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**review**

# Metabolic Bone Disease In Premature Neonates- An Unmet Challenge

**Chacham S et al. Preterm Metabolic Bone Disease**

[1]Swathi Chacham, [2]Rachna Pasi, [3]Madhuradhar Chegondi, [1]Najeeb Ahmad, [1]Shanti Bhusan Mohanty
[1]India institute of Institute of medical sciences, Rishikesh, Uttarakhand, India
[2]Himalayan Institute of Medical sciences, Dehradun, Uttarakhand,India.
[3]University of Iowa, Carver College of Medicine, Iowa city, IA 52242 USA.

Abstract
The metabolic bone disease is an important morbidity in premature, very low birth weight and sick infants. If left undiagnosed, leads to structural deformities & spontaneous fractures.It is defined as impaired bone mineralization in a neonate with lower than the estimated bone mineral levels in either fetus or neonate of comparable gestational age / weight coupled with biochemical abnormalities with or without radiological manifestations. It has been reported to occur in 16% to 40% of extremely low birth weight neonates. Insufficient calcium and phosphorous stores during the phase of accelerated growth predispose to it along with use of medications (caffeine, steroids), prolonged parenteral nutrition & chronic immobilization. It presents by 6-16 weeks after birth. Enhanced physical activity in preterm infants facilitates bone mineralization and weight gain. Biochemical abnormalities tend to worsen significantly, as the severity of disease progresses. They consist of hypocalcemia, hypophosphatemia, hyperphosphatasia and secondary hyperparathyroidism. In addition, urinary phosphate wasting and hypo vitaminosis D can complicate these abnormalities. Conversely, biochemical abnormalities may not be accompanied by rachitic changes.
Newer diagnostic modalities include bone densitometry by quantitative ultrasound over mid-tibial shaft (non-invasive tool). The management of metabolic bone disease includes adequate calcium, phosphorous and vitamin D supplementation along with optimum nutrition and physical activity. Similarly, preventive strategies for metabolic bone disease should target nutritional enhancement alongside enhanced physical activity.
Conclusion: Metabolic bone disease is a preventable morbidity in preterm, VLBW neonates and requires optimum nutritional supplementation and enhanced physical activity.
Keywords: Extremely premature, hypocalcemia, hypophosphatemia, neonate, osteopenia, premature, rickets, very low birth weight.

Swathi Chacham MD, India institute of Institute of medical sciences, Rishikesh, Uttarakhand, India
91-98494-47306, 91-75053-98951
swathi.m.lahiri@gmail.com
https://orcid.org/0000-0002-9349-1114

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## Introduction

Metabolic bone disease (MBD) in neonates is associated with reduced bone mineral content (BMC) leading to impaired skeletal mineralization. It is also called as osteopenia of prematurity and is a common consequence of numerous nutritional and biomechanical factors in premature neonates. The BMC is inversely proportional to gestational age and birth weight. It is influenced by the adequacy of calcium and phosphorus intake in postnatal life (1,2). MBD may or may not be accompanied by rachitic changes. Although, advanced neonatal intensive care enabled enhanced survival of extremely preterm infants, this is not truly translated into reduced morbidity and optimum growth.

Definition: It is defined as decreased bone mineralization in neonates when compared to inutero or exutero bone mineral density of neonates with equivalent gestational age or birth weight along with biochemical evidence and or radiological findings.

Magnitude of the problem: It has been reported that 55% of infants with extremely low birth weight (ELBW : ≤ 1000 grams birth weight) and 23% of infants with very low birth weight (VLBW: < 1500 grams) have MBD. Similarly, it is more frequent in neonates under 28 weeks of gestation(10,11). Incidence of MBD in breastfed premature infants is 40% and in formula fed preterm infants (with oral calcium and phosphorus supplements) is 16%. As proportion of extremely preterm and ELBW neonates is increasing, incidence of MBD is on the rise.

**Osteopenia** occurs in about 50% of the VLBW neonates and majority of the ELBW infants at 40 weeks of post conceptional age, without adequate calcium and phosphorous supplementation (10-15). It could be more prevalent in developing countries, where the financial constraints hamper adequate mineral supplementation.

Etiology: MBD is often multifactorial (as shown in Table:1). The leading causes are inadequate mineralization include, intrauterine growth restriction, pro-longed parenteral nutrition (without phosphate) and delayed enteral nutrition. Neonates with insufficient calcium, phosphorous and vitamin D intake are at further risk of MBD when they are subjected to extended periods of immobilization (3-12). The onset of MBD ensues between $6^{th}$ and $16^{th}$ week of life or by 40 weeks of corrected age, although, it may go unnoticed till marked demineralization takes place ( loss of 20 – 40% of BMC). The physiologic basis of MBD is inadequate calcium and phosphorus stores in the face of accelerated fetal growth during third trimester. In- utero calcium and phosphorus accretion occurs at the rate of 120 mg/kg/day and 60 mg /kg/day respectively (15,16). However, impaired supplementation and absorption of these minerals in post natal life leads to sub optimally mineralized new and remodelling skeletal system. Preterm human milk perse has insufficient quantity of calcium, phosphorous and vitamin D, necessitating their supplementation. Vitamin D concentration in human milk is 25 to 50 IU/L which is grossly insufficient to keep serum 25-hydroxyvitamin D (25(OH)D) level greater than 20 ng/mL in premature infants. This Vitamin D deficiency leads to hypocalcemia, secondary hyperparathyroidism which leads to phosphaturia. Also, undue fluid restriction, use of term formula, soy-based and lactose-free formulas in preterm neonates can contribute to MBD (17-21). However, VLBW neonates can produce adequate 1,25-dihydroxyvitamin D levels after the initial few weeks of life if they have optimum dietary vitamin D supplementation. Medications used in preterm infants are frusemide, steroids and methyl xanthines, which enhance osteoclastic activity, decrease osteoblastic proliferation, reduce calcium absorption and promote renal calcium wasting leading to osteopenia (19-21). Similarly, extended administration of phenobarbital or phenytoin in neonates with seizures can lead to enhanced 25(OH)D metabolism and osteopenia (21).

Maternal vitamin D deficiency, often manifests when lactating mothers have inadequate vitamin D (less than 600 IU/ day) supplementation. This often manifests with neonatal hypocalcemia and can result in congenital rickets. Neonates with cholestatic liver disease can have exaggerated malabsorption and impaired 25 - hydroxylation of vitamin D which further aggravates osteopenia. Rare causes of hypovitaminosis D like hereditary pseudovitamin D deficiency: type I (abnormal or absent 1-α-hydroxylase activity) or type II (1,25-dihydroxyvitamin D resistance in tissues) can also lead to MBD (21). Also, chronic renal failure leads to renal osteodystrophy and osteopenia.

Maintaining calcium and phosphorus levels in parenteral nutrition (PN) is difficult due to their restricted solubility and temperature lability. Aminoacid, glucose , lipid concentration, pH and methods of preparation of calcium salts determine the bioavailability of calcium and phosphorus. Lowering the pH with cysteine enhances solubility.

Pathophysiology

Calcium and phosphorus homeostasis: Structural matrix of the skeletal system is constituted by calcium, phosphorus, magnesium and their homeostasis play a key role in bone integrity. Total body calcium (99%) and phosphorus (80%) are present in the bone as microcrystalline hydroxyapatite. Rest of the total body calcium (1%) lies within the extracellular fluids and soft tissues. However, only 50% of total serum calcium is biologically active as it is in the ionized form. The remaining calcium is bound to proteins (albumin and globulin: 40%) and the rest of it (10%) to organic and inorganic acids. Similarly, a major proportion of magnesium (60%) is present in the bone matrix. Numerous factors like vitamin D, parathyroid hormone, calcitonin followed by dietary calcium and phosphorous content, intestinal absorption, bone accretion, resorption and final urinary excretion determine calcium and phosphorus homeostasis. (15).

Role of parathyroid hormone: soon after the birth, irrespective of gestational age and persisting mineral requirement, there is fall in calcium, with a nadir attained by 24–30 hours in preterm infants. As a result, there is PTH surge., PTH augments calcium reabsorption in the kidney and on the other hand, it causes urinary phosphate wasting. PTH aids in the production of calcitriol ($1,25(OH)_2D$), by activating renal 25 (OH) D3-1-alpha-hydroxylase which increases intestinal calcium and phosphate absorption. Also, PTH promotes bone resorption and subsequent release of calcium and phosphate. On the whole, **PTH has maximum action in the kidney for regulating calcium metabolism**. When there is insufficient calcium intake for prolonged periods as with MBD, these metabolic changes persist (5).

Fetal bone homeostasis: The amount of minerals required for proper accretion of the skeleton are vary according to the age of the babies. Fetus has a higher rate of skeletal growth especially during the last trimester. There is an enormous increase in bone volume with advanced gestational age due to bone remodelling and augmented bone synthesis (trabecular thickness). It has been shown that, the rate of trabecular thickening is 240 times rapid in the fetus when compared to children.Fundamentally, the osteoblasts produce osteoid / organic bone matrix into which embodiment of calcium and phosphate hydroxyapatite takes place. This osteoblastic activity enhances exponentially (involving 80% of mineral accretion) during 24 to 37 weeks of gestation (22-26).

Fetal nutrient supply of protein, energy and minerals is ample for fetal growth and skeletal development (1.2 cm/ week).The physical density of bone (expressed as bone mass divided by bone volume) is highest in term neonates. The calcium and phosphate deposition during last trimester of fetal life is around 20 grams and 10 grams respectively, which corresponds to calcium and phosphate accretion rate of 100–120 mg/kg/day and 50–65 mg/kg/day respectively (15,16).

Placenta has a pivotal role in fetal skeletal development as calcium is actively transported transplacentally with the aid of calcium pump in the basement membrane (22-26) with a maternal to foetal calcium gradient of 1:4. In addition, activation of vitamin D to 1, 25-dihydroxy cholecalciferol also occurs by the placenta, which is an essential element of transplacental phosphate transfer (26). Thus, there is hypercalcemic status in fetal life due to increased estrogen levels, resulting in enhanced bone modelling and endocortical bone formation (27). All these processes are hampered in preterm neonates predisposing them to under mineralization of the bone. Alongside, chronic placental inflammation (chorioamnionitis), insufficiency (intrauterine growth retardation) impairs transplacental transfer of calcium and phosphorous creating osteopenic mileu in the fetus. As placental calcium levels and fetal bone accretion depend on maternal dietary calcium intake, calcium supplementation of 2 grams on or after 22 weeks of gestation to pregnant women enhances neonatal bone mineral content (BMC) (15,26).

Neonatal bone homeostasis

It has been noted that from birth to 6 months of age, bone physical density is reduced by one third in term neonates (15, 27). This results from the preferential rapid widening of the bone marrow cavity when compared to the cortical surface area. However, term neonates maintain bone integrity unlike preterm infants. There is a fall in transplacentally transferred estrogens and serum calcium levels after birth leading to rise in PTH, (28,29). However, within the first 48 hours of life falling serum calcium levels do not bring the corresponding rise in serum PTH levels resulting in nadir in serum calcium levels. It is also seen that serum PTH levels in term neonates are lower than the fetal levels (17).

The calcium absorption in post natal life is a function of type and amount of calcium intake, gastrointestinal function (both active and passive transport of calcium) and vitamin D levels in the mother. Preterm neonates with reduced intake and inefficient absorption of calcium and phosphorous from the gut are at a two fold disadvantage and are prone for MBD. Calcium oral bioavailability is at stake when associated with large gastric aspirates, vomiting, abdominal distension and constipation which are often seen in preterm neonates. The interplay of calcium and phosphorous absorption is such that when the dietary levels are disproportionate, one reduces other's absorption. Apart from nutritional supplementation another important factor regulating osteoblastic activity is physical activity during fetal life (quickening against the uterine wall) which may be lost in sick, preterm neonates who are less active in post natal life. Reduced physical activity enhances osteoclastic activity and inhibits osteoblastic activity leading to bone resorption and urinary calcium wasting (30-33). Interestingly, in- utero rise in bone mineral apparent density (BMAD) is faster than that of ex utero. BMAD is measured by dividing bone mineral content with the surface area of bone (BMC/BA = g/cm$^3$) and is a measure of volumetric BMD. It initially falls after birth but is maintained later on (33). Preterm neonates will have fall in mineral accretion when compared to fetal life, although the skeletal growth remains comparable and thus leading to osteopenia of prematurity. However, after adequate nutritional supplementation, catch up bone growth begins in preterm VLBW infants.

Clinical features and diagnosis: The clinical manifestations are diverse depending up on the degree of demineralization. MBD can either remain unnoticeable or can present with florid rickets. It can also present as arrested growth velocity and with features of hypocalcemia (jitteriness, tetany). Though, not usual, these neonates have large head, craniotabes, frontal bossing, sutural separation in the skull, wide fontanelle, costochondral thickening, hypotonia, protruding abdomen.It can manifest with multiple pathological / spontaneous fractures of ribs and long bones (3) ( seen in 10% of premature neonates) which present as pain while handling (as shown in Table:2). Rib softening and/or fractures may lead to deranged pulmonary function and respiratory distress around 5 to 11 weeks of age (34,35). These infants can have prolonged ventilator requirement or difficulty in weaning from ventilator.

Diagnosis

The mainstay of diagnosis is by estimation of biochemical markers i.e; serum calcium, phosphorous, alkaline phosphatase, urinary calcium levels and PTH. (as shown in Table:3). The predominant biochemical change includes decreased serum phosphorus levels. Hypophosphatemia is an early indicator of disrupted calcium metabolism and it manifess by 7–14 days of life. This can occur either due to isolated phosphate deficiency or due to elevated PTH levels. **Phophate depletion increases calcitriol synthesis and may lead to hypercalcemia which supressesses PTH levels.** Also phosphate reabsorption is increased by kidney and thus tubular reabsorption of phosphate (TRP) is a measure of phosphate homeostasis.

**Serum alkaline phosphatase levels ≥ 900 I U/l show 100% sensitivity and 70% specificity for MBD.** It is observed that alkaline phosphatise levels may increase by 5 fold in MBD (35). **Elevated alkaline phosphatase levels may be seen in hepatic and gastrointestinal diseases as it is also produced by the liver and**

**gastrointestinal tract. And hence, estimating the bone iso enzyme is more specific to diagnose MBD. PTH level is an early indicator of MBD when compared to ALP**. PTH levels >180 pg /ml or phosphate level <4.6 mg dl at 3 weeks of chronologic age have 100% sensitivity and 94% specificity to diagnose severe MBD (36,37,38).

These markers should be estimated at initial diagnosis and later in follow up to monitor the response to treatment (Figure:1,every 4 weeks). The fundamental principle in treating these neonates is to establish normocalcemia, normophosphatemia and to prevent urinary calcium wasting. With the normalization of calcium, phosphorus and ALP, evaluation of these parameters can be done every month up to 6 months and later on they can be done once in 3 months.

Imaging: various imaging modalities have been used to diagnose MBD (as shown in Table:3). X-ray shows osteopenia, reduced cortical thickness, rib fractures, and widening of the epiphysis, uneven margins (39). Dual Energy X-Ray Absorbitometry (DEXA): is an imaging tool to detect even small changes in BMC and BMD and to predict the probability of impending fractures It has been standardized in both term and preterm neonates. Although, it has diagnostic precision for bone mineralization, it imposes the risk of radiation and cannot be done bedside (40,41).

Another newer, non-invasive diagnostic modality for MBD is measuring bone speed of sound (SOS) by quantitative ultrasound. It has no risk of radiation, can be done bedside and has reference standards for both term and preterm infants (at birth and in follow up). It measures bone density, delineates the structure and enables prediction of bone turnover in preterm infants. This is usually noted over the mid-tibial shaft. This bone SOS is shown to be more in term infants (median 3079 m/s) as compared to preterm infants (median 2911 m/s). Similarly, there is a good correlation between gestational age and bone SOS. Also, bone SOS was noted to be low in preterm infants even at a corrected age of 40 weeks when compared to term infants (42-45).

Management: The principles of management of MBD in preterm neonates are multidimensional (as depicted in Table:4,figure:2)(29) .Mineral requirements of Infants: The requirements of calcium and phosphorus are based on for intrauterine bone mineral accretion rates. The ideal calcium to phosphorus ratio for optimum skeletal mineralization is 1.7:1. (46). While on PN, use of soluble forms of calcium and phosphorus (sodium and potassium phosphate, glycerol phosphate or sodium-glucose phosphate) improves their bio availability (15, 21). The vitamin D requirement is a function of gestational age and maternal vitamin D levels. The fetus is able to activate the vitamin D to 1,25(OH) 2 vitamin D from 24th week of gestation. It is recommended to provide 400 I U of vitamin D daily for all premature neonates after establishment of full feeds (21).

Calcium and phosphorus requirements in preterm neonates are 123 to 185 mg Ca/100 kcal and 80 to 110 mg P/100 kcal respectively. This can be achieved with fortification of human milk and with formula milk. Calcium is in the form of soluble calcium glycerol phosphate in formula milk achieving 90 mg/kg/day of calcium absorption (88% of the total). And thus, fortification and supplementation is often mandatory in preterm neonates.

Effects of human milk fortifiers on skeletal mineralization are indeterminate as per cochrane systematic review and meta analysis (46). Also, it can predispose to necrotizing entero colitis with higher doses of calcium due to increased gastrointestinal transit time, fecal calcium and reduced absorption of fat.

Prognosis and outcome: As metabolic bone disease resolves spontaneously with adequate calcium, phosphorous and vitamin D supplementation, it carries a good prognosis. Although there are difference of opinions about duration, amount and route of mineral supplementation, it has been reported that infants receiving formula feeds until 9 months of age have higher bone mineral content. Also, it has been stated that preterm infants have an adequate catch up by one year of life with optimum supplementation as depicted by quantitative ultrasound and DEXA. Skeletal mineralization of term and preterm infants is comparable in later childhood. Similarly, studies have shown that reduced spinal BMC at a later childhood in LBW neonates who are stunted.

Assisted physical exercise is a newer preventive modality which adds to nutritional management in stable premature neonates. Chen, et al. found that early assisted exercise in VLBW neonates enhances bone strength (43). The assisted physical exercise gives either tactile stimulation with moderate pressure strokes or kinaesthetic stimulation with passive flexion and extension of both upper limbs and lower limbs. It was noted to enhance the body weight, bone mineralization and osteogenesis. Some studies have shown that the exercise could attenuate the postnatal reduction in bone speed of sound (47-51).

It is interesting that nutrition plays a dual role in MBD, both therapeutic and preventive. Focusing on the optimum supply of minerals and of vitamin D, by using human milk fortifier,calcium and phosphorous supplementation or preterm formula is vital to prevent MBD. Supplementing mothers with 600IU/day of vitamin D helps in preventing MBD(52-64).

Conclusions

Optimum nutritional supplementation of neonates with calcium, phosphorus, vitamin D along with assisted physical exercise plays a key role in preventing MBD. These measures inhibit pathological bone resorption in the initial few weeks of life and enhance the growth of premature infants. It is vital to identify the biochemical abnormalities in MBD in a timely manner to initiate therapeutic interventions at the earliest and

thus prevent spontaneous/pathological fractures. Periodic estimation of phosphate and alkaline phosphatase levels is important to estimate the risk of osteopenia along with assessment of the treatment efficacy. Similarly, DEXA and quantitative ultrasound enable quantification of bone mineralization and assist in nutritional rehabilitation. Additionally, maternal vitamin D supplementation is another essential preventive strategy for MBD.

KEY MESSAGES

- Osteopenia is an important morbidity in premature neonates which can be prevented by optimum nutritional supplementation with human milk fortifiers,calcium, phosphorous, vitamin D and physical activity.
- Use of medications like caffeine, furosemide,corticosteroids which are often required by premature neonates with apnea, bronchopulmonary dysplasia can potentially lead to MBD when coupled with nutritional inadequacy.
- Novel investigation modalities to diagnose MBD include quantitative measurement of the tibial speed of sound and novel preventive strategies for MBD focus on enhancing physical activity with assisted physical exercise.

**Ethics**

**Ethics Committee Approval**: As it was a review, as per the institute rules, there was no need for ethical committee approval

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**Authorship Contributions**

**Surgical and Medical Practices**: Dr.Swathi Chacham & Dr.Rachna pasi & Dr.Najeeb Ahmad

**Concept**: Dr.Swathi Chacham & Dr.Rachna pasi & Dr.Madhuradhar & Dr.Najeeb Ahmad

**Design**: Dr.Swathi Chacham & Dr.Rachna pasi & Dr.Madhuradhar & Dr.Najeeb Ahmad

**Data Collection or Processing**: Dr.Najeeb Ahmad & Dr.Shanti Bhusan Mohanty

**Analysis or Interpretation**: Dr.Swathi Chacham, Dr.Rachna pasi, Dr.Madhuradhar, Dr.Najeeb Ahmad & Dr.Shanti Bhusan Mohanty

**Literature Search**: Dr.Swathi Chacham, Dr.Rachna pasi, Dr.Madhuradhar, Dr.Najeeb Ahmad & Dr.Shanti Bhusan Mohanty

**Writing**: Dr.Swathi Chacham, Dr.Rachna pasi, Dr.Madhuradhar, Dr.Najeeb Ahmad & Dr.Shanti Bhusan Mohanty

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**Figure: 1: Algorithm for screening of MBD**

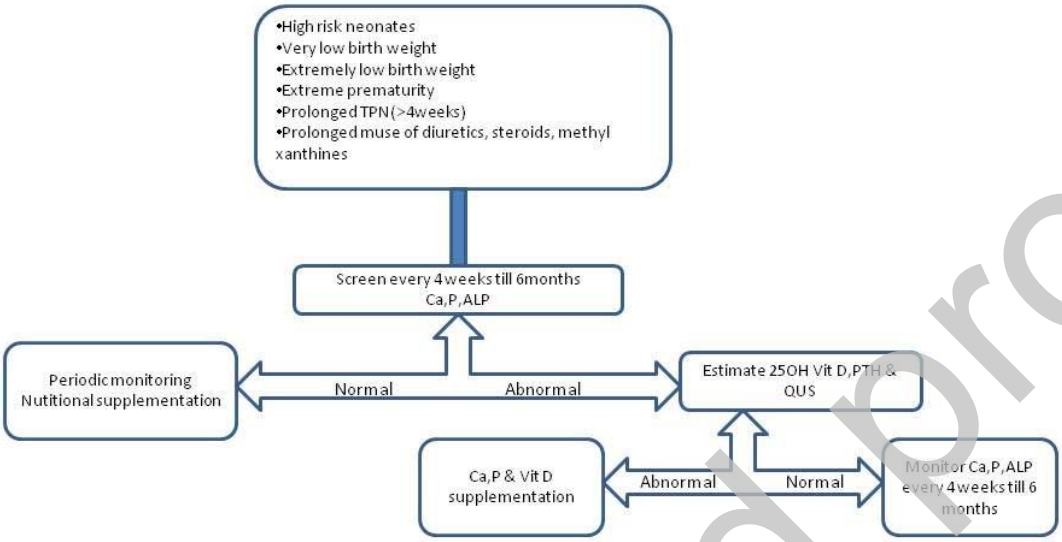


Figure :3 : Mineral requirements during TPN and enteral feeds (AAP) (Ref:29,65,66)

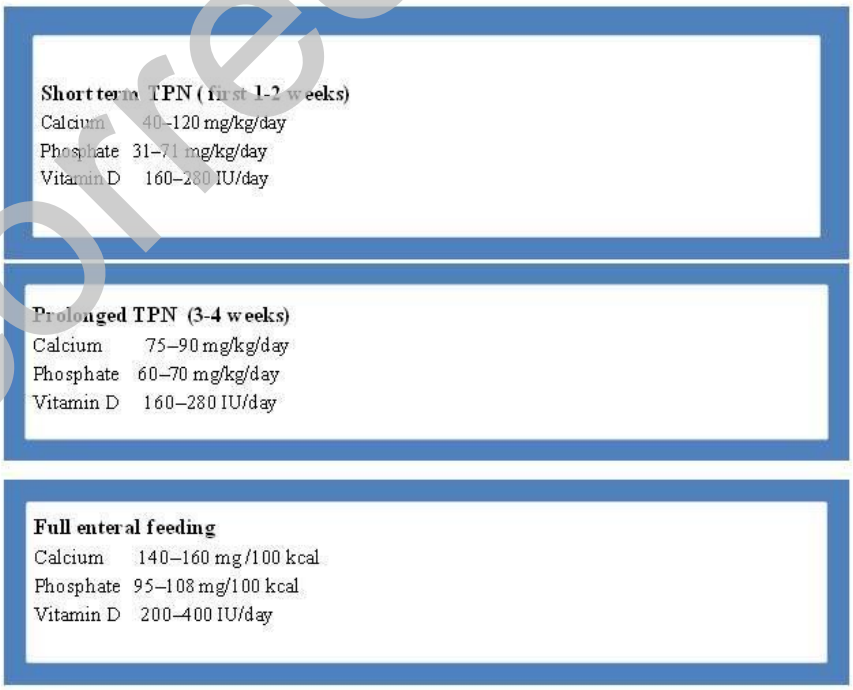

Table:1: Etiological factors of Metabolic Bone Disease

| | |
|---|---|
| Inutero | • Deficient maternal calcium & phosphorus stores<br>• Maternal vitamin D deficiency<br>• Accelerated physiological fetal growth in 3rd trimester |
| Exutero | **Maternal**<br>• Inadequate nutritional supplementation to lactating mother ( calcium, phosphorus, Vitamin D)<br>**Neonatal**<br>• Insufficient supplementation of calcium, phosphorus, Vitamin D<br>• Excessive fluid restriction in VLBW neonates<br>• Urinary calcium wasting ( phosphorus deficiency)<br>• Use of term formula in preterm infants<br>• Use of soy based or lactose free formula<br>• Neonatal cholestasis<br>• Hereditary pseudovitamin D deficiency: Type I (abnormal or absent 1-α-hydroxylase activity) or Type II (1,25-dihydroxyvitamin D resistance in tissues)<br>• Medications: furosemide, steroids, methylxanthines, phenobarbitone, phenytoin. |

Table: 2: Clinical features of Metabolic Bone Disease

| |
|---|
| • Arrested growth velocity (reduced linear growth with normal head growth) |
| • Features of hypocalcemia (jitteriness, tetany) |
| • Features of rickets |
| • Spontaneous fractures of ribs and long bones |

- Pain while handling
- Respiratory distress
- Deranged pulmonary function
- Difficulty in weaning from ventilator

Table: 3: Diagnosis of Metabolic Bone Disease

**Biochemical:**

- Decreased serum phosphorus levels (<3.5 to 4 mg/dL (1.1 to 1.3 mmol/L),
- Increased serum alkaline phosphatase levels
- Elevated bone isoenzymes of alkaline phosphatase
- Low or normal serum calcium levels
- Low or normal Serum 25(OH)D levels
- Elevated serum PTH levels(often variable)
- Low urinary calcium and phosphorus levels

**Radiological**

- Radiograph of long bone: widening of epiphyseal growth plates; metaphysis rarefaction, cupping, fraying, subperiosteal new bone formation and osteopenia,
- Radiograph of the skull, spine, scapula: **osteopenia**
- Radiograph of the Chest: osteopenia and rachitic changes, pathologic fractures in ribs
- Dual Energy X-ray Absorbitometry (DEXA): Reduced bone mineral content
- Quantitative ultrasound : Reduced bone Speed of sound (SOS)

Table:4 : Treatment of Metabolic Bone Disease

| |
|---|
| • Early enteral feeding |
| • Fortified human milk |
| • Premature formulas |
| • Adequate calcium and phosphorus intake |
| • Vitamin D supplementation of 400 IU/day (ensures adequate vitamin d stores) |
| • Preferable use of thiazide diuretics over furosemide |
| • Assisted physical exercises |
| • Avoid forceful chest physiotherapy |
| • Calcitriol (special circumstances) |