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Journal of Pediatrics & Neonatal Care

Research Article

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Metabolic bone disease in preterm babies: are we underestimating it?"

Abstract

The current body of evidence shows a notable increase in the prevalence of osteopenia of prematurity or metabolic bone disease (MBD) over the past few decades, mainly as a consequence of the significant improvement in the survival rates of premature infants. Therefore, a growing number of research has been conducted in order to develop appropriate screening, diagnostic and monitoring modalities for MBD. Nevertheless, the published literature shows conflicting data regarding how to diagnose and monitor MBD. Birth weight less than 1000g, gestational age less than 28weeks, prolonged loop diuretics usage, and total parenteral nutrition for more than 14days are commonly used by physicians as indicators to initiate screening for MBD. While most neonatologists nowadays are using serum calcium, phosphorus, and alkaline phosphatase (ALP) to screen for MB; dual-energy X-ray absorptiometry (DEXA) and bone ultrasonography represent promising screening tools. While serum vitamin D level has been reported to be of no value in diagnosing or monitoring MBD. Supplementing neonates at high risk with fortified milk formulae that is rich in calcium, phosphate salts and vitamin D is the mainstay of therapy, which is used to ultimately attain mineral accumulation rate similar to that in the fetal life. Additional administration of calcium and phosphorus in the form calcium glaciate, calcium carbonate, and potassium phosphate may be required for infants who are suffering from serious diseases. In this article, we review the postnatal mineral homeostasis, pathophysiology of MBD, and the current guidelines pertaining to screening, monitoring and diagnosing of MBD.

Volume 9 Issue 2 - 2019

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Received: October 04, 2018 | **Published:** March 13, 2019

Introduction and background

The terms metabolic bone disorder(MBD), osteopenia of prematurity, or rickets are used interchangeably to indicate the decrease in bone mineral density status in preterm neonates. Despite, the lack of consensus over the definition of MBD, it is generally accepted that MBD represents a significant decrease in the bone mineral content relative to size or gestational age with associated biochemical and/or radiographic changes.[1,2] As a result of different definitions, the reported incidence of MBD varies greatly across the published studies. However, the incidence of MBD is inversely correlated with gestational age and neonatal weight.[3] It has been found to occur at a rate of 23% and 60% in neonates whose weight is less than 1500g and 1000g respectively.[4,5] This estimation was reported to be even higher in infants who are exclusively breast-fed since 16% and 40 % of formula-fed and breast-fed infants, respectively have been found to experience MBD.[6] Regarding the long-term effects of low birth weight and preterm birth, it has been shown that preterm neonates whose birth weight is < 1500 g are more likely to have less bone mineral density at the age of 7years than their peers.[7] This was confirmed by another study which indicated that Dual-energy X-ray absorptiometry (DEXA) scan that was performed at around the age of 7years on children who were born at 40weeks of gestation, denoted more bone mass than those who were preterm.[8]

Development of fetal skeleton

25(OH) vitamin D plays a substantial role in the growth of fetal skeleton. It is transferred transplacentally and activated by adding additional hydroxyl group in the kidneys of the embryo to become 1, $25(OH)_2$ vitamin D. The last trimester is the period in which the skeleton of the embryo ossifies and subsequently requires a more active form of vitamin D from the mother.[9] Therefore, there is increased skeletal mobilization and gastrointestinal absorption of minerals in pregnant mothers in order to boost their serum calcium levels and subsequently enhance the trans-placental transfer of calcium to the fetus. Additionally, an experimental study has shown that fetal mobilization enhances cortical bone development through its mechanical force effect, so preterm neonates who are deprived of these movements have underdeveloped cortical bones.[10] Hence making preterm neonates susceptible to develop MBD than other neonates.

Causes of MBD

There are a wide variety of causes that could be responsible for MBD, these causes can be either antenatal or postnatal causes.

Antenatal causes

While the serum calcium and phosphorus level are 20% higher in fetus than mother in the second trimester, there are a dramatic increase in fetal demands of both minerals during the third trimester. Therefore, there is an increased skeletal mobilization and gastrointestinal absorption of minerals in pregnant mothers that enhance the trans-placental transfer of calcium to the fetus.[11] Consequently, any reduction in maternal Calcium intakes and/or absorption can lead to MBD.[12] Additionally, chronic placental disorders, pre-eclampsia, chorioamnionitis, and placental infections, can affect mineral hemostasis in infants and increase the risk of rickets in preterm babies.[13]

Postnatal causes

Neonates who have been deprived of Enteral feeding for a long time such as extremely low birth weight infants, are at high risk of

developing MBD. Central nervous system pathology, neonatal sepsis, metabolic acidosis or any disease that could lead to a lengthy duration of immobilization and insufficient supplementation of the essential elements, such as calcium, phosphorus and vitamin D in the postnatal period increase the risk of rickets.[8] Furthermore, it has been found that there is a molecular mechanism that could be responsible for MBD, the thymidine-adenine base pair sequence which encodes for proteins that act as estrogen receptor has been detected in a lower number among preterm with MBD than those without. On the other hand, adequate weight at birth weight and the use of fortified formulae of human milk have been reported to decrease the risk of MBD.[14]

Postnatal mineral hemostasis and pathophysiology of MBD

After delivery, the increase in bones' needs of calcium results in a dramatic reduction in serum calcium levels which reaches its nadir by 18hours of age. As a result, parathyroid hormone (PTH) transiently increases in the first 2days after delivery, and serum calcium often returns to its normal level even in preterm babies, provided that they are healthy.[10] Hypocalcemia may be more intense and enduring in ill preterm neonates particularly among those who are suffering from hypoxic disorders. It has been found that a compromise in tissue oxygenation entrains a subsequent increase in intracellular calcium entry.[15] The reduction in serum calcium stimulates parathyroid gland to release PTH. PTH acts mainly on kidney by retaining calcium and trashing phosphate. PTH also facilitates 1, 25-dihydroxycholecalciferol formation in kidneys which subsequently enhances calcium and phosphate absorption from the gastrointestinal tract. PTH increases the serum level of calcium as well as phosphate through enhancing bone resorption. Ultimately, hyperparathyroidism results in an increase in the circulating calcium and reduction in the serum phosphate.[16]

The first element to be affected in response to any disturbances in the bone mineralization process is phosphate, hence hypophosphatemia is the most frequently and early seen abnormal serum marker in MBD. Hypophosphatemia restrains PTH release, which subsequently eliminate the phosphate trashing effect of PTH, but it has a positive feedback action on the synthesis process of 1,25-dihydroxycholecalciferol which is enhanced accordingly.[17] At the end, hypophosphatemia facilitates the gastrointestinal absorption of calcium and phosphate, thus it increases serum calcium level, urinary calcium excretion, and as a result, kidney stones are more likely to be seen among this subset of patients.

Screening, monitoring and diagnosing

Currently, there are no standardized universal recommendations that physicians can follow to screen, diagnose and manage MBD.[18] There is a considerable proportion of heterogeneity in the published reports regarding these guidelines.[1] Hence, MBD has long been diagnosed by neonatologists individually without any objective criteria. The scarcity of the qualified published data pertaining to this issue encouraged researchers to perform surveys to investigate whether there is a coherent consensus among neonatologists in the United Kingdom and the United States in their clinical practice concerning MBD. These surveys have emphasized that physicians have become more familiar and knowledgeable about MBD at the same time; it also reflected the lack of harmony in their clinical practice regarding the screening of MBD.[19]

The presentation of osteopenia of prematurity varies according to the degree of bone mineral density loss. MBD could be asymptomatic or may present with profound complaints up to fractures. Therefore, early detection represents the most important step in the management of this disease.[20] Many risk factors have been associated with the development of osteopenia of prematurity and represent benchmarks for clinicians to initiate screening for MBD. A survey based on 246 neonatal intensive care units (NICUs) found that gestational age from below 28 to below 36weeks has been the most widely used indicator to start screening for MBD. It has been used in about 71% of these units. Birth weight less than 1000 g comes in the second place that has been used in about 64 % of these units. Both variables may have been used by the same unit simultaneously. Frequent loop diuretics utilization, exclusive human milk-based feeding, complete parenteral nutrition for more than 14days have also been used by many physicians as screening thresholds.[19] Yet, this survey was restricted to level IIIB and IIIC NICUs according to the American Academy of Pediatrics (AAP) definitions. Another survey that involved any level of NICUs in the USA concluded that birth weight below than 1500g as well as 1200g instead of 1000 g and total parenteral nutrition for more than 4weeks rather than 2weeks should commonly be used as screening thresholds.[21]

There are many tests that are used for screening for MBD. Measuring serum calcium, serum phosphate and ALP are used by the majority of physicians as screening tests. X-ray, Urine calcium, urine phosphate, PTH, 25-hydroxy vitamin D, and 1,25 dihydroxy vitamin D have less commonly been utilized for screening.[19]Additionally, tubular reabsorption of phosphate has also been used by many neonatologists to observe the disease development.[22]

With regard to the role of ALP in the screening in MBD, the current body of evidence shows a conflicting recommendations. A serum ALP level of 700 -750 IU/L points out an increase in the bone turnover, and is found to correlate with osteopenia, which might be clinically silent at that stage.[23] Moreover, the AAP has also reported that serum ALP more than 1000IU/L can be used as indicator but not as evidence of MBD.[17] Unexpectedly, a recent prospective cohort study that has been carried out on 120 neonates of both sex who were born ≤34weeks' gestational age and <1500g birth weight indicated that a cutoff value of 500 IU/L of serum ALP level could be used as a predictor to reveal most MBD with 100% sensitivity and 80.77 % specificity ($P<0.001$).[24] However, the plasma level of ALP has been found to be not predictive of the severity and radiologic findings of MBD.[25]

Based on all the above-mentioned reports, ALP cannot be used alone as a trustworthy screening modality for MBD. Therefore, using another modality besides the serum ALP measurement is highly recommended. A previous study suggested that a serum ALP above 900 IU/L along with serum phosphate less than 1.8 g/dl can be used for screening of MBD with a sensitivity and a specificity of 100% and 70 %, respectively.[26] In patients with bile flow-related problems where total serum ALP is high, use of bone-specific isoenzyme of ALP has been found beneficial.[27] However, there are no sufficient data to adopt this approach as a global guideline. Furthermore, it has been shown that bone-specific isoenzyme of ALP and total ALP have been found to be comparable to each other, and there is no need to use such an expensive specific marker for screening.[26]

Serum calcium does not accurately reflect the calcium content in bone as it may stay normal at the cost of skeletal calcium loss,

Citation: El-Atawi K, Elhalik M, Kulkarni T, et al. Metabolic bone disease in preterm babies: are we underestimating it?" *J Pediatr Neonatal Care.* 2019;9(2):36–41. DOI: 10.15406/jpnc.2019.09.00372

whereas serum phosphate correctly represents the skeletal phosphorus content. Therefore, serum calcium level cannot be used as a reliable indicator to identify neonates at high risk of MBD.[28] Additionally, hypocalcemia may occur simultaneously with MBD in the category of infants who have been receiving loop diuretics for a prolonged period. The low calcium level will trigger the parathyroid gland to secrete PTH which in turn will trash phosphate through kidneys and enhance the gastrointestinal absorption of calcium and phosphate.[29] This fluctuation in serum calcium makes it an unreliable indicator for anticipating the actual state of bone mineralization and subsequently cannot be used alone as a predictor marker for MBD.

The renal threshold of phosphate trashing of neonates born before 25weeks of gestation has been found to be less than any other preterm neonates and consequently, they have more urinary phosphorus excretion.[30] Since Phosphate isn't bound to albumin like calcium, urinary phosphate excretion is preferable than urinary calcium for the screening of MBD. Renal TRP (Tubular Reabsorption of Phosphate) more than 95% suggest that there might be insufficient supplementation of either calcium or phosphate.[31] Moreover, Calcium to creatinine or Phosphorus to creatinine ratios could be used to screen for MBD, however they should be interpreted cautiously as they are influenced by the nutritional supplementation and medications such as loop diuretics and theophylline.[32]

Despite the fact that, DEXA can accurately identify those who are at risk of developing fractures, and it being a reliable modality to assess the bone mineralization status,[33] there are many obstacles that impede its use as a universal screening device for MBD. Such an expensive equipment is not available in limited-resource countries and the long time it takes to produce an image represent the main barriers to its wide use.[34] Qualitative ultrasound (QUS) findings have been found to be significantly correlated with serum ALP and risk factors for a reduced bone mineralization.[35] Therefore, it is a useful modality to detect neonates at high risk of MBD, but it is not predictive of the cortical bone width.[36] Furthermore, data are insufficient to adopt it as a standardized screening approach, moreover, the data pertaining to the standard values of QUS and DEXA are insufficient as well. Whilst serum osteocalcin is a specific biomarker of bone cellular activity and could be a dependable modality to diagnose MBD. However, it has been reported that there is no association between the serum osteocalcin and skeletal mineral content in the first few months in neonatal life limiting its use in diagnosing MBD.[37]

To date, there are no systematic approaches for physicians to follow on when to monitor MBD progression, the current recommendations are just based on individual clinical practice. A group of researchers suggested that checking the serum phosphate and ALP every 1 or 2weeks would be a valuable approach to monitor the disease progression.[18] Another team recommended to gauge the serum calcium, serum phosphate, urine calcium, urine phosphate, and calcium: creatinine ratio every 7days for preterm neonates who are under the age of 3weeks, and then every 2weeks when they become older than the age of 3weeks.[38]

X-ray film on one of the long bones, such as tibia, femur, radius and ulna is required to confirm the diagnosis of rickets, a chest x-ray is insufficient to establish the diagnosis. It is routinely performed by physicians for all patients with MBD since it's able to assess the severity of the disease and detect the rachitic changes, mineralization status, and fractures. Therefore, it is recommended to do an x-ray film routinely every 5-6weeks to make sure that the mineralization is getting better.[39] Vitamin D has no value in diagnosing or monitoring MBD since it has been found that its serum level is alike in neonates with or without MBD. Therefore, additional studies are required to demonstrate whether administration of vitamin D is of any value to these patients.[40]

Prevention and treatment

The approach that neonatologists follow currently either to manage or to prevent the incidence of MBD to some extent similar to each other. These approaches are based mainly on: painstakingly observing serum calcium, phosphorus, ALP and vitamin D levels and keep them at normal levels through adequate supplementation; cessation of the drugs that deplete these mineral, such as steroids, furosemide, and methylxanthines(2); and applying daily physical exercise program to enhance bone growth. The ultimate target of mineral supplementation is to attain mineral accretion rate similar to that in the fetal life. Calcium and phosphorus are required elements for many physiological processes, so the adequate supplementations of elements that are necessary for the development of infants' bone represent a challenge to health care providers.

Preterm neonates can absorb up to 60 % and 80% of calcium and phosphorus, respectively from breast milk, giving 180-200 ml per day of unmodified human milk does not achieve more than one-third of the minerals accumulation rate in the fetal life.[41] Furthermore, even unfortified formulae do not contain the appropriate concentrations of calcium and phosphorus.[19] So, there is an urgent need to provide those infants at high risk with fortified human milk. There are different recommendations regarding the optimal dose of the enteral vitamin D, calcium, and phosphorus that should be delivered with the fortified formula. Many reports suggest supplementation of these neonates with calcium at doses that range from 100-220mg/kg/day,[42,43] however the Canadian pediatric society recommended providing a diet that delivers about 160-240mg/kg/day of calcium.[44] With regard to phosphorus supplementation, most reports recommend providing phosphorus at doses that extend from 75-140mg/kg/day, however Rigo et al.,[42] suggested to administer it at lower doses of 60-90 mg/kg/day.[42]

Reports are also conflicting and unstandardized regarding vitamin D supplementation. Despite that neonatologists often increase the daily dose of vitamin D up to 600 IU in cases with serum markers not returning to their normal levels, there are no qualified data to adopt this recommendation as a universal guideline. The AAP advocated in 2008 clinical report that infants who are supplemented with < 1000ml of vitamin D-fortified milk per day should be administered with additional 400 IU per day of vitamin D until their serum markers normalise.[45] These recommendations still hold true in the 2013 clinical report which recommended to supplement vitamin D at a dose of 200-400 IU per day,[19] whereas the Canadian pediatric society suggested to administer of vitamin D at 400-800IU per day.[44] Another researcher group also advocated increasing the supplemented dose up to 1000 IU per day to decrease the manifestations of osteopenia.[42] TPN supplements infants with only 160IU/kg of vitamin D, so infants who receive TPN for a prolonged period at risk of developing vitamin D deficiency, therefore they need vitamin D supplementation.[46]

The concentration of calcium and phosphate in the given solution are not the only factor that determine how much of these elements are retained in neonates. Calcium/phosphate ratio has also been found to affect the retention rate. It should be optimized at a ratio from 1.3:1

to 1.7:1.54.[47] The restricted solubility of these minerals in the given solutions reduces its delivery to neonates and achieves at most 50 % of the retention rate of the fetal life, hence infants who are kept at parenteral nutrition for a prolonged period are at a high risk of developing MBD. Additional research is needed to overcome these obstacles and enhance the delivery of these minerals with appropriate retention rates. Additionally, the co-supplementation of calcium and phosphorus has been shown to be more beneficial than individual supplementation. Phosphorus enhances the absorption rate of calcium, calcium absorption rate increases up to 100 % when both calcium and phosphorus are supplemented together. Similarly, calcium boosts the absorption rate of phosphate, it could rise up to 90%.[48,49] However, they should be administered cautiously since they are associated with metabolic acidosis and hypercalciuria that subsequently increases the risk of renal stone formation.

In a study that has been carried out on 40 VLBW infants, daily physical activity programs has been found to promote anthropometric measurements and speed of sound of the tibia and humerus.[48] Despite that, a recent review endorsing the beneficial impact of physical activity programs on bone growth, data has been insufficient to evaluate the long-term effects of these programs. Therefore, they still cannot be adopted as a standard universal approach, and additional extended prospective cohort studies are needed to evaluate their effects.[49]

Neonates who were born before 28weeks of gestation, those whose birth weight is less than 1500g, those who have been on total parenteral nutrition for more than 30days and infants who have been taking furosemide or steroids for a prolonged period should be monitored weekly by measuring their serum phosphate, calcium, and ALP. In the case of serum ALP above 500IU/L and serum phosphate below than 1.8mmol/L, TRP should be evaluated, if it overshoots 95%, phosphorus administration should be initiated. If serum ALP continues to go up and serum phosphate does not increase then, ergocalciferol should be started.[59] It is recommended to gauge the serum level of 25(OH)D to administer the amount that's required to attain the normal level accordingly. Thereafter, the serum level should be checked 3months later to make sure that the therapeutic goal has been reached.[64]

It has been found that infants who have serious diseases still have a risk of developing MBD even if they are supplemented with fortified preterm formula, so additional administration in the form calcium gluconate, calcium carbonate or potassium phosphate may be required. A dose of 20-100 mg/kg/day of either calcium glubionate or calcium gluconate may be provided enterally or parenterally, respectively when neonates' requirements exceed the supplemented doses in the fortified formulae.[19,39] Similarly, 10-50 mg/kg/day of potassium phosphate could be administered either enterally or parenterally for the same reason. This approach can be followed provided that serum calcium, phosphorus, and urinary calcium are frequently monitored since such an administration would not be convenient for all cases.[20]

Administration of protein to enhance the growth and prevent the development of any catabolic condition has long been a familiar practice among physicians in NICUs. Previously, two observational studies have reported that amino acid supplementation in the first week of life promotes the intracellular influx of phosphorus which subsequently reduces the circulating phosphorus level.[65,66] Further studies are required to investigate the effect of low phosphorus on developing MBD. Serum level of minerals can guide neonatologists to decide which therapeutic approach they are going to follow. For instance, when hypophosphatemia is accompanied by hypoparathyroidism and high TRP, this means that there is an insufficient phosphorus intake which may have caused the decrease in urinary phosphate trashing. As a result, phosphate administration should be considered in such cases.[59] Other obtainable forms of phosphate salt like powder also contain additional salts such as sodium and potassium, therefore infants who receive spironolactone should also be observed painstakingly for hyperkalemia and other electrolyte disturbances. On the other hand, when low TRP comes along with high PTH level, calcium administration should be considered in such a case even if the serum calcium is at normal or high levels.[67]

Calcitriol has a negative feedback effect on PTH and suppresses its secretion which subsequently limits the urinary phosphate trashing effect of the PTH whilst enhancing the intestinal uptake of calcium. Calcitriol may be given at a dose of 0.5-0.2mcg/kg/day to neonates who have secondary hyperparathyroidism and if their medical condition necessitates TPN for a prolonged period.[68]

Post-discharge management

VLBW infants are often discharged from hospitals by the age of 40weeks of post conception age. Bone mineral contents usually get better faster in the early few months of preterm neonates' life and attain values that mimic that of well term infants.[69] There are no sufficient data to guide health care professionals in the nutritional supplementation after discharge, and are adjusted individually according to anthropometric measurements of each infant and each provider's experience. Infants whose birth weight was above 1500g are usually performing well when they are kept on standard term formulae or breast milk, whereas VLBW infants should go on fortified milk after discharge.[19] There are different recommendations regarding how long human milk fortified formula or transitional formula could be given to neonates after discharge. Some suggested to give it up to 52weeks post conception,[70] whilst others advocate to reducing the amount when infants become 3000g to avoid the risk of hypervitaminosis A.[71] Nutrient-enriched formula could also be provided for a period up to 6months of age if there are growth problems observed.[72]

Authors' conclusion

The incidence of MBD is inversely related to gestational age and neonatal weight. Extended prospective cohort studies are required to evaluate the long-term effects of low birth weight and preterm birth on bone mineral density status beyond the age of 7years since the only available studies report data until 7years. Screening and preventing of MBD represent the most important steps in management. Reports are conflicting regarding the screening thresholds; while there are different recommendations regarding the efficiency of ALP as well as the cutoff value above which neonates could be considered rachitic. Measuring both serums ALP along with serum phosphorus have been found to be more reliable in screening for MBD. More studies are needed to investigate the reliability of bone-specific isoenzyme of ALP as a screening tool. PTH along with TRP may be used to differentiate between the possible causes of hypophosphatemia. DEXA is an accurate modality in identifying the bone mineral density status, but it is not that feasible and handy device. More studies are required to precisely evaluate the role of QUS in screening since data are not sufficient enough to acknowledge it as a standardized modality. Anecdotal reports recommend checking the serum biomarkers

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either biweekly or every three weeks, as regards to how frequently biomarkers should be measured. A cohort study with a large sample size is warranted to address this issue. It is also recommended to perform an x-ray every 5-6weeks to assess the mineralization status of bone.

Physicians usually tend to increase the daily dose of vitamin D up to 600 IU per day if the serum biomarkers do not return to their normal levels after the initial supplementation, but qualified data are not supporting this approach. Intestinal absorption of calcium and phosphorus does not increase when administering vitamin D at doses higher than 400IU per day. Additional efforts are necessitated to improve the solubility of calcium and phosphorus in the given solution in order to ameliorate the retention rate of these solutions. Serum calcium, phosphorus, and urinary calcium should be frequently monitored in patients who are taking calcium glubionate, calcium gluconate or potassium phosphate. The long-term effects of physical activity programs also need to be investigated before recommending these programs routinely. Calcitriol may be given in the subset of patients who have high PTH level.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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Citation: El-Atawi K, Elhalik M, Kulkarni T, et al. Metabolic bone disease in preterm babies: are we underestimating it?" *J Pediatr Neonatal Care.* 2019;9(2):36–41. DOI: 10.15406/jpnc.2019.09.00372