Prematurity is a very important risk factor because transplacental transport of Ca and P is higher after 24 weeks of gestation. Almost 66% of fetal Ca accumulation occurs during this period.Overall, it is estimated that 80% of mineral accumulations occur in the 3rd trimesters of pregnancy. As a result, premature babies have low bone mineral deposits that rise may not be sufficient for rapid bone growth that occurs during the post-natal period.(5,9)

##### b.Lack of mechanical stimulation

Bone development is strongly influenced by forces that are exerted upon the bones therefore preterm infants are vulnerable due to lack of mechanical stimulation. the lack of mechanical stimulation may lead to increased bone resorption, decreased bone mass and increased urinary Ca loss . The skeletal structure remodels according to the prevalent forces, leading to increased bone strength at areas where this is most needed. Inactivity due to immobilisation (incubator) stimulate osteoclastic bone reabsorption and urinary excretion of calcium plus low muscle activity prevents the formation of new bone.(20)

##### c. Drugs administration

Neonatologists and other specialists should be careful in the prolonged administration of drugs. In preterm infants, the use of long term methylxanthines and diuretics such as furosemide, increase renal Ca excretion required for bony growth. Also, use of high dose systemic corticosteroids has been demonstrated to impair bony growth.

##### d. Other pathological conditions

Sepsis, cerebral pathology, neuromuscular disorders may result in prolonged periods of immobility associated with poor bone mineralization. In addition chronic damage to placenta may alter the phosphate transport; therefore babies with intrauterine growth restriction may be osteopenic (14). Demineralization is observed also in mother with chorioamnionitis and placental infection.

##### Clinical features

Most cases of MBD are evolving asymptomatic. This disease remains silent until a severe demineralisation occurs.

The most evident clinical findings of osteopenia (MBD) are deformity of the skull (diastasis of the suture, enlargement of the sagittal fontanelle and frontal bosses, craniotabe), thickening of the chondrocostal junctions and of the wrists, rib and long bones fractures. Softening and/or fractures of the ribs can cause pulmonary changes and respiratory distress, typically between 5 and 11 weeks of age.

Often, the earliest clinical features of osteopenia in neonates are these complications. High risk infants, such as VLBW infants or neonates received for 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.

##### Laboratory investigations

Diagnosis of osteopenia is mainly done by serum analysis. Serum alkaline phosphatase (APS) - the single investigation - correlates poorly with bone mineral status. 90 % of APS serum bone originates. APS babies grow at all in the first 2 weeks after birth and then further increase in conditions of insufficient intake of minerals. APS values above 1000 IU / L is often associated with fractures and growth failure.(3,16)

Serum P values <2 mmol / l suggests risk MBD while values < 1.8 mmol / l is associated with radiologically evident rickets.Using serum APS and P values increases the sensitivity and specificity of the diagnosis MBD. Serum calcium is not a useful marker of bone mineral 's status as the level of calcium is maintained in the normal range on account of long bone reabsorption and may be elevated even under hypophosphatemia.(7)

Markers of nutritional status should be assessed baseline, and then weekly during the initial phase; once the newborn is stable, assessment must be done at the starting of total enteral nutrition and successively every 2–3 weeks. If MBD is diagnosed and nutritional supplementation is started, a periodic assessment of laboratory data is necessary to evaluate the response to treatment also when babies are discharged from hospital. The key clinical goal is to maintain normocalcemia and normophosphatemia and to

avoid an excessive calciuria. Once levels of APS, calcium and phosphorus normalize, serum analysis can be performed monthly up to 6 months of age and then every 3 months.(4)

More sensitive markers of bone mineralization deoxypyridinoline , pyridinoline , C - terminal propeptide of type 1 collagen - collagen metabolism intermediates and osteocalcin - a non-collagenous bone matrix protein secreted by osteoblast. However, these tests are not widely available.

ELBW premature infants have a low threshold of urinary excretion of P leading to deletions increased P and decreased serum phosphate. Tubular reabsorption of P of 95 % suggests an insufficient intake of P and is associated with hypercalciuria.

Determination of vitamin D has low sensitivity and specificity for the diagnosis BMOP and vitamin D has a role in the etiology of the disease.

Radiologic appearance depends on the severity and duration of impairment and bone mineralization radiological diagnosis is imprecise. Radiological changes of long bones are not radiographically detectable bone mineral to decrease by over 20% usually changes early, acute are hardly highlighted.

Ultrasound is a method available bone quantitative, inexpensive, simple and non-invasive assessment of bone density.(18) The sonographic studies have shown the development of bone and early after birth have demonstrated that the severity of the process, is correlated with gestational age .(19)

Dual energy X-ray absorbitometry (DEXA) is able to determine the bone mass content of neonates and can predict the risk of fractures since it is sensitive in detecting small changes in BMC and BMD. (13)Its use is now validated in neonates both term and preterm ones.DEXA reflects most accurately the state of bone mineralization in preterm infants.(14)

#### Profilactic treatment

To a very large extent of MBD prevention methods overlap disease therapy. Early nutritional interventions decrease the prevalence and severity of MBD.

Most infant formulas for premature infants are fortified with Ca and P in order to compensate for the deficiency of intestinal absorption (compared to human milk ) and provide a surplus of Ca and P . (15) Provides fortified milk intake of Ca and P much improved and fortified breast milk feeding preterm nutrition is a safe method that results in improving weight gain and waist. In the absence of breast milk invigorator recommended premature breast milk supply and administration of calcium, phosphorus and vitamins per os.(17)

Deficits largest bone and waist were reported in infants under 1250g who experienced and intrauterine growth restriction. Enter hence the non- nutritive factors discussed role of breast milk in preventing long-term effects of MBD.

Studies have shown that bone mineralization is much better for premature infants fed preterm formula compared with infants fed standard formula (for mature newborn) demonstrating that poor dietary intake has major role in the etiology MBD.

In the case of an insufficient enteral intake (unfortified breast milk) is recommended calcium and phosphorus per os until the weights of 2.5 kg: total intake of 200 mg/kg/day calcium and 100 mg/kg/day of phosphorus. Calcium and phosphorus by preterm milk breast - fed less than 1500 g birth weight recommended by the age of 8 weeks or at least until the weight of 2000g .(8)

Fortification of human milk with fortifier containing calcium and phosphorus nutrition intervention is the best long-term results. Using the formulas for preterm nutrition is safe and effective alternative if the milk is not available or is not. If premature MBD or other obvious nutritional deficiencies (usually ELBW) is advised that breast milk fortification, supplementation or administration of preterm formulas continue until the weight of 3.5 kg or even up to the age corrected 9 months.(10,12)

If radiological evidence of rickets and enteral intake of minerals is not enough despite administration of fortified breast milk or preterm formula (usually premature NG under 800g ) may be used per bone mineral supplementation: up to 40 mg/kg/day as elements up to 20 mg/kg/day elemental P. When used orally supplements of calcium and phosphorus is recommended that they not be added to milk (breast or formula) (risk of precipitation).

Orally mineral supplementation is stopped when APS is below 500 IU/day. Vitamin D is the only adjuvant therapy MBD, providing optimal nutritional intake of energy, protein and minerals are based therapy. The recommended daily dose is 400 IU/day summand vitamin D dose administered via nutritional supplement vitamin D per os. Breast milk contains 22-100 IU/liter, the amount varying according to the mother's diet, sun exposure, pigmentation and type of maternal supplementation with vitamin D. The formulas contain about 400 IU/liter. (6) There is evidence that higher doses of vitamin D are not necessary and do not influence the evolution of MBD but increases the risk of toxicity. Maximum tolerable limit for vitamin D is 1000 IU. Maternal supplementation with 4000 IU/day vitamin D increases the concentration of vitamin D in breast milk to 100 IU/l and improves bone mineralization rate of child. More studies show that the initiation of a program of early passive motion when it supports handling leads to increased bone mineralization (increased bone length, bone mass, lean body mass) and weight gain.(11)

#### **Conclusions**

1. Optimizing energy intake, protein and mineral of prematurity is the most important preventive measure and therapeutic MBD.
2. Breast milk and formula for premature babies are the best options for feeding preterm infant in the first months of life.
3. Spontaneous movements (mainly antigravity flexion and extension) are important for bone structure and mineralization in premature infants. QUS may become an important diagnostic modality for the evaluation, treatment, and follow-up of bone strength and osteopenia in this unique population.

4. Prognosis of MBD is good, short and long term if the correct nutritional intake.

5. No need for a higher intake of 400 IU vitamin D / day.

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