Nare *et al.*
Egyptian Pediatric Association Gazette (2024) 72:25
https://doi.org/10.1186/s43054-024-00268-0

Egyptian Pediatric Association Gazette

RESEARCH Open Access

Profile of metabolic bone disease in extremely low birth weight (ELBW) and very low birth weight (VLBW) neonates

Rajesh Nare[1], Vishal Dnyaneshwar Sawant[2*] and Rahul Surve[3]

Abstract

Background Metabolic bone disease (MBD) is an important cause of morbidity in premature, very low birth weight (VLBW), and sick infants and, if left undiagnosed, may lead to structural deformities and spontaneous fractures. The objective of the present study was to study the profile of MBD and to determine the incidence of MBD in infants ≤ 32 weeks/≤ 1250 g at birth.

Method A total of 57 infants ≤ 32 weeks/≤ 1250 g at birth admitted in our NICU from October 2020 to July 2021 were included in the study. These infants underwent screening for MBD at 4 weeks of age. They were stratified into three groups based on their gestation (≤ 28 weeks, 29–30 weeks, 31–32 weeks).

Results MBD was observed in 100% of extreme preterm babies and 69% of very preterm babies. Overall, the incidence of MBD was 73%. Serum phosphorus level normalized by 42–44 weeks post menstrual age (PMA) across all gestations. Alkaline phosphatase (ALP) levels normalized by 42–44 weeks only in very preterm babies. Seventeen babies ≤ 30 weeks required inorganic phosphorus supplementation in addition to calcium phosphate supplementation in order to correct the MBD. Drugs like caffeine, steroids, and furosemide have significant impact on the development of MBD. The time to reach full feeds with fortification had no statistically significant effect on the incidence of MBD as detected by serum phosphorus level and serum ALP level.

Conclusion The profile outlined in the present study matches the literature reports in many aspects, revealing the importance of characterizing this group for the prognosis and short- and long-term follow-up of newborns with bone metabolic disease.

Keywords Metabolic bone disease (MBD), Gestations, Serum phosphorus, Alkaline phosphatase, Calcium phosphate, Caffeine, Steroids, Furosemide, Mother's own milk (MOM), Donor human milk (DHM), Day of life (DOL), Postmenstrual age (PMA), Postnatal age (PNA),Total parenteral nutrition (TPN), Tubular reabsorption of phosphorus (TRP)

Background

Metabolic bone disease (MBD) is defined as impaired bone mineralization in a neonate with lower-than-expected bone mineral levels in either a fetus or a neonate of comparable gestational age and/or weight, coupled with biochemical abnormalities with or without accompanying radiological manifestations. MBD has been reported to occur in 16% to 40% of extremely low birth weight neonates and presents by 6–16 weeks after birth [1]. Patients tend to be asymptomatic, and the diagnosis

*Correspondence:
Vishal Dnyaneshwar Sawant
vsawant1989@ymail.com
[1] Department of Pediatrics, Lokmanya Municipal Medical College and General Hospital, Mumbai, Maharashtra 400022, India
[2] Department of Pediatrics, Topiwala National Medical College and B.Y.L. Nair Charitable Hospital, Mumbai, Maharashtra 400008, India
[3] Department of Pediatrics, Kurla Bhabha Hospital, Mumbai, Maharashtra 400070, India

of the diseases is based on laboratory and radiographic findings of spontaneous, non-traumatic fractures, especially in the legs, arms, and ribs [2, 3].

However, MBD includes complications such as rickets and osteopenia; rickets is defined on the basis of radiographic evidence in the growing ends of long bones, while osteopenia implies low bone mineralization [4]. In addition, the prevalence of rickets in LBW infants and neonates with normal weight was reported to be 13.4% and 4.9%, respectively, between 12 and 14 weeks of corrected age [5].

The major causes of MBD among preterm infants are deficiency of calcium, phosphorus, and magnesium [6]. During pregnancy, the total amount of calcium increases from 5 g at the end of the second trimester to 30–35 g at term, and 80% of calcium and phosphorus transmission from the mother to fetus occurs during the third trimester of pregnancy; preterm birth disrupts this transfer [7]. On the other hand, breast milk and usual formula are not able to provide the infant with the essential calcium and phosphorus independently. Therefore, early provision of highly bioavailable minerals and the correction of vitamin D deficiency and phosphorus concentrations are recommended as helpful methods of MBD prevention [3]. Among other risk factors of MBD are delayed breastfeeding, soy formula, obstructive jaundice, prolonged use of total parenteral nutrition (TPN), and medications such as diuretics, methylxanthines, and corticosteroids [2].

In previous research, out of 32 ELBW infants, 18 cases showed radiologic signs of rickets, and 14 had osteopenia without rickets. Therefore, early screening for MBD is recommended in preterm infants, specialty those with birth weight of < 600 g or alkaline phosphatase (ALP) of > 800 IU/L [8]. Evidence suggests that ALP concentrations of > 750 IU/L may cause osteopenia of prematurity. As a result, weekly measurement of biochemical bone profile (i.e., Ca, P, and ALP) has been recommended for early detection of MBD in high-risk neonates [9]. Very few studies are available from India showing the exact prevalence of MBD. Normalization of biochemical parameters is expected by term-corrected age, as found in many studies done in well-developed countries. Whether this holds true in Indian babies is not known. This study aims to determine the incidence of MBD in extremely low and very low birth weight (VLBW) neonates. Secondarily, the time required for normalization of biochemical parameters in babies who were diagnosed with MBD during neonatal period was also be studied.

Methods

After obtaining written informed consent from the parent/s, this prospective observational cross-sectional study was conducted on 57 infants ≤ 32 weeks/≤ 1250 g at birth admitted in our NICU from October 2020 to July 2021. These neonates underwent screening for MBD at 4 weeks of age. Neonates with cholestatic disorder, skeletal anomalies, and genetic syndrome were excluded from the study.

As per existing unit policy, all neonates ≤ 32 weeks/≤ 1250 g at birth were started on feeds once hemodynamically stable with minimal enteral nutrition (MEN) of 10–20 ml/kg/day, increased at a rate of 15–30 ml/kg/day as per tolerance. The feed was fortified with human milk fortifier (HMF) when the baby tolerated feed of 100 ml/kg/day, and feeds were subsequently increased to 150–200 ml/kg/day, to provide a total calorie intake of 120–140 kCal/kg/day. One sachet of HMF of 1 g (Lactodex-HMF) provides 3.37 kCal energy, 0.27 g protein, 15.8 mg calcium, 7.9 mg phosphorus, and 132 IU vitamin D. They underwent laboratory evaluation with serum calcium, phosphorus, alkaline phosphatase (ALP), and urine analysis for tubular reabsorption of phosphorus (TRP) at 4 weeks of age as a screening test for detection of MBD. Serum calcium, phosphorus, ALP, and TRP levels were done as in-house tests in our NABL-accredited biochemistry laboratory. A urine calcium/creatinine ratio and calcium/phosphorus ratio were done fortnightly to calculate the TRP(percentage).

$$\text{TRP} = 1\text{-}[\text{Up/Sp} \times \text{Scr/Ucr}] \times 100 \ (\text{Up} - \text{urinary phosphorus}, \text{Sp} - \text{serum phosphorus}, \text{Scr} - \text{serum creatinine}, \text{Ucr} - \text{urinary creatinine})$$

MBD was diagnosed when serum phosphorus was < 5.5 mg/dl and/or ALP > 900 IU/L [10]. TRP > 95% indicates increased reabsorption of phosphorus and therefore phosphorus deficiency. After the initial measurement, subsequent measurements were done fortnightly till term-corrected age (40 weeks) by which time the risk of MBD becomes reasonably low. If serum phosphorus was < 5.5 mg/dl and ALP > 900 IU/L (as per existing MBD diagnostic protocol), the babies received calcium phosphate supplements and vitamin D along with fortified human milk. If TRP remained > 95% despite the above, only phosphorus supplementation was increased by adding sodium phosphate. Extra calcium was supplemented only if there is documented hypocalcemia (serum calcium < 7 mg/dl). Supplementation range used for calcium was 150–220 mg/kg/day; for phosphorus, it was 50–90 mg/kg/day and vitamin D 800–1600 IU/day (ESPHGAN recommendation). Subsequent investigations with the above biochemical tests were done every 2 weeks, for monitoring till normalization of the biochemical parameters.

Kidney, ureter, and urinary bladder ultrasonography (USG KUB) was done prior to discharge to look for nephrocalcinosis due to calcium supplementation. The growth of the baby during stay in the unit was monitored using Ehrenkranz and Intergrowth-21 growth chart for weight, length, and head circumference. Those babies who had abnormal biochemistry parameters at discharge were subsequently followed up in high-risk follow-up outpatient department (OPD). Serum calcium, phosphorus, and ALP were monitored in them monthly till normalization. The study was started after the approval of the institutional ethics committee (IEC/313/21).

Statistical analysis

Statistical analysis was carried out for qualitative and quantitative variables. Frequency and percentage were calculated for qualitative data. Mean and standard deviation were calculated for quantitative data. To test the association between three or more dependent variables, repeated measures "ANOVA" was used. *P* value (significance) of < 0.05 was deemed statistically significant. Microsoft Excel 2010 was used to code raw data, and SPSS 25.0 was used to analyze data.

Results

During the study period of 10 months from October 2020 to July 2021, 78 babies ≤ 32 weeks or with birth weight ≤ 1250 g were eligible for MBD screen at 4 weeks in our NICU. Of these, 57 babies developed MBD and were stratified into three groups based on their gestation (≤ 28 weeks, 29–30 weeks, 31–32 weeks). Their baseline demographic characteristics are given in Table 1, and feeding details are given in Table 2.

Table 1 Baseline demographic characteristics

Demographic characteristics		≤ 28 week (*n* = 10)	29–30 weeks (*n* = 32)	31–32 weeks (*n* = 15)
Gender	Male, *n* (%)	7/10 (70%)	15/32 (46.80%)	7/15 (46.60%)
Pregnancy	Multiple (*n* = 14)	2/10 (20%)	8/32 (25%)	4/15 (26.60%)
Mode of delivery	LSCS (*n* = 33)	6/10 (60%)	16/32 (50%)	11/15 (73.33%)
Postnatal steroid	Yes (*n* = 8)	4 (50%)	2 (25%)	2 (25%)
Drugs	Caffeine (*n* = 55)	10 (18.18%)	32 (58.18%)	13 (23.64%)
	Furosemide (*n* = 3)	1 (33.33%)	2 (66.67%)	0 (00%)
	Caffeine + furosemide (*n* = 3)	1 (33.33%)	2 (66.67%)	0 (00%)
	Caffeine + steroids (*n* = 8)	1 (12.50%)	6 (75%)	1 (12.50%)
Birth weight (grams)		970.00 ± 135.89	1073.75 ± 119.67	1157.33 ± 181.67
Birth length (cm.)		38.20 ± 2.2	37.938 ± 2.05	39.200 ± 2.8
Birth head circumference (cm)		25.650 ± 2.88	26.797 ± 1.813	27.967 ± 2.12
Weight at discharge (grams)		2060.00 ± 554.59	1852.50 ± 404.49	1758.67 ± 241.716
Length at discharge (cm)		45.38 ± 2.2	47.52 ± 2.3	48.50 ± 2.4
Head circumference at discharge (cm)		32.78 ± 2.48	33.97 ± 2.13	34.78 ± 2.32
Duration of hospital stay (days)		70.70 ± 22.191	57.91 ± 23.54	46.27 ± 23.987

Table 2 Baseline nutritional characteristics

Nutritional characteristics		≤ 28 weeks *n* = 10	29–30 weeks *n* = 32	31–32 weeks *n* = 15	P value
Babies received parenteral nutrition, *n* (%)		10 (100%)	32 (100%)	15 (100%)	---
Duration of parenteral nutrition in days, mean (SD)		20 ± 7.226	21.22 ± 8.579	10.47 ± 8.340	< 0.001
Minimal enteral nutrition started on DOL in days, mean (SD)		5 ± 2.309	4.63 ± 3.635	2.53 ± 2.066	0.070
Fortification received, *n* (%)		10 (100%)	32 (100%)	15 (100%)	---
Fortification started on DOL in days, mean (SD)		20.80 ± 7.005	25.38 ± 11.103	13.87 ± 8.766	0.002
Time to reach full feed in days, mean (SD)		29.50 ± 12.721	24.56 ± 10.740	16.47 ± 7.95	0.009
Maximum feed volume given (ml/kg/day), mean (SD)		± 17.670	197.81 ± 14.916	203.33 ± 11.127	0.427
Maximum calories given (kCal/kg/day), mean (SD)		147.60 ± 12.45	149.59 ± 17.292	151.33 ± 21.632	0.876
Type of feed	No of babies received exclusive MOM, *n* (%)	0 (0%)	3/32 (9.3%)	2/15 (13.3%)	0.165
	No of babies received MOM+DHM, *n* (%)	8/10 (80%)	28/32 (87.5%)	13/15 (86.6%)	
	No of babies received MOM+ formula, *n* (%)	2/10 (20%)	1/32 (3.1%)	0 (0%)	
Feed intolerance		5/10 (50%)	24/32 (75%)	8/15 (53.3%)	

Abbreviations: *DOL*, day of life; *MOM*, mother's own milk; *DHM*, donor human milk

Among the baseline nutritional characteristics, there was a significantly longer duration of parenteral nutrition in ≤ 28 weeks and 29–30 weeks as compared to 31–32 weeks (Table 2). The time to reach full feeds, initiation of fortification, and number of days of fortification prior to the first evaluation of MBD was significantly prolonged in the lower gestations. However, the maximum feed volume and calorie received, type of milk fed, and feed intolerance episodes were comparable among the three groups.

The overall incidence of MBD in the present study population was 73%, while 100% of ≤ 28 weeks babies had MBD at discharge (Table 3). Fifty-four percent of babies was available for at least 1 follow-up post discharge.

Seventeen babies of ≤ 30 weeks required inorganic phosphorus supplementation in addition to calcium phosphate supplementation in order to correct the MBD. All infants required almost the same average doses of calcium, phosphorus, or vitamin D supplementation with no significant difference in the average dosage in the three groups (Fig. 1).

There was no significant difference found in the serum calcium and serum phosphorus of the three groups at the varied postnatal age (PNA) of estimation and also at follow-up when they received optimum supplementation. The serum calcium level was maintained throughout in all the three groups. USG KUB was done in 51 infants prior to discharge to look for nephrocalcinosis due to calcium supplementation. None of them had evidence of nephrocalcinosis. The serum phosphorus level improved to > 5.5 mg/dl by 14 weeks in ≤ 28 weeks babies, by 12 weeks in 29–30 weeks babies, and by 12 weeks in 31–32 weeks babies when optimally supplemented. Serum phosphorus level normalized in all the babies by 42–44 weeks PMA. However, no significant difference was found in the serum ALP level of the three groups at the varied PNA of estimation except at 12 weeks PNA as the serum ALP level normalized by this time, i.e., 42–44 weeks PMA. The serum ALP level did not normalize till the last follow-up, i.e., 1.5 month corrected age in ≤ 28 weeks, which indicates that a longer time is required for normalization of this biochemical parameter in this subgroup (Table 4).

Methylxanthines, diuretics, and corticosteroids are known to increase the chance of development of metabolic bone disease. Infants who received caffeine with or without steroids or diuretics had a significantly higher incidence of hypophosphatemia and higher alkaline phosphatase levels at 4 weeks of age and also at discharge (Table 5).

The time to reach full feeds with fortification had no statistically significant effect on the incidence of metabolic bone disease as detected by serum phosphorus level and serum alkaline phosphatase level (Table 6).

The mean duration of hospital stay was 10 weeks in ≤ 28 weeks, 8 weeks in 29–30 weeks, and 6 weeks in 31–32 weeks of babies. Thus, the duration of hospital stay was higher in ≤ 28 weeks as compared to the other two groups due to obvious reasons of prematurity-related complications and the longer time required by

Table 3 Incidence of MBD and follow-up rates of babies with MBD

Variables	≤ 28 weeks (*n*/*N* = 10/10)	29–30 weeks (*n*/*N* = 32/36)	31–32 weeks (*n*/*N* = 15/32)
Incidence of MBD at discharge	100%	88.8%	46.8%
Available for follow-up *n* (%)	8 (80%)	13 (40.6%)	10 (66%)

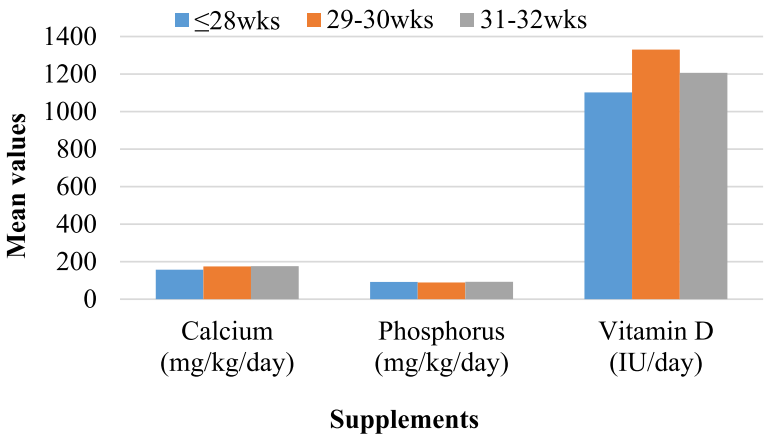

Fig. 1 Average supplementation of calcium, phosphorus, and vitamin D

Table 4 Metabolic profile of infants with MBD at different postnatal ages

Metabolic profile		≤ 28 weeks	29–30 weeks	31–32 weeks	*P* value
Mean serum calcium	4 weeks (*n* =57)	9.390 ± 0.937	9.038 ± 1.170	9.140 ± 0.864	0.668
	6 weeks (*n* =43)	9.629 ± 0.645	9.240 ± 1.042	9.7 ± 1.004	0.369
	8 weeks (*n* =32)	9.843 ± 0.310	9.411 ± 0.654	9.486 ± 0.767	0.312
	10 weeks (*n* = 23)	9.300 ± 0.985	9.300 ± 1.225	9.925 ± 0.654	0.403
	12 weeks (*n* = 18)	9.500 ± 0.608	10.100 ± 0.819	9.950 ± 0.212	0.490
	14 weeks (*n* = 13)	9.700 ± 0.141	9.800 ± 0.352	9.920 ± 0.622	0.836
	18 weeks (*n* = 2)	9.500	--	10.100	---
Mean serum	4 weeks (*n* = 57)	3.760 ± 1.297	4.335 ± 1.186	4.500 ± 1.577	0.380
Phosphorus	6 weeks (*n* = 43)	3.900 ± 1.044	4 ± 1.216	5.027 ± 1.449	0.068
	8 weeks (*n* = 32)	4.571 ± 0.743	4.294 ± 1.223	5.129 ± 1.525	0.317
	10 weeks (*n* = 23)	4.8 ± 0.608	4.825 ± 1.217	5.050 ± 1.421	0.915
	12 weeks (*n* = 18)	4.867 ± 0.306	5.723 ± 0.896	5.700 ± 0.283	0.281
	14 weeks (*n* = 13)	5.733 ± 0.404	5.783 ± 0.943	5.540 ± 0.792	0.881
	18 weeks (*n* = 2)	5.200	---	3.600	----
Mean serum	4 weeks (*n* = 57)	1222.30 ± 624.7	892.54 ± 489.33	760.27 ± 460.51	0.090
Alkaline	6 weeks (*n* = 43)	1413.43 ± 301.0	1151.76 ± 746.95	871.36 ± 353.87	0.192
Phosphatase	8 weeks (*n* = 32)	1891.71 ± 819.7	1315.89 ± 532.45	1169.71 ± 648.7	0.078
	10 weeks (*n* = 23)	1576 ± 856.2	1291.92 ± 452.01	1002.00 ± 848.5	0.408
	12 weeks (*n* = 18)	1608.33 ± 527.1	705.31 ± 274.89	645.00 ± 148.49	0.001
	14 weeks (*n* = 13)	1025.00 ± 318.2	1240.67 ± 685.93	947.20 ± 1054.4	0.824
	18 weeks (*n* = 2)	1354	---	3267.00	----

Table 5 Effect of drugs on metabolic bone disease

Drugs	S. phosphorus (< 5.5 mg/dl)	S. phosphorus (> 5.5 mg/dl)	*P* value	S. AP (> 900 IU/dl)	S. AP (< 900 IU/dl)	*P* value
At 4 weeks						
Caffeine + steroid *n* = 10	09 (90%)	01 (10%)	0.0001	09 (90%)	01 (10%)	0.0001
Caffeine + diuretic *n* = 3	03 (100%)	00 (0.0%)	0.014	03 (100%)	00 (0.0%)	0.014
Caffeine only *n* = 44	34 (77.2%)	10 (22.7%)	0.0001	34 (77.2%)	10 (22.7%)	0.0001
At discharge						
Caffeine + steroid *n* = 10	09 (90%)	01 (10%)	0.0001	09 (90%)	01 (10%)	0.0001
Caffeine + diuretic *n* = 3	03 (100%)	00 (0.0%)	0.014	03 (100%)	00 (0.0%)	0.014
Caffeine only *n* = 44	34 (77.2%)	10 (22.7%)	0.0001	34 (77.2%)	10 (22.7%)	0.0001

S. AP (> 900 IU/dl), S. alkaline phosphatase; *n*, number of neonates

the extremely preterm babies to reach suck-swallow-breathing coordination.

Discussion

In the present study, MBD was observed in 100% of extreme preterm babies and 69% of very preterm babies. Overall, the incidence of MBD was 73% in study population of ≤ 32 weeks/≤ 1250 g babies. The incidence of MBD reported in prior studies is variable. Peruri GP et al. reported that the incidence of MBD in the entire cohort and among very low birth weight (VLBW) neonates was 10.9% (19 out of 174) and 18.5% (15 out of 81), respectively [11]. Abdallah et al. found evidence of osteopenia in x-ray in 13.3% of their prospective cohort of 120 newborns born at < 34 weeks gestational age and < 1500 g birth weight. All the

Table 6 Effect of feeding and fortification on metabolic bone disease

Full feed with fortification	S. phosphorus (< 5.5 mg/dl) (*N* = 46)	S. phosphorus (> 5.5 mg/dl) (*N* = 11)	Odds ratio (95% CI)	S. AP (> 900 IU/dl) (*N* = 37)	S. AP (< 900 IU/dl) (*N* = 20)	Odds ratio (95% CI)
At 4 weeks				At 4 weeks		
Achieved before 3 weeks (*n* =36)	29	07	0.9748 (0.2486–3.823)	23	13	0.8846 (0.2847–2.749)
Achieved after 3 weeks (*n* = 21)	17	04		14	07	
At discharge				At discharge		
Achieved before 3 weeks (*n* = 36)	29	07		23	13	
Achieved after 3 weeks (*n* = 21)	17	04		14	07	

osteopenic infants had < 1000 g birth weight [12]. In the Perrone M et al. study, the rate of MBD was 22% in VLBW neonates with gestational age < 32 weeks, in which they are at an increased risk of developing MBD during hospital stays [13]. In Avila-the Alvarez A et al. study, using early biochemical criteria to identify infants at greater risk of MBD, they detected a prevalence of MBD of 12.3% [14]. However, Chinoy A et al. retrospectively reviewed the data of 57 ELBW infants of which 19 were diagnosed with rickets (33%) [15].

In the present study, most of the babies diagnosed with MBD were either on MOM or on combination of MOM with DHM. Serum phosphorus level normalized (increased to > 5.5 mg/dl) by 12–14 weeks of PNA, i.e., 42–44 weeks PMA. The serum ALP level also normalized by 42–44 weeks PMA in the very preterm population. The group of ≤ 28 weeks extremely preterm gestation babies had high ALP levels even at 42–44 weeks PMA. A larger sample size with a longer duration of follow-up is required to opine about the time when biochemical parameter normalizes in the various subgroups of preterm babies. These findings are in accordance with the study conducted by Alejandro Avila-Alvarez et al. [14]. In a review done by Faienza et al., it was found that phosphate supplementation should be considered for values < 5.5 mg/dl (1.3 mmol/L), but one may wait till values fall below < 4 mg/dl (1 mmol/L), to promote bone mineralization and to prevent hypercalciuria [16]. In the present study too, we found that 17 babies required inorganic phosphorus supplementation in addition to calcium phosphate supplementation in order to correct the MBD. This was observed predominantly in babies less than 30 weeks age. Thus, there may be requirement of additional phosphorus in this group which may be a separate entity to MBD in 30 weeks and below.

All neonates below 30 weeks gestation required parenteral nutrition, and majority (88.8%) had developed MBD which is comparable to a retrospective case-control study of infants with gestation age < 30 weeks and birth weight < 1000 g wherein they found longer period of parenteral nutrition to be associated with MBD [17]. Average duration of parenteral nutrition was 21 days. Abdallah et al. found that birth weight and gestational age were significantly inversely related to serum ALP levels [12]. This was also observed in our study. They also considered that high levels of ALP can be considered a reliable biomarker to predict the status of bone mineralization and the need for radiological evaluation in premature infants particularly those with < 1000 g birth weight and < 32 weeks gestation. We found higher values of alkaline phosphatase in our cohort of ELBW babies too; however, we had only 10 extreme preterms in our cohort which is a limitation in our study.

Some drugs frequently used in the NICU have been previously associated with MBD in preterm infants. Examples include hypercalciuric drugs such as furosemide or methylxanthines, both of which increase calcium loss, and steroids, which decrease bone formation by supporting osteoclast differentiation and inhibiting osteoblast growth [14]. In the current study, we observed that use of drugs like caffeine, steroids, and furosemide can increase the risk for development of MBD. However, the time taken to reach full feeds with fortification had no significant effect on development of MBD. MBD is a significant problem in very preterm infants which can lead to both short term and long-term implications. These findings are correlated with the study done by Ukarapong et al. [17] and Ali et al. [18].

Limitations

The sample size was small. Only 54% of infants enrolled in the study completed the last follow-up because of the migrant nature of the population and the lockdowns imposed in the COVID-19 pandemic. Vitamin D and PTH levels were not done due to financial constraints.

Conclusion

The overall incidence of MBD was 73% in the study population of ≤ 1250 g babies. The profile outlined in the present study matches the literature reports in many aspects, revealing the importance of characterizing this group for the prognosis and short- and long-term follow-up of newborns with bone metabolic disease. However, drugs like caffeine, steroids, and furosemide have significant impact on the development of metabolic bone disease. A larger sample size with a longer duration of follow-up is required to opine about the time when the biochemical parameter normalizes in the various subgroups of pretem neonates.

Abbreviations

MBD	Metabolic bone disease
PMA	Post menstrual age
ALP	Alkaline phosphatase
VLBW	Very low birth weight
ELBW	Extremely low birth weight
OPD	Outpatient department
DOL	Day of life
MOM	Mother's own milk
DHM	Donor human milk

Acknowledgements
Not applicable

Authors' contributions
RN: data collection and idea of research. RS: idea of research, writing, and proof reading. VS: analysis and interpretation of data. All authors have read and approved the manuscript.

Funding
Nil

Availability of data and materials
The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was submitted and approved by the institutional ethics committee of LTMMC and GH, and written informed consent from parents to participate in the study was taken.

Consent for publication
Written consent for publication from the parent was taken.

Competing interests
The authors declare that they have no competing interests.

Received: 11 December 2023 Accepted: 16 February 2024
Published online: 29 February 2024

References

1. Chacham S, Pasi R, Chegondi M, Ahmad N, Mohanty SB (2020) Metabolic bone disease in premature neonates: an unmet challenge. J Clin Res Pediatr Endocrinol 12(4):332–339
2. Lothe A, Sinn J, Stone M (2011) Metabolic bone disease of prematurity and secondary hyperparathyroidism. J Paediatr Child Health 47:550–553
3. Pieltain C, de Halleux V, Senterre T, Rigo J (2013) Prematurity and bone health. World Rev Nutr Diet 106:181–188
4. Chen HY, Chiu LC, Yek YL, Chen YL (2012) Detecting rickets in premature infants and treating them with calcitriol: experience from two cases. Kaohsiung J Med Sci 28:452–456
5. Agarwal R, Virmani D, Jaipal ML, Gupta S, Gupta N, Sankar MJ et al (2012) Vitamin D status of low-birth-weight infants in Delhi: a comparative study. J Trop Pediatr 58:446–450
6. Mihatsch W, Trotter A, Pohlandt F (2012) Calcium, and phosphor intake in preterm infants: sensitivity and specifity of 6-hour urine samples to detect deficiency. Klin Padiatr 224:61
7. Greenbaum LA (2011) In: Kliegman RM (ed) Rickets and Hypervitaminosis D, 19th edn. ELSEVIER, Philadelphia, p 208
8. Mitchell SM, Rogers SP, Hicks PD, Hawthorne KM, Parker BR, Abrams SA (2009) High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support. BMC Pediatr 9:47
9. Dokos C, Tsakalidis C, Tragiannidis A, Rallis D (2013) Inside the "fragile" infant: pathophysiology, molecular background, risk factors and investigation of neonatal osteopenia. Clin Cases Miner Bone Metab 10(2):86–90
10. Cloherty and Stark's Manual of neonatal care, South Asian Edition (2021). Osteopenia (metabolic bone disease) of prematurity. 2021; 59:884.
11. Peruri GP, Murugesan A, Mondal N, Govindarajalou RK, Keepanasseril A, Bobby Z, Kamalanathan S (2023) Metabolic bone disease in preterm neonates with fetal growth restriction (FGR): a prospective cohort study. Indian Pediatr 60(10):829–833
12. Abdallah EAA, Said RN, Mosallam DS, Moawad EMI, Kamal NM, Mohammed GE-D, Fathallah. (2016) Serial serum alkaline phosphatase as an early biomarker for osteopenia of prematurity. Medicine 95(37):e4837
13. Perrone M, Casirati A, Stagi S, Amato O, Piemontese P, Liotto N, Orsi A, Menis C, Pesenti N, Tabasso C, Roggero P, Mosca F (2022) Don't forget the bones: incidence and risk factors of metabolic bone disease in a cohort of preterm infants. Int J Mol Sci 23(18):10666
14. Avila-Alvarez A, Urisarri A, Fuentes-Carballal J, Mandiá N, Sucasas-Alonso A, Couce ML (2020) Metabolic bone disease of prematurity: risk factors and associated short-term outcomes. Nutrients. 12(12):3786
15. Chinoy A, Mughal MZ, Padilela R (2019) Metabolic bone disease of prematurity: causes, recognition, prevention, treatment, and long term consequences. Arch Dis Child Fetal Neonatal Ed 104:F560-6
16. Faienza MF, D'Amato E, Natale MP, Grano M, Chiarito M, Brunetti G, D'Amato G (2019) Metabolic bone disease of prematurity: diagnosis and management. Front Pediatr 7:143
17. Ukarapong S, Venkatarayappa SKB, Navarrete C, Berkovitz G (2017) Risk factors of metabolic bone disease of prematurity. Early Hum Dev 112:29–34
18. Ali E, Rockman-Greenberg C, Moffatt M, Narvey M, Reed M, Jiang D (2018) Caffeine is a risk factor for osteopenia of prematurity in preterm infants: a cohort study. BMC Pediatr 18(1):9

Publisher's Note