

Clinico-Demographic Profile and Risk Factors of Metabolic Bone Disease among Preterm Neonates at a Tertiary Care Centre in North India: A Prospective Observational Study

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Received: 01-06-2026 / Revised: 15-07-2026 / Accepted: 21-08-2026

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Conflict of interest: Nil

Abstract

Background: Metabolic bone disease (MBD) of prematurity is an important cause of morbidity among very low birth weight (VLBW) and extremely low birth weight (ELBW) preterm infants. While its pathophysiology and risk factors are well characterised in Western cohorts and some Indian centres, regional data from Southern Rajasthan remain sparse.

Objectives: To study the clinical and demographic profile and risk factors of preterm neonates with MBD, and to compare these characteristics with preterm neonates without MBD, at a tertiary care centre in North India.

Methods: This prospective observational study was conducted in the neonatal intensive care unit (NICU) of Geetanjali Medical College and Hospital, Udaipur, Rajasthan, over 18 months (May 2024 – November 2025). Ninety-seven preterm neonates with gestational age <34 weeks and birth weight <1500 g were enrolled and followed prospectively until discharge or 40 weeks corrected gestational age. MBD was diagnosed at 28 days of life when serum alkaline phosphatase (ALP) exceeded 500 IU/L with serum phosphorus below 4.5 mg/dL. Data were analysed using IBM SPSS Statistics version 20.0. Continuous variables were compared using Student's t-test and categorical variables using the chi-square test (or Fisher's exact test where appropriate), with a two-tailed p-value <0.05 considered statistically significant.

Results: MBD was identified in 18 of 97 neonates (18.6%). Affected neonates had significantly lower mean gestational age (28.22 ± 0.81 vs 30.13 ± 2.01 weeks, $p < 0.001$), lower birth weight (898.6 ± 68.0 vs 1153.6 ± 239.9 g, $p < 0.001$), and longer duration of parenteral nutrition (12.67 ± 3.33 vs 8.65 ± 4.05 days, $p < 0.001$) than unaffected neonates. Maternal risk factors and most acute neonatal morbidities were not significantly associated with MBD, although respiratory distress syndrome (55.6% vs 29.1%) and bronchopulmonary dysplasia (22.2% vs 7.6%) were more frequent among affected infants. All 18 affected neonates demonstrated complete biochemical resolution by 40 weeks corrected age.

Conclusions: MBD affected nearly one in five very preterm/very low birth weight neonates in this cohort. Low gestational age, low birth weight, and prolonged parenteral nutrition were the principal determinants, and a low serum phosphorus with raised alkaline phosphatase provided a reliable biochemical marker for early identification.

Keywords: Metabolic Bone Disease; Osteopenia Of Prematurity; Preterm Neonate; Extremely Low Birth Weight; Alkaline Phosphatase; Parathyroid Hormone.

DOI: 10.25258/ijcpr.18.9.177

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Introduction

Metabolic bone disease (MBD) of prematurity — also known as osteopenia of prematurity or rickets of prematurity — refers to a reduction in bone mineral content below that expected for gestational age and is among the more troublesome complications encountered in the modern neonatal intensive care unit. [1,2] With improving survival of extremely preterm and very low birth weight (VLBW) infants, MBD is increasingly recognised,

disproportionately affecting the smallest and most immature infants. [1] Terminology has evolved as understanding of the underlying biology has grown. “Osteopenia” denotes a generalised reduction in bone mass from inadequate mineralisation of osteoid due to calcium and phosphorus deficiency, whereas “rickets” refers specifically to defective endochondral ossification at the growth plate, characterised radiologically by metaphyseal

widening and cupping and biochemically by elevated alkaline phosphatase (ALP) with reduced serum phosphorus. Unlike vitamin-D-deficiency rickets of later childhood, MBD of prematurity is primarily a disorder of substrate (calcium and phosphorus) deficiency. [2] “Metabolic bone disease” is now the preferred umbrella term, reflecting the multiple overlapping nutritional, hormonal, mechanical and iatrogenic contributors to the disorder. [3]

Reported prevalence of MBD is inversely related to gestational age and birth weight, reaching as high as 55% in extremely low birth weight (ELBW, ≤ 1000 g) infants and around 23% in VLBW (1000–1500 g) infants in some cohorts. [1] Recognised risk factors include extreme prematurity, very low birth weight, prolonged parenteral nutrition, delayed enteral feeding, chronic lung disease, immobilisation, and exposure to loop diuretics, methylxanthines and corticosteroids. [1,2]

Diagnosis relies chiefly on biochemistry rather than imaging, since plain radiographs remain unremarkable until a substantial proportion of bone mineral has already been lost; serial monitoring of ALP and serum phosphorus from the third to fourth week of life is therefore recommended, with radiography reserved for infants in whom fracture or advanced rickets is suspected. [4] Left undetected, MBD predisposes to pathological fractures, chest-wall instability and impaired postnatal growth. While the pathophysiology and risk factors of MBD have been extensively characterised in Western cohorts and in some Indian centres, regional data from Southern Rajasthan remain sparse. The present study was therefore undertaken to assess the clinical and demographic profile and risk factors of preterm neonates with MBD attending a tertiary care neonatal unit in North India, and to compare these characteristics with those of preterm neonates who did not develop MBD.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted in the neonatal intensive care unit (NICU) of Geetanjali Medical College and Hospital, Udaipur — a tertiary care referral centre serving Southern Rajasthan — over a period of 18 months (May 2024 to November 2025), following approval from the Institutional Ethics Committee.

Study Population: Preterm neonates with gestational age <34 weeks and birth weight <1500 g, admitted to the NICU during the study period, were enrolled. Gestational age was assigned from first-trimester ultrasonography where the last menstrual period was unavailable, with confirmation by the New Ballard Score. (5)

Sampling Technique and Sample Size: This was a time-bound study; all consecutive eligible neonates admitted during the study period were enrolled, yielding a total sample of 97 neonates.

Eligibility Criteria: Inclusion criteria: preterm neonates of gestational age <34 weeks with birth weight <1500 g. Exclusion criteria: neonates with major congenital anomalies, chromosomal abnormalities or renal disorders, and refusal of parental consent.

Data Collection and Clinical Assessment: Baseline demographic (gestational age, birth weight, sex), maternal (age, parity, antenatal history), perinatal (mode of delivery, antenatal steroid coverage) and neonatal (Apgar scores, resuscitation, respiratory support) data were recorded at admission on a pre-structured proforma. Feeding and nutritional management followed unit protocol, including calcium gluconate, potassium phosphate and human milk fortifiers as indicated. Serum calcium, phosphorus, vitamin D, ALP and parathyroid hormone (PTH) were measured serially, beginning at 28 days of life, in all neonates except those on bone-active medication or with cholestasis; screening continued until ALP fell below 800 IU/L and phosphate rose above 5 mg/dL on two occasions two months apart. Serum vitamin D was additionally measured at 40 weeks corrected age. Skeletal radiography was performed where clinically indicated. Growth was monitored using the modified Fenton chart until 40 weeks corrected age. (6)

Diagnosis of Metabolic Bone Disease: MBD was diagnosed when serum ALP exceeded 500 IU/L together with serum phosphorus below 4.5 mg/dL at 28 days of life, a widely used and practical biochemical threshold. (7)

Outcome Measures: The primary outcome was the clinical and demographic profile of preterm neonates with MBD; secondary outcomes included biochemical, radiographic, morbidity, growth and survival differences between neonates with and without MBD.

Statistical Analysis: Data were analysed using IBM SPSS Statistics version 20.0. Continuous variables were expressed as mean $\pm$ SD and compared using Student's t-test; categorical variables were expressed as frequencies and percentages and compared using the chi-square test (or Fisher's exact test where appropriate). A two-tailed p-value <0.05 was considered statistically significant.

Ethical Clearance: The study was approved by the Institutional Ethics Committee of Geetanjali Medical College and Hospital, Udaipur, and written informed consent was obtained from parents or legal guardians of all participants before enrolment.

Results

During the 18-month study period, 97 preterm neonates with gestational age <34 weeks and birth weight <1500 g were enrolled in the NICU of Geetanjali Medical College and Hospital, Udaipur, and followed prospectively until discharge or 40

weeks corrected gestational age. MBD, diagnosed on the basis of serum ALP >500 IU/L with serum phosphorus <4.5 mg/dL at 28 days of life, was identified in 18 neonates, giving a prevalence of 18.6% in this cohort of very low and extremely low birth weight preterm infants.

Table 1: Prevalence of Metabolic Bone Disease among the Study Population (n = 97)

Variable	n (%) / Mean $\pm$ SD
Metabolic bone disease	18 (18.6%)
No metabolic bone disease	79 (81.4%)

Table 2 compares demographic, clinical and biochemical parameters between neonates with and without MBD. Neonates with MBD had significantly lower gestational age, lower birth weight, and longer duration of parenteral nutrition than unaffected neonates (all $p < 0.001$). NICU stay was longer in the MBD group, though this difference did not reach significance ($p = 0.158$).

Maternal age, Apgar scores, time to full feeds and antibiotic duration did not differ significantly between groups. Biochemically, neonates with MBD had markedly lower serum phosphorus, higher ALP, lower vitamin D, and higher PTH than unaffected neonates (all $p < 0.001$), while serum calcium did not differ significantly between groups ($p = 0.635$).

Table 2: Comparison of Demographic, Clinical and Biochemical Parameters between Neonates with and Without Metabolic Bone Disease (n = 97)

Variable	MBD (n=18) Mean $\pm$ SD	Non-MBD (n=79) Mean $\pm$ SD	p value
Gestational age (weeks)	28.22 $\pm$ 0.81	30.13 $\pm$ 2.01	<0.001
Birth weight (g)	898.6 $\pm$ 68.0	1153.6 $\pm$ 239.9	<0.001
Birth weight (<1000 g)	17 (94.4%)	18 (22.8%)	<0.001
Birth weight (1000–1499 g)	1 (5.6%)	61 (77.2%)	<0.001
Vaginal delivery	6 (33.3%)	17 (21.5%)	0.358
Caesarean section (LSCS)	12 (66.7%)	62 (78.5%)	0.358
Maternal age (years)	29.5 $\pm$ 6.5	29.4 $\pm$ 4.9	0.948
NICU stay (days)	45.4 $\pm$ 21.5	37.4 $\pm$ 17.7	0.158
Apgar score at 1 minute	6.39 $\pm$ 2.15	6.77 $\pm$ 2.20	0.502
Apgar score at 5 minutes	8.00 $\pm$ 0.97	8.27 $\pm$ 1.22	0.326
TPN duration (days)	12.67 $\pm$ 3.33	8.65 $\pm$ 4.05	<0.001
Time to full feeds (days)	14.0 $\pm$ 9.0	14.7 $\pm$ 10.9	0.794
Antibiotic duration (days)	7.67 $\pm$ 3.96	7.85 $\pm$ 4.10	0.863
Serum calcium (mg/dL)	9.26 $\pm$ 0.57	9.18 $\pm$ 0.61	0.635
Serum phosphorus (mg/dL)	3.23 $\pm$ 0.49	5.65 $\pm$ 0.63	<0.001
Serum alkaline phosphatase (IU/L)	854.3 $\pm$ 240.2	440.8 $\pm$ 136.5	<0.001
Serum vitamin D (ng/mL)	14.29 $\pm$ 4.62	25.35 $\pm$ 7.23	<0.001
Serum parathyroid hormone (pg/mL)	123.4 $\pm$ 46.7	42.6 $\pm$ 15.6	<0.001

Table 3 summarises the association of maternal and neonatal risk factors, and neonatal morbidities, with MBD.

None of the maternal risk factors reached statistical significance, although maternal anaemia (66.7% vs 46.8%) was more frequent and full antenatal steroid coverage less frequent (11.1% vs 26.6%) among

mothers of MBD neonates. Small-for-gestational-age status was less common among MBD neonates (16.7% vs 39.2%, $p = 0.100$).

Respiratory distress syndrome (55.6% vs 29.1%) and bronchopulmonary dysplasia (22.2% vs 7.6%) were more frequent among MBD neonates, though neither reached statistical significance.

Table 3: Factors Associated with Metabolic Bone Disease among Study Participants (n = 97)

Variable	MBD n (%)	Non-MBD n (%)	p value
Maternal anaemia	12 (66.7%)	37 (46.8%)	0.209
Pregnancy-induced hypertension	3 (16.7%)	25 (31.6%)	0.259
Hypothyroidism	4 (22.2%)	14 (17.7%)	0.738
Gestational diabetes mellitus	1 (5.6%)	6 (7.6%)	1.000
Fetal distress	6 (33.3%)	22 (27.8%)	0.861
Full antenatal steroid course	2 (11.1%)	21 (26.6%)	0.226
Small for gestational age	3 (16.7%)	31 (39.2%)	0.100
Respiratory distress syndrome	10 (55.6%)	23 (29.1%)	0.063
Bronchopulmonary dysplasia	4 (22.2%)	6 (7.6%)	0.085
Patent ductus arteriosus	5 (27.8%)	12 (15.2%)	0.355
Clinical sepsis	8 (44.4%)	29 (36.7%)	0.733
Shock	2 (11.1%)	17 (21.5%)	0.512
Birth asphyxia	2 (11.1%)	9 (11.4%)	1.000
Mechanical ventilation required	5 (27.8%)	18 (22.8%)	0.760

On skeletal radiography performed at 28 days of life, 68 of 96 neonates (70.8%) had normal findings, while 19 (19.8%) showed mild osteopenia and 9 (9.4%) showed osteopenia with metaphyseal cupping or fraying — a larger number than the 18 neonates diagnosed biochemically, reflecting the relative insensitivity of plain radiography in early disease. All 18 neonates with MBD were followed to 40 weeks corrected age, and in every case the biochemical disturbance resolved: mean ALP fell from 854.3 to 380.2 IU/L, phosphorus increased from 3.23 to 5.63 mg/dL, PTH decreased from 123.4 to 35.5 pg/mL, and vitamin D approximately doubled following supplementation. At 40 weeks corrected age, growth assessed on the modified Fenton chart in the 86 surviving neonates showed that 24.7% remained below the 10th centile for weight. Overall, 86 of 97 neonates (88.7%) survived to discharge; all 11 deaths (11.3%) occurred among neonates without MBD, attributable chiefly to overwhelming sepsis and severe respiratory failure, while all 18 MBD-affected neonates survived to discharge.

Discussion

The present study describes the clinical and demographic profile of preterm neonates who developed MBD and compares them with those who did not. Of 97 very low and extremely low birth weight neonates, 18 (18.6%) were affected. The affected group was characterised by lower gestational age, lower birth weight, and longer duration of parenteral nutrition, with the classical biochemical triad of low phosphorus, raised alkaline phosphatase, and secondary hyperparathyroidism. Maternal factors and most acute neonatal morbidities did not differ significantly between groups, and biochemical resolution was complete in every affected infant by 40 weeks corrected age.

Prevalence of MBD: The prevalence of 18.6% observed in this study is consistent with figures

reported elsewhere, which vary with the population studied and the diagnostic criteria applied. He et al. [8] reported MBD in 19.4% of VLBW and 38.5% of ELBW infants in a large Chinese multicentre study, closely comparable to our result. Higher rates of 30.9% were reported by Viswanathan et al. [9] in ELBW infants alone, while Perrone et al. [10] estimated 16–23% in VLBW and 40–60% in ELBW neonates to be at increased risk. Avila-Alvarez et al. [11] reported 12.3% in neonates ≤ 32 weeks, and the Indian cohort of Kolisambavevi and Pournami [12] found 20.9% in infants < 30 weeks even after implementing a bone-protective nutritional protocol. The variation across series largely reflects differences in gestational age and birth weight composition of the populations studied.

Gestational age and birth weight: An inverse relationship between maturity and disease was evident: none of the moderate preterm neonates (32–33 weeks) developed MBD, whereas rates were 23.1% among very preterm and 27.3% among extremely preterm neonates, and mean gestational age was significantly lower in the affected group ($p < 0.001$). This is consistent with He et al. [8], who reported rates rising from 21.7% below 32 weeks to 45.5% below 28 weeks, and with the nomogram of Liang et al. [13], in which gestational age independently predicted disease. This reflects the physiological reality that approximately 80% of fetal calcium and phosphorus accretion occurs in the third trimester, so greater prematurity confers a proportionately larger mineral deficit. [14]

Birth weight discriminated the two groups even more sharply: 17 of 18 MBD cases weighed under 1000 g, and mean birth weight was significantly lower in the MBD group ($p < 0.001$). Similar associations were reported by Viswanathan et al. [9], and low birth weight was identified as the sole independent risk factor on multivariate analysis by Avila-Alvarez et al. [11]. Males predominated

among affected neonates (72.2%), in keeping with the male preponderance reported by Liu et al. [15], although statistical significance was not reached in either study.

Parenteral nutrition: Duration of parenteral nutrition was significantly longer in the MBD group ($p < 0.001$), reflecting the difficulty of delivering adequate calcium and phosphorus parenterally without exceeding solubility limits in the infusate. Perrone et al. [10] and Liang et al. [13] both identified parenteral nutrition duration as an independent predictor of disease, while Tan et al. [16] linked prolonged parenteral exposure to early hypophosphataemia, consistent with the biochemical picture observed here.

Maternal and neonatal risk factors: No maternal variable — anaemia, hypertensive disorders of pregnancy, hypothyroidism, gestational diabetes, or antenatal steroid coverage — reached statistical significance, consistent with Ukarapong et al. [17] and Tabatabaei et al. [18], both of whom found maternal factors to be inconsistent predictors compared with neonatal determinants. Small-for-gestational-age status was, unexpectedly, less common among affected neonates (16.7% vs 39.2%, $p = 0.100$), most likely because the affected infants were predominantly appropriately grown but extremely premature, a pattern also observed by Peruri et al. [19]

Respiratory morbidity — respiratory distress syndrome (55.6% vs 29.1%) and bronchopulmonary dysplasia (22.2% vs 7.6%) — was more frequent, though not statistically significant, among MBD neonates, echoing associations reported by Perrone et al. [10], Liang et al. [13], and Chen et al. [20], and likely reflecting shared vulnerability related to extreme prematurity rather than a direct causal link.

Biochemical profile and resolution: The biochemical picture reproduced the classical pattern of MBD: a low serum phosphorus with markedly raised ALP (both $p < 0.001$), a low vitamin D, and an elevated PTH, while serum calcium — defended within narrow limits at the expense of the skeleton — did not differ between groups. The combination of low phosphorus with raised ALP is widely regarded as the most useful biochemical screening pair; Backstrom et al. [21] and Figueras-Aloy et al. [7] both derived comparable diagnostic thresholds against bone densitometry, and the elevated PTH observed here is consistent with a phosphorus-deplete pattern of disease as described by Czech-Kowalska et al. [22] Reassuringly, biochemical resolution was complete in all 18 affected neonates by 40 weeks corrected age following phosphate supplementation and human milk fortification, in keeping with the generally self-limiting nature of MBD of

prematurity; however, evidence that survivors may attain a lower peak bone mass, as shown by Markopoulou et al. [23] in a cohort followed to a mean age of eleven years, argues for continued surveillance of bone health beyond the neonatal period.

Radiography, growth and outcome: Radiography detected osteopenia in a larger number of neonates (28) than were diagnosed biochemically [18], reflecting the well-recognised insensitivity of plain films until 30–40% of bone mineral has already been lost; biochemical screening therefore remains the preferred first-line strategy. Nearly a quarter of survivors remained below the 10th centile for weight at 40 weeks corrected age, underscoring the shared nutritional determinants of poor mineralisation and extrauterine growth restriction. All 18 MBD neonates survived to discharge, while all 11 deaths occurred in the unaffected group; because MBD could only be diagnosed at 28 days of life, neonates who died earlier could not be classified as affected, introducing a survivor bias that should temper interpretation of this finding — an effect also noted by Viswanathan et al. [9], whose cohort, ascertained earlier in the neonatal course, recorded higher mortality among MBD-affected infants.

Beyond nutrition, mechanical loading also contributes to bone health; Vignochi et al. [24] demonstrated that assisted physical activity reduces bone resorption and increases bone formation in preterm infants, a measure not formally assessed in this cohort but complementary to nutritional strategies. Current recommendations for calcium, phosphorus and vitamin D intake in enterally fed preterm infants provide a sound basis for structured, bone-protective nutritional protocols. [25]

Strengths and Limitations: The prospective design, standardised biochemical diagnostic criteria, and structured follow-up to 40 weeks corrected age are strengths of this study. Limitations include its single-centre design; the modest number of affected neonates ($n = 18$), which may have limited power to detect smaller associations, particularly among maternal and acute neonatal variables; the inherent survivor bias arising from diagnosis at 28 days of life; and the absence of dual-energy X-ray absorptiometry, the gold-standard measure of bone mineralisation, which was not available at this centre.

Conclusion

MBD remains a common metabolic morbidity among very preterm and extremely low birth weight infants, affecting nearly one in five neonates in this cohort. Low gestational age, low birth weight, and prolonged parenteral nutrition were the

principal determinants, while the combination of a low serum phosphorus with a raised alkaline phosphatase provided a reliable means of identification. With timely biochemical screening from the third to fourth week of life and appropriate nutritional management, the disease follows a favourable course, as reflected by the complete biochemical resolution observed in all affected neonates in this study.

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