



Original Research Article

Prevalence and Management of Osteopenia of Prematurity in the Indian Context

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Abstract: Preterm infants are at significantly higher risk of developing osteopenia of prematurity owing to inadequate phosphorus and calcium supply. However, its accurate prevalence is difficult to assess as there are various methods that are used to assess infants at risk and also from difficulty of results interpretation, it is continuously increasing with more immature neonates' survival resulting from advances in neonatal care. **Aim:** The present study was aimed to assess the prevalence and management of Osteopenia of Prematurity in the Indian Context. **Methods:** The present study assessed 202 preterm babies aged <32 weeks of gestation. In all the neonates, biochemical parameters were evaluated including 25-OH vitamin D3, alkaline phosphatase (ALP), phosphate (P), and calcium (Ca) on day 1 of their lives followed by weekly for 4 weeks and then at discharge. Also, on day 1 of their lives, X-ray of the wrist was taken. **Results:** The study results showed that at the time of admission, 77.2% (n=156) neonates had osteopenia where 60% and 17% subjects respectively had Grade I and Grade II osteopenia. It was seen that calcium levels were not significantly lower, whereas, vitamin D3 and serum phosphorus levels were significantly low. ALP levels in the serum were significantly high. **Conclusions:** The present study concludes that infants born prematurely are highly predisposed to osteopenia of prematurity. Serum calcium levels alone are not a good marker to assess osteopenia of prematurity as its level is maintained at the expense of loss of calcium from the bone. However, vitamin D, serum ALP, and serum phosphorus levels are good indicators of the disease.

Keywords: ALP, Bone mineral density, calcium, Metabolic bone disease, Osteopenia of prematurity, vitamin D.

INTRODUCTION

Bone health in neonates is vital and has a high concern, particularly in premature infants that are a high risk for development of rickets. Owing to the increased awareness concerning neonatal bone health and its effect on childhood, adolescents, and even adults, there has been increase interest significantly. Majority of fetal phosphorus and calcium accretion and bone mineralization is seen in third trimester of pregnancy. In nearly 24 weeks of gestation onwards, fetus accumulate nearly 30 grams

weight daily including 170 grams phosphorus and 310 grams of calcium per day.¹

Neonatal MBD (metabolic bone disease), rickets of prematurity, neonatal rickets, and osteopenia of prematurity are the terms being used for describing the conditions having characteristic of reduced BMC (bone mineral content) of preterm infant. It affects nearly 55% infants weighing infants with weight <1000 grams at birth and 20% infants with birth weight <1500 grams. It has high prevalence in

infants born before 28 weeks of gestation. Previous literature data has reported that MBD has prevalence of nearly 40% in breastfeeding premature infants in comparison to 16% prevalence in infants feeding on formula fortified with phosphorus and calcium.²

Homeostasis of magnesium, phosphorus, and calcium is vital for structural matrix of the bone. Serum calcium is not a reliable tool for screening as newborns can have normal serum calcium level despite of losing bone calcium, whereas, hypophosphatemia usually serve as early biochemical indicator for impaired mineral metabolism, especially seen in 7-14 days after birth. Serum phosphate levels of <5.6mg/dl have strong association to radiological rickets in preterm infants with mean 30 weeks of gestation. Despite strong association of serum phosphate levels and osteopenia of prematurity, it lacks sensitivity for detection of infants with low bone mineral content. Combined assessment of serum phosphate and ALP (alkaline phosphate) levels, a significant improvement is seen for diagnostic sensitivity of osteopenia of prematurity. Serum ALP levels of >500IU/l and >700 IU/l have been linked with impaired bone hemostasis and bone demineralization respectively.³

Sufficient vitamin in neonates is not absorbed from breast milk and is reflected from maternal deficiency and persist in neonates that are exclusively on breastfeed. In first month, calcium absorption is primarily via paracellular mechanism, however, in preterm infants, it is not fully understood. However, supplementation is still recommended owing to low endogenous vitamin D levels in preterm infants with recommended daily dose of 400 IU. Radiographic bone abnormality diagnosis in preterm infants is challenging in early stages where fracture/demineralization is not apparent. Koo score describes alterations as grade 1, 2, and 3 where it depicts presence of bone rarefaction, presence of bone rarefaction associated with metaphyseal

alterations, shadow, and subperiosteal bone formations, and associated with the presence of spontaneous fractures respectively.⁴ The present study was aimed to assess the prevalence and management of Osteopenia of Prematurity in the Indian Context.

Materials and methods

The present prospective cross-sectional study was aimed to assess the prevalence and management of Osteopenia of Prematurity in the Indian Context. The study subjects were from Department of Pediatrics, SMBT Institute of Medical Sciences and Research Centre, Nashik, Maharashtra. Verbal and written informed consent were taken from all the subjects before study participation.

The inclusion criteria for the study were 202 newborn preterm babies aged <32 weeks of gestation and where parents were willing to participate in the study. The exclusion criteria for the study were babies on steroid therapy or diuretics, consent refused by the subjects, gross congenital malformations, and infants with conjugated hyperbilirubinemia.

After final inclusion of the study subjects, blood samples were collected from all the subjects for assessment of 25- OH vitamin D3, alkaline phosphatase (ALP), phosphate (P), and calcium (Ca) in the serum of the subject. These assessments were done on day 1 of the life of the infant followed by weekly for 4 weeks and then while discharge.

In all the subjects, radiographic assessment was done including the wrist X-ray which was taken on day 1 of the life of neonate. Grading of the radiograph was done as normal, mild hypomineralization or grade 1, moderate hypomineralization or grade 2, sever hypomineralization or grade 3 using the Koo's criteria (Table 1).

S. No	Koo's grading of radiological features	Radiological features
1.	Grade 0	Normal bones
2.	Grade 1/mild hypomineralization	Minimal rarefaction only
3.	Grade 2/moderate hypomineralization	Cupping and fraying of metaphysis
4.	Grade 1/severe hypomineralization	Changes in grade 1/2 with fractures

Table 1: Koo's criteria for radiological grading of the bone mineralization

Statistical analysis of the data was done using the chi-square test, Fisher's exact test, Mann Whitney U test, and SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk. NY, USA) using ANOVA, chi-square test, and student's t-test. The significance level was considered at a p-value of <0.05.

RESULTS

The present study assessed 202 neonates where there were 51.5% (n=104) neonates in gestational age of 30-32 weeks, 33.7% (n=68) neonates from 28-30 weeks, 10.9% (n=22) neonates from 26-28 weeks and 4% (n=8) neonates from age of <26 weeks. Following Koo's radiological grading, 77.2% (n=156) neonates had osteopenia with grade1 and 2 osteopenia in 60.4% and 16.8% neonates, whereas, grade 0 or no osteopenia was seen in 46 neonates (Table

2).

S. No	Gestational age (weeks)	Females		Males	
		With OOP	Without OOP	With OOP	Without OOP
1.	<26 (n=8)	2	0	6	0
2.	26-28 (n=22)	10	2	6	4
3.	28-30 (n=68)	32	8	22	6
4.	30-32 (n=104)	40	12	38	14

Table 2: Distribution of study neonates based on OOP to gender and age

It was seen that at the time of admission, serum calcium levels of <8mg/dl were seen in 20.8% (n=42) neonates where 6 neonates were <26 weeks, 10 were in 26-28 weeks, 14 neonates were in age of 28-30 weeks, and 12 neonates were aged 30-32 weeks of gestation. Calcium level of 8-10mg/dl was seen in 53.4% (n=108) neonates where gestational age of <26, 26-28 weeks, 28-30 weeks, and 30-32 weeks was seen in 2, 6, 32, and 68 neonates respectively. Calcium levels of >10 mg/dl were seen in 25.7% (n=52) neonates where 0, 6, 22, and 24 neonates were in gestational age of <26, 26-28, 28-30, and 30-32 weeks respectively. For serum phosphorus levels, levels of <5mg/dl were seen in 66.3% (n=134) neonates where there were 6, 14, 42, and 72 neonates were aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age. Levels of ≥5 mg/dl were seen in 32.6% (n=66) neonates where 2, 8, 32, and 36 neonates were aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age respectively.

It was seen that at admission, among 202 neonates, serum ALP levels of <300 IU/I were seen in 8.9% (n=18) neonates where there were 0, 2, 4, and 12 neonates were aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age. Serum ALP levels of 300-400 IU/I were seen in 17.8% (n=36) neonates where there were 0, 4, 16, and 16 neonates aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age. Serum ALP levels of 400-500 IU/I were seen in 37.6% (n=76) neonates where there were 6, 10, 24, and 36 neonates aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age. Serum ALP levels >500 IU/I were seen in 35.6% (n=70) neonates where there were 2, 6, 24, and 40 neonates aged ≤26 weeks, 26-28, 28-30, and 30-32 weeks of gestational age respectively.

The study results showed that at the time of admission from 202 neonates, serum vitamin D3 levels of <10 ng/ml were seen in 40.6% (n=82) neonates. Serum vitamin D3 levels of 10-20 ng/ml were seen in 52.4% (n=106) neonates where 4, 18, 36, and 48 neonates were aged <26, 26-28, 28-30, and 30-32 weeks respectively. Serum vitamin D3 levels of >20 ng/ml were seen in 6.9% (n=14) neonates where there were 0, 4, and 10 neonates aged <26, 28-30, and 30-32 weeks respectively.

It was also seen that for biochemical parameters, they were repeated every 4 weeks and at discharge time. An increase was seen for the trends of vitamin D3, serum phosphorus, and serum calcium levels from admission to discharge, whereas, a decrease was seen serum ALP levels from admission to discharge. It can be attributed to early vitamin D3 and calcium supplementation. Serum calcium levels were not significantly different in various OOP grades at day 1, week 1, week 2, week 3, week 4, and at discharge with p=0.64, 0.81, 0.06, 0.64, 0.37, and 0.65. Lower levels of serum phosphorus were seen in grade 1 and grade 2 compared to grade 0 at day 1, week1, and week 2 with p=0.01, 0.01, and 0.02. Higher levels of alkaline phosphatase were seen in grade2 and grade 1 compared to grade 0 at day 1 with <0.01.

DISCUSSION

There were 202 neonates in the study with 51.5% (n=104) neonates in gestational age of 30-32 weeks, 33.7% (n=68) neonates from 28-30 weeks, 10.9% (n=22) neonates from 26-28 weeks and 4% (n=8) neonates from age of <26 weeks. Following Koo's radiological grading, 77.2% (n=156) neonates had osteopenia with grade1 and 2 osteopenia in 60.4% and 16.8% neonates, whereas, grade 0 or no osteopenia was seen in 46 neonates. It was seen that at the time of admission, serum calcium levels of <8mg/dl were seen in 20.8% (n=42) neonates where 6 neonates were <26 weeks, 10 were in 26-28 weeks, 14 neonates were in age of 28-30 weeks, and 12 neonates were aged 30-32 weeks of gestation. Calcium level of 8-10mg/dl was seen in 53.4% (n=108) neonates where gestational age of <26, 26-

28 weeks, 28-30 weeks, and 30-32 weeks was seen in 2, 6, 32, and 68 neonates respectively. Calcium levels of >10 mg/dl were seen in 25.7% (n=52) neonates where 0, 6, 22, and 24 neonates were in gestational age of <26, 26-28, 28-30, and 30-32 weeks respectively. For serum phosphorus levels, levels of <5mg/dl were seen in 66.3% (n=134) neonates where there were 6, 14, 42, and 72 neonates were aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age. Levels of ≥5 mg/dl were seen in 32.6% (n=66) neonates where 2, 8, 32, and 36 neonates were aged ≤26 weeks, 26-28, 28-30, and 30-32 gestational age respectively. These results were consistent with the findings of Abrams et al⁵ in 2013 and Wagner CL et al⁶ in 2008 where authors reported results comparable to the present study in their respective studies.

The study results showed that at admission, among 202 neonates, serum ALP levels of <300 IU/l were seen in 8.9% (n=18) neonates where there were 0, 2, 4, and 12 neonates were aged ≤ 26 weeks, 26-28, 28-30, and 30-32 gestational age. Serum ALP levels of 300-400 IU/l were seen in 17.8% (n=36) neonates where there were 0, 4, 16, and 16 neonates aged ≤ 26 weeks, 26-28, 28-30, and 30-32 gestational age. Serum ALP levels of 400-500 IU/l were seen in 37.6% (n=76) neonates where there were 6, 10, 24, and 36 neonates aged ≤ 26 weeks, 26-28, 28-30, and 30-32 gestational age. Serum ALP levels >500 IU/l were seen in 35.6% (n=70) neonates where there were 2, 6, 24, and 40 neonates aged ≤ 26 weeks, 26-28, 28-30, and 30-32 weeks of gestational age respectively. These findings were in agreement with the results of Binder C et al⁷ in 2015 and Mitchell SM et al⁸ in 2009 where results for serum ALP levels reported by the authors in their studies was comparable to the results of the present study.

It was seen that at the time of admission from 202 neonates, serum vitamin D3 levels of <10 ng/ml were seen in 40.6% (n=82) neonates. Serum vitamin D3 levels of 10-20 ng/ml were seen in 52.4% (n=106) neonates where 4, 18, 36, and 48 neonates were aged <26, 26-28, 28-30, and 30-32 weeks respectively. Serum vitamin D3 levels of >20 ng/ml were seen in 6.9% (n=14) neonates where there were 0, 4, and 10 neonates aged <26, 28-30, and 30-32 weeks respectively. These results were in line with the findings of Jahan I et al⁹ in 2016 and Betto M et al¹⁰ in 2014 where results for serum D3 levels comparable to the present study were also reported by the authors in their respective studies.

The study results also showed that for biochemical parameters, they were repeated every 4 weeks and at discharge time. An increase was seen for the trends of vitamin D3, serum phosphorus, and serum calcium levels from admission to discharge, whereas, a decrease was seen serum ALP levels from admission to discharge. It can be attributed to early vitamin D3 and calcium supplementation. Serum calcium levels were not significantly different in various OOP grades at day 1, week 1, week 2, week 3, week 4, and at discharge with p=0.64, 0.81, 0.06, 0.64, 0.37, and 0.65. Lower levels of serum phosphorus were seen in grade 1 and grade 2 compared to grade 0 at day 1, week1, and week 2 with p=0.01, 0.01, and 0.02. Higher levels of alkaline phosphatase were seen in grade2 and grade 1 compared to grade 0 at day 1 with <0.01. These findings were in line with the results of Agostoni C et al¹¹ in 2010 and Kaundal S et al¹² in 2025 where results for biochemical parameters comparable to the present study were also reported by the authors in their studies.

CONCLUSION

Considering its limitations, the present study concludes that infants born prematurely are highly predisposed to osteopenia of prematurity. Serum calcium levels alone are not a good marker to assess osteopenia of prematurity as its level is maintained at the expense of loss of calcium from the bone. However, vitamin D, serum ALP, and serum phosphorus levels are good indicators of the disease.

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