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Original Research Article

Status of osteopenia of prematurity in Sub-Himalayan region of India - a single centre experience

Shanki Kaundal, Seema Sharma*, Milap Sharma

Department of Paediatrics, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda, Himachal Pradesh, India

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***Correspondence:**
Dr. Seema Sharma,
E-mail: dr.seema73.ss@gmail.com

ABSTRACT

Background: Preterm infants are at significant risk to develop osteopenia of prematurity (OOP) due to inadequate supply of calcium and phosphorus. Although its exact prevalence is difficult to quantify because of the different methods used to screen infants at risk and also because of the difficulty in the interpretation of these results, it has been steadily increasing with the survival of more immature neonates as a result of advances in neonatal care. Objective of the study was to find out the status of OOP in Sub-Himalayan region of India.
Methods: In this cross-sectional prospective study 101 preterm babies <32 weeks of gestation were evaluated. Biochemical parameters which included serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP), and 25-OH vitamin D3 was done on day 1 of life, then weekly for 4 weeks and then at discharge. X-ray wrist was taken on day 1 of life.
Results: At admission 78 (77.2%) neonates were osteopenic (60.4% with grade-1 and 16.8% grade-2). Calcium levels were not significantly low whereas serum phosphorus levels and vitamin D3 levels were significantly low. Serum ALP levels were found significantly high.
Conclusions: Infants born prematurely have a predisposition to OOP. Serum calcium alone is not a good marker since its level is maintained at expense of loss of bone calcium. But serum phosphorus, ALP and vitamin D are better indicators of disease.

Keywords: ALP, Bone mineral content, Bone mineral density, Metabolic bone disease, Osteopenia of prematurity

INTRODUCTION

Neonatal bone health is a critically important concern especially for premature infants who are at elevated risk of developing rickets. Because of the increasing awareness of neonatal bone health and its impact upon childhood, adolescent and even adult, interest in this field has significantly increased. The majority of fetal calcium and phosphate accretion and bone mineralization occur in the third trimester of pregnancy. From approximately 24 weeks of gestation onward, the fetus accumulates about 30 grams in weight daily, which includes around 310 mg of calcium and 170 mg of phosphorus per day.[1]

Neonatal metabolic bone disease (MBD), osteopenia of prematurity (OOP), neonatal rickets or rickets of prematurity, are terms used to describe the conditions characterized by reduced bone mineral content (BMC) of the preterm infant. This condition affects up to 55% of infants weighing less than 1000 grams at birth and approximately 23% of those with a birth weight less than 1500 grams. It is especially prevalent among infants born before 28 weeks of gestation.[2,3] Studies also show that the prevalence of MBD is about 40% in breastfed premature infants, compared to 16% in those fed with preterm formulas fortified with calcium and phosphorus.[4,5]

The homeostasis of calcium, phosphorus and magnesium is essential for structural matrix of the bone. Calcium and phosphate are primary inorganic component of bone, with 99% of the body's calcium and 80% of its phosphorus stored in bone tissue as microcrystalline apatite. However, serum calcium levels are not a reliable screening tool because newborns can maintain normal calcium values despite a bone calcium loss. hypophosphatemia often serves as an early biochemical indicator of impaired mineral metabolism, typically appearing between 7 and 14 days after birth. Serum phosphate levels below 5.6 mg/dl (1.8 mmol/l) have been strongly linked to radiological confirmed rickets in preterm infants averaging 30 weeks gestation and 1490 grams at birth.[6] While phosphate levels are closely associated with OOP, they lack sensitivity for detecting all infants with low bone mineral content. However, combining phosphate measurements with alkaline phosphatase (ALP) levels significantly improves diagnostic sensitivity for risk of OOP. ALP is a bone turnover marker which physiologically rises over the first 3 weeks of life and peaking between 6–12 weeks of age.[7] ALP concentrations exceeding 500 IU/l may indicate impaired bone homeostasis and levels >700 IU/l are often correlated with bone demineralization even in the absence of clinical symptoms.[8]

Human breast milk alone does not provide sufficient vitamin D to meet neonatal needs.[9] Vitamin D deficiency in infants is often a reflection of maternal deficiency and tends to persist in exclusively breastfed infants. In the first month, calcium absorption occurs largely through a passive, vitamin D-independent pathway—likely via a paracellular mechanism. However, in preterm infants, the timeline and proportion of calcium and phosphorus absorption that depends on vitamin D are not yet fully understood. Despite these gaps in knowledge, supplementation is recommended due to low endogenous vitamin D levels in preterm infants, stemming from limited placental transfer. The American Academy of Pediatrics recommends a minimum daily intake of 400 IU of vitamin D.[10-12] The European Society for Pediatric Gastroenterology Hepatology and Nutrition recommends 800–1000 IU per day.[13,14]

Radiological diagnosis of bone abnormalities in preterm infants presents challenges, especially in the early stages when demineralization or fractures may not be apparent. X-rays often lack sensitivity at early stage of bone disease in neonates due to the absence of significant demineralization or fractures.[15] The Koo's score describes the radiological alterations as - grade 1: presence of bone rarefaction; grade 2: presence of bone rarefaction associated with metaphyseal alterations, shadow, and subperiosteal bone formations; and grade 3: associated with the presence of spontaneous fractures (Table 1).[2]

Objective of this study is to determine the prevalence of osteopenia of prematurity intertiary care centre of sub-Himalayan region of India by estimating various biochemical parameters like serum values of calcium, phosphorus, vitamin D and ALP and radiological diagnosis based on Koo's criteria.

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

S. no.	Koo's grading radiological features	Radiological features
1	Grade 0	Normal bones
2	Grade 1 or mild hypomineralisation	With mineral rarefaction only
3	Grade 2 or moderate hypomineralisation	Fraying and cupping of metaphysic
4	Grade 1 or severehypomineralisa-tion	Changes in grade 1 or 2 with fractures

METHODS

A cross-sectional prospective study was conducted in the neonatal intensive care unit (NICU), Department of Pediatrics of Dr. Rajendra Prasad Government Medical College, Tanda, Kangra,

Himachal Pradesh for the period of one year (01 August 2019 to 31 July 2020). Written consent was obtained from all the parents of participating newborns prior to study.

Inclusion criteria

101 inborn preterm babies <32 weeks of gestation were included in this study.

Exclusion criteria

Babies receiving diuretics or steroid therapy, babies with conjugated hyperbilirubinemia, gross congenital malformations, and refusal for consent by parents, were excluded.

Methodology

This study was taken after approval from institutional ethical committee. After enrollment the blood samples were sent for investigation which included serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP), and 25-OH vitamin D3. This was done on day 1 of life, then weekly for 4 weeks and then at time of discharge. Radiological investigation included X-ray of wrist which was taken on day 1 of life. Radiographs were graded as normal, grade 1 or mild hypomineralisation, grade 2 or moderate hypomineralisation, and grade 3 or severe hypomineralisation using Koo's criteria.

Statistical analysis

Independent (unpaired) Student's t-test and Chi-square test were used to analyze these parameters. A $p<0.05$ was considered statistically significant.

RESULTS

Our study group out of total 101 neonates, there were 52 (51.5%) neonates of GA between 30 and 32 weeks, 34 (33.7%) neonates were of GA between 28 to 30 weeks, 11 (10.9%) neonates were of GA between 26 to 28 weeks and 4 (4%) neonates with GA of <26 weeks. Based on Koo's radiological grading, out of total 101 neonates, 78 (77.2%) neonates were osteopenic (60.4% with grade-1 or 16.8% with grade-2), and 23 were non-osteopenic (grade 0) (Table 2).

Table 2: Distribution of neonates on the basis of OOP, gestational age, and gender.

S. no.	Gestational age (weeks)	Male (n=48)		Female (n=53)	
		With OOP (n=36)	Without OOP (n=12)	With OOP (n=42)	Without OOP (n=11)
1	<26 (n=4)	3	0	1	0
2	26-28 (n=11)	3	2	5	1
3	28-30 (n=34)	11	3	16	4
4	30-32 (n=52)	19	7	20	6

At admission serum calcium level less than 8 mg/dl were present in 21 (20.8%) neonates; of which 3 neonates were of GA less than 26 weeks, 5 neonates were of GA between 26-28 weeks,7 neonates were of GA between 28-30 weeks and 6 neonates were of GA between 30-32 weeks. Calcium level between 8-10 mg/dl were found in 54 (53.4%)) neonates of which 1 neonate was of GA less than 26 weeks,3 neonates were of GA between 26-28 weeks, 16 neonates were of GA between 28-30 weeks and 34 neonates were of GA between 30-32 weeks. Calcium levels more than 10 mg/dl were found in 26 (25.7%) neonates of which none was of GA less than 26 weeks, 3 neonates were of GA between 26-28 weeks, 11 neonates were of GA between 28-30 weeks and 12 neonates were of GA between 30-32 weeks (Figure 1).

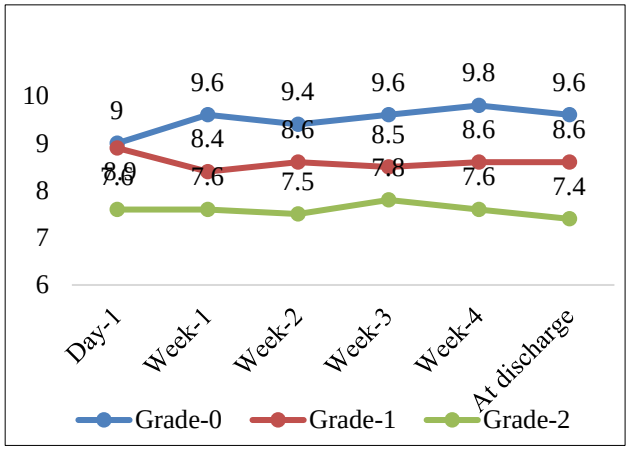

Figure 1: Trends of change in serum calcium levels in different Koo's grade.

Serum phosphorus level were found to be ≤5 mg/dl in 67 (66.3%) neonates; of which 3 neonates were of GA ≤26 weeks, 7 neonates were of GA between 26-28 gestational weeks, 21 neonates were of GA between 28-30 weeks and 36 neonates were of GA between 30-32 weeks. Phosphorus levels ≥5 mg/dl were found in 33 (32.6%) neonates of which 1 neonate was in GA ≤26 weeks, 4 neonates were of GA between 26-28 weeks, 16 neonates were of GA between 28-30 weeks and 18 neonates were of GA between 30-32 weeks (Figure 2).

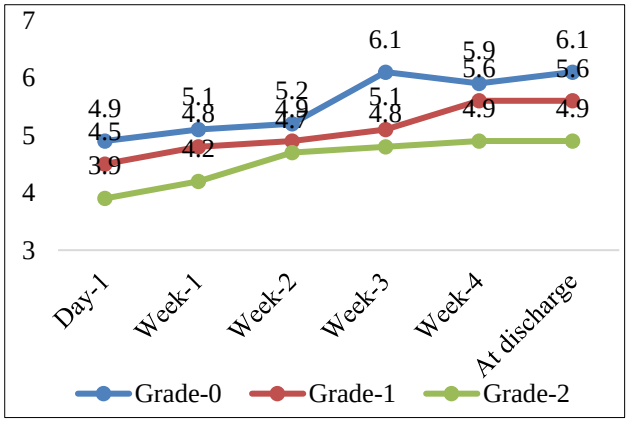

Figure 2: Trends of change in serum phosphorus levels in different Koo's grade.

At admission, out of total 101 neonates, serum ALP levels were found to be less than 300 IU/l in 9 (8.9%) neonates; of which none of the neonates was of GA less than 26 weeks, 1 neonate was of GA between 26-28 weeks, 2 neonates were of GA between 28-30 weeks and 6 neonates were of GA between 30-32 weeks. Serum ALP levels between 300-400 IU/l were found in 18(17.8%) neonates; of which none of the neonates was of GA less than 26 weeks, 2 neonates were of GA between 26-28 weeks,8 neonates were of GA between 28-30 weeks and 8 neonates were of GA between 30-32 weeks. Serum ALP levels between 400-500 IU/l were found in 38(37.6%) neonates; 3 neonates were of GA less than 26 weeks, 5 neonates were of GA between 26-28 weeks, 12 neonates were of GA between 28-30 weeks and 18 neonates were of GA between 30-32 weeks. Serum ALP levels more than 500 IU/l were found in 3635.6% neonates; 1 neonate was of GA less than 26 weeks, 3 neonates were of GA between 26-28 weeks, 12 neonates were of GA between 28-30 weeks and 20 neonates were of GA between 30-32 weeks (Figure 3).

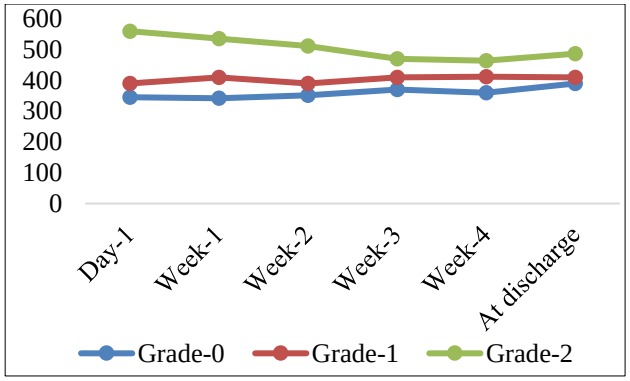

Figure 3: Trends of change in serum ALP levels in different Koo's grade.

At admission, out of total 101 neonates, serum vitamin D3 level were found to be less than 10 ng/ml in 41 (40.6%) neonates; of which 2 neonates were of GA less than 26 weeks, 2 neonates were of GA between 30-32 weeks. Serum vitamin D3 level between 10-20 ng/ml were found in 53 (52.4%) neonates, of which 2 neonates were of GA less than 26 weeks, 9 neonates were of GA between 26-28 weeks, 18 neonates were of GA between 28-30 weeks and 24 neonates were of GA between 30-32 weeks. Serum vitamin D3 level more than 20 ng/ml were found in 7 (6.9%) neonates, of which none of the neonates was of GA less than 26 weeks,2 neonates were of GA between 28-30 weeks and 5 neonates were of GA between 30-32 weeks (Figure 4).

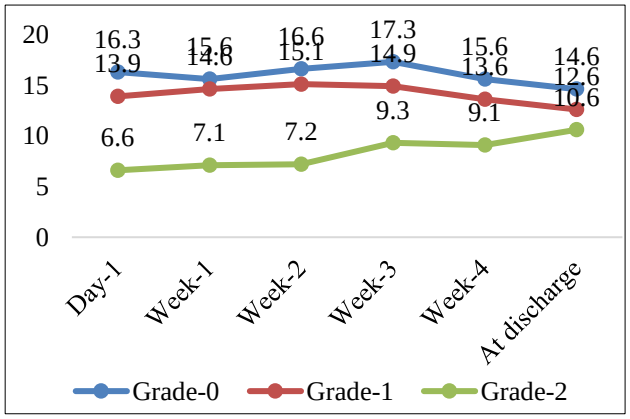

Figure 4: Trends of change in serum vitamin D levels in different Koo's grade.

All biochemical parameters were repeated weekly for 4 weeks and then at the time of discharge. Serial calcium, phosphorous and vitamin D3 levels showed increasing trends from the period of admission to the period of discharge whereas serum ALP levels decreased from the period of admission to the period of discharge. This may be due to early supplementation of calcium and vitamin D3.

Our study observed that serum calcium levels were not significantly different in different grades of OOP including grade 0, grade 1, and grade 2 at day-1 ($p=0.623$), week-1 ($p=0.835$), week-2 ($p=0.087$), week-3 ($p=0.667$), week-4 ($p=0.397$), and at discharge ($p=0.672$). We observed lower levels of serum phosphorous in grade 2 and grade 1 in comparison to grade 0 at day-1 ($p=0.01$), week-1 ($p=0.01$), and week-2 ($p=0.02$). Higher levels of alkaline phosphatase were found in grade 2 and grade 1 in comparison to grade 0 at day-1 ($p<0.01$), week-1 ($p<0.01$), and week-2 ($p<0.01$). Lower levels of vitamin D3 were observed in grade 2 and grade 1 in comparison to grade 0 from day-1 to week-4 ($p<0.01$).

DISCUSSION

OOP also known as neonatal metabolic bone disease is a condition characterized by reduced bone mineral content in preterm infants. This reduction is primarily due to the deprivation of intrauterine mineral supply, which adversely affects bone mineralization during critical developmental periods. Key biochemical features of OOP include hypophosphatemia, elevated alkaline phosphate levels, and late-onset radiology findings indicative of bone demineralization. The incidence of neonatal osteopenia is inversely correlated with GA and birth weight. In the preterm infants, a combination of inadequate reserves and increased loss of essential minerals is common and frequently compounded by difficulties in obtaining an intake sufficient to replace losses and restore reserves. Deficiencies in calcium and phosphate and disturbed balance between them are frequently encountered, and may lead to significant impairment of bone deposition.

During the last trimester of pregnancy, there is a rapid accretion of calcium and phosphorus due to active transport across the placenta.[16] The osteopenia makes the preterm newborn more susceptible to fractures during minimally invasive procedures and even the routine handling while in the NICU. Because of the increased advances in neonatal intensive care, survival of preterm infants has increased over past few years; as a consequence, the problem of less imminent, slowly progressing disorders such as OOP has been emerging. Osteopenia or metabolic bone disease of prematurity has been reported in 55% of ELBW and 23% of VLBW infants.[19] Exact data on OOP is scarce from India.

In our study, incidence of OOP was 77.2% with no gender preponderance. We observed that incidence of OOP was 100% in neonates with GA<26 weeks, 73% in neonates with GA 26-28 weeks, 79% in neonates with GA 28-30 weeks, and 75% in neonates with GA 30-32 weeks. In our study, all neonates with GA<26 weeks were found to have OOP; this showed incidence of OOP is higher with extreme prematurity. GA<28 weeks is considered as an important predictor of OOP. Mean calcium levels were not significantly low; this could be because infants can maintain a normal calcium level at the expense of a loss of bone calcium. Jahan et al assessed serum calcium level in 78 neonates and observed mean serum calcium level of 8.2±0.31 mg/dl (n-36) in osteopenic neonates and 8.4±0.51

mg/dl (n-42) in non osteopenic neonates in first 4 weeks of life.[17]

In our study serum phosphorus levels at admission less <5 mg/dl were found in 64/101 (63.3%) cases. Significantly lower levels of serum phosphorous levels were observed in infants with grade 1 and grade 2 OOP as compared to non osteopenic infants at the time of admission. Hypophosphatemia is the earliest marker of disrupted mineral metabolism. Serum phosphate levels <5.6 mg/dl have been strongly associated with the presence of radiological evident rickets in preterm infants.

Mean levels of serum ALP levels were found significantly high in infants with grade 1 and grade 2 OOP as compared to non osteopenic infants at the time of admission. In our study 74/101 (73.2%) neonates had ALP levels >300 IU/l, 17/101 (16.8%) had ALP levels >500 IU/l. James et al observed ALP level >13 KA units (exceeding six times the upper limit) in all 17 preterm neonates which is suggestive of underlying radiological bone disease. Plasma alkaline phosphatase activity was significantly inversely correlated with GA ($p<0.001$).[18] Mitchell et al studied a cohort of 113 infants with birth weight <1000 g and found that elevation of ALP >600 IU/l was very common in ELBW infants. Peak-APA of infants <600 g (957±346 IU/l, n=20) and infants 600–800 g (808±323 IU/l, n=43) were both significantly higher than peak-APA of infants 800–1000 g (615±252 IU/l, n=50), $p<0.01$.[19]

Vitamin D levels were significantly low in neonates with grade 1 and grade 2 OOP as compared to non-osteopenic neonate. Binder et al in a retrospective analysis all clinical reports of preterm infants with a birth weight less than 1500 gm with osteopenic fractures, and reported 80% (8/10) suffered from vitamin D3 insufficiency (mean 52.9±18.1 mmol/l).[20]

The radiological diagnosis of bone impairment in preterm infants remains a difficult challenge. X-rays are not much reliable at early stage of bone disease in neonates due to the absence of significant demineralization or fractures.[15] Bone mineralization must be reduced by 20–40% to be identifiable and usually it occurs later in life. Radiologic evidence of OOP was defined according to screening criteria of Koo et al; presence of loss of dense zone of provisional calcification at metaphysis, increased submetaphyseal lucency, thinning of cortex, fraying, splaying, or cupping of metaphysisls throughout the hospitalization for early detection of OOP. Koo et al did a sequential BMC in preterm infants with or without fractures and observed that 23 out of 74 infants have evidence of rickets or fracture.[2]

OOP is well established complication of premature infants and is related to long term morbidity and mortality. Early screening and optimum nutritional supplementation of neonates with calcium, phosphorus, and vitamin D has been shown to be effective in preventing much MBD. Periodic estimation of phosphate and alkaline phosphatase concentrations is important to estimate the risk of osteopenia and assessment of treatment efficacy.

Strengths

Statistical co-relation of biochemical markers from admission till discharge i.e., 6 lab values of serum calcium, phosphorous, ALP and vitamin D and its relation with Koo's radiological grading is the highlight of our study.

Limitations

Although dual energy absorptiometry (DEXA) is said to be the gold standard for diagnosis of OOP, but in resource limited countries, the biochemical lab values can be used as an alternative method for diagnosis of OOP.

CONCLUSION

All preterm neonates (less than 32 weeks of gestation) should be screened for OOP as soon as 72 hours of life to prevent this significant morbidity. Metabolic profile including phosphate, ALP and vitamin D3 are better indicator of MBD in preterms.

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