The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 2038-2045

Biochemical Markers and Radiological Findings in Premature Osteopenic Neonates

Abdulbasset Mustafa Saleem*[1], L. M. Alsayed[1], Ihab A. Ahmed[1], Noha A. Rezk[2]
Departments of Pediatrics[1] and Medical Biochemistry[2], Faculty of Medicine, Zagazig University, Egypt
***Corresponding Author:** Abdulbasset Mustafa Saleem**, E-Mail:** abdulbassetbelgharat86@gmail.com

ABSTRACT

Background: Neonatal rickets, also known as metabolic bone disease (MBD), and osteopenia of prematurity (OOP) are serious but common concerns for parents of premature babies.

Objective: to evaluate the wrist and arm X-ray changes and compared with evaluated the alkaline phosphatase (ALP) as a marker to predict MBD.

Patients and Methods: 36 preterm infants with GA < 36 weeks and postnatal age > 6 weeks were included at Neonatal Intensive Care Unit of Zagazig University Hospitals. Serum parathyroid hormone (PTH), ALP, calcium (Ca), phosphorus (P), and vitamin D were all measured simultaneously during the first six postnatal weeks of pregnancy. It was determined that OOP was present by taking wrist radiographs at six weeks old.

Results: A significant difference in X-ray was found in the case with biochemical and radiological change. Regarding ALP levels, a significant difference was detected among the three studied groups; the median of ALP was significantly higher in the group (I), and in the group compared to group (III). Only ALP was associated with occurrence of osteopenia in neonates.

Conclusion: According to early biochemical criteria (serum ALP and phosphate), more than one in ten very preterm infants are affected by MBD.

Keywords: Neonates, Osteopenia, Premature.

INTRODUCTION

Reduced bone mineralization results in osteopenia of prematurity, or low bone density. There are ways to avoid it. An increase in the rate of OOP is associated with an increase in the survival of premature newborns **(1).**

An X-ray of the wrist at 6 to 8 weeks of age is still a useful tool for determining whether a child has overt rickets. Premature babies weighing less than 1500 gm, or 1000 gm are at 30% and 50% higher risk of developing rickets. Among newborns with a weight of 800 grammes, this rate rises to 73% **(2).**

Neonatal rickets, or metabolic bone disease (MBD), is one of the most common and important concerns for preterm infants **(3).** The incidence of OOP has increased as a result of medical advancements that have allowed more very low birth weight (VLBW) infants to survive **(4, 5).** Rickets and osteopenia risk is inversely proportional to the intrauterine gestational age of the baby. Between the ages of 6 and 8 weeks following birth, clinical rickets typically manifests itself **(6).**

Premature infants have a much greater risk of developing rickets. Vitamin D deficiency is not the primary cause of rickets in premature infants. Vitamin D intake of 400 IU per day is recommended for bone health in preterm and full-term infants, based on research and most guidelines **(7).** Deficiencies in phosphorus, calcium, and vitamin D are also included. Ca and phosphorous supplies are in short supply when premature infants are fed human milk. For normal bone mineralization, human milk provides 25% of the calcium and phosphorus that are required. Preventing OOP necessitates vitamin D, calcium, and phosphorus supplements **(8).**

Placental and maternal vitamin D deficiency, as well as genetic etiology, are risk factors for bone disease among preterm infants. Immobility, diuretics, corticosteroids, and feeding with unsupplemented human milk are all postnatal risk factors, as is a lack of adequate Ca and P supply from prolonged total parenteral nutrition (TP) **(7).** Extensive review of serum 25(OH)D and vitamin D status has been done by the Institute of Medicine **(9)**.

A healthy skeleton and active (transcellular) calcium absorption depend on vitamin D. Infants who do not receive adequate amounts of vitamin D have an increased risk of developing low bone mineral density, which can lead to rickets **(10).** It is essential for bone health that all infants receive adequate amounts of vitamin D, regardless of whether they are breastfed or formula fed, and it should also be given to their mothers as a high-dose supplement **(11).**

Because 25(OH)D is not the primary active form of vitamin D, it should not be considered a reliable indicator of physiologic vitamin D function. Rather, the serum vitamin D concentration is useful in assessing the vitamin D status of both individuals and populations **(12).**

The goal of this work was the identification of risk factors and refinement of biomarkers for neonatal bone health.

PATIENTS AND METHODS

Thirty-six newborns with osteopenia of prematurity among neonates who were included in this study < 36 week of gestational age and very low birth weight (VLBW) <1.500 g at Zagazig University Hospitals, in the Neonatal Intensive Care Unit (NICU) served as the subjects for this cross-sectional trial.

Ethical consent:

Zagazig University's Research Ethics Committee approved the study as long as all participants' parents signed informed consent forms and submitted them to Zagazig University (ZU-IRB#6976). We adhered to the

Received: 21/11/2021
Accepted: 19/01/2022

Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.

Inclusion criteria: All participated newborns < 36 weeks of gestational age were included, birth weight < 1.500 g, and both sexes.

Exclusion criteria:

An inborn metabolic error and fatal syndromes are among the many chromosomal abnormalities, infants with bilirubin levels of more than 2 mg/dl, liver impairment, renal impairment, and suspected bone or muscular diseases.

According to the biochemical and radiological evidence, According to the presence or absence of radiographic changes, the patients were categorized into three groups.

Group I: included (n = 5) osteopenic preterm infants with biochemical (serum P <4.5 mg/dl and ALP >500 IU/L) and radiological evidence. They were 3 (60%) males and 2 (40%) females. However, 60 % of preterm infants ranged from 29-30 weeks, followed 40% > 32 weeks of gestational age and VLBW <1.500 g was found in 80% of them.

Group II: included (n = 3) osteopenic preterm infants with biochemical evidence (serum P <4.5 mg/dl and ALP >500 IU/L) and without radiological evidence. They were 2 (66.7%) males and 1 (33.3%) female. However, the preterm infants ranged from <29 and >32 weeks of gestational age and VLBW <1.500 g.

Group III: included (n = 28) preterm infants with normal biochemical (serum P >4.5 mg/dl and ALP< 500 IU/L) and normal radiological evidence. They were 15 (53.6%) males and 13 (46.4%) females. However, 32.1 % of preterm infants ranged from 29-30 weeks, followed 25% ranged from 30 – 31 weeks, and 39.3% > 32 weeks of gestational age and VLBW <1.500 g.

This is what all of the participants in this research had to go through:

History: The patient's age, sex, gender, maternal risk factors, gestational age, prenatal, natal history were all recorded in a thorough medical history.

Clinical examination:

Weight of a newborn, Suckling and Moro reflexes (Moro) were performed on the newborns as well as vital parameters such as heart rate and respiration rate, spotting the early indications of sepsis: Restlessness, sleepiness, pallor, and mottled skin characterize the infant's condition, and fluctuation in temperature, either hyperthermia or hypothermia, problem with the respiratory system.

Laboratory evaluation:

ALP and P were measured weekly or biweekly for all preterm infants in the NICU as part of our institution's standard biochemistry protocol. During radiography, ALP and P levels were recorded.

Two board-certified pediatric radiologists (S.K.Y. and S.M.L., each with seven years of experience) blinded to the clinical findings prospectively reviewed the first and subsequent wrist and arm radiography. According to previous studies, the wrist radiography was used to grade the presence of MBD as follows[13, 14]: Grade 0: Radial or ulnar epiphysis is normal. Submetaphyseal lucency and/or cortex thinned. Grade 1: with or without loss of the dense white line. Grade 2: Metaphyseal irregularity, fraying, splaying, or cupping. Grade 3: Fractures of the second degree.

Statistical analysis

One-way ANOVA test was employed to compare quantitative data using SPSS version 23, in the analysis of the differences between the groups. Proportions were compared using the Chi-square test (X^2). P value of 0.05 was considered statistically significant. It was judged highly significant (HS) when the P value was 0.001.

RESULTS

Overall, a total of 36 neonates were admitted to the NICU during the study period, where the gestational age is demonstrated in the table 1. The maternal age ranged from 20.00 to 36.00 years. Only 38.9% of patients' mothers received maternal vitamin (Vit.) D supplement. Mean± SD of serum vitamin D of mothers was 26.91±9.16. The mean± SD serum Vit. D level in the newborn was 24.18±10.76 **(Table 1).**

Table (1): Demographic characteristics among the studied group

Variable	Total (n=36)
GA [weeks], N (%)	
<29	2 (5.6%)
29-30	13 (36.1%)
30-31	7 (19.4%)
>32	14 (38.9%)
Mean ± SD	30.97± 1.50
Range	28.00-34.00
BWT (gm), No (%)	
<1000	1(2.8%)
1000-<1500	35(97.2%)
Median (IQR)	1330.00 (1162.50-1427.50)
Range	950.00-1490.00
Sex, No (%)	
Male	20(55.6%)
Female	16(44.4%)
Mode of delivery, N (%)	
CS	28 (77.8%)
VD	8 (22.2%)
AS	
Median (IQR)	678.00(567.00-788.00)
OFC (cm)	
Median (IQR)	28.50 (27.78-29.38)
Length (cm)	
Mean ± SD	39.28±1.09
Maternal age (Years)	27.92±4.500
Mean ± SD	20.00-36.00
Range	
Maternal Vit. D supplement, N (%)	
No	22 (61.1%)
Yes	14 (38.9%)
Maternal Vit. D	
Mean ± SD	26.91±9.16
Newborn Vit. D Level	24.18±10.76
Mean ± SD	

BWT: Birth weight. GA: Gestational age. CS: caesarean section. VD: Vaginal delivery. OFC: Occipito-frontal circumference. AS: Apgar score. Vit.: vitamin. IQR: Interquartile range. Data presented as N (%) for qualitative data or mean±SD and range or median (IQR) for quantitative data

Among the studied neonates 13.9% had biochemical evidence with the radiological examination (grade I and II according to Koo's score), 8.3% had biochemical evidence without radiological alterations (grade 0) and 77.8% had no biochemical alterations **(Table 2).**

Table (2): Biochemical and radiological evidences of cases

Group	Findings	n=36 [N (%)]
I	Biochemical and radiological evidence of osteopenia	5 (13.9%)
II	Biochemical evidence without radiological evidence of osteopenia	3 (8.3%)
III	Normal (No biochemical or radiological evidence)	28 (77.8%)

Table (3) shows that there was a statistically significant difference among the studied group regarding BWT and maternal Vit. D supplement. Pairwise comparison in BWT and maternal Vit. D supplement showed that this difference is mainly significant between group I and group III. Also, it shows a significant difference in the mean of Vit. D level among the three studied groups where post-hoc analysis showed that group (III) had a significantly higher mean of Vit. D Level compared to group (I).

Table (3): Comparison of demographic characteristics among the studied group

Variables	Group (I) (n=5)	Group (II) (n=3)	Group (III) (n=28)	X^2/ F	P-value	P-value within group
GA [weeks], N (%)						
<29	0 (0.0%)	1 (33.3%)	1 (3.6%)	7.588	0.270 [a]	-
29-30	3 (60.0%)	1 (33.3%)	9 (32.1%)			
30-31	0 (0.0%)	0 (0.0%)	7 (25.0%)			
>32	2 (40.0%)	1 (33.3%)	11 (39.3%)			
Mean ± SD	31.20±2.17	30.67±3.06	30.96±1.23	0.220	0.896 [c]	-
Range	29.00-34.00	28.00-34.00	28.00-33.00			
Sex, N (%)						
Male	3 (60.0%)	2 (66.7%)	15 (53.6%)	0.235	0.889[a]	-
Female	2 (40.0%)	1 (33.3%)	13 (46.4%)			
Mode of delivery, N (%)				2.939	0.230 [a]	-
CS	5 (100.0%)	3 (100.0%)	20 (71.4%)			
VD	0 (0.0%)	0 (0.0%)	8 (28.6%)			
BWT (gm), N (%)						P1= 0 .408 P2=0 .016* P3= NA
<1000	1 (20.0%)	0 (0.0%)	0 (0.0%)	6.377	0.041[a]*	
1000-<1500	4 (80.0%)	3 (100.0%)	28 (100.0%)			
Mean ± SD	1256.00±182.84	1150.00±150.00	1313.21±152.98	3.284	0.194[c]	-
AS Mean ± SD	591.60±85.76	748.33±164.81	674.68±161.46	2.716	0.257[c]	-
OFC (cm) Mean ± SD	28.90±1.14	27.07±0.93	27.64±5.03	4.850	0.088[c]	-
Length (cm) Mean ± SD	39.18±1.03	38.13±1.21	39.42±1.05	2.012	0.150[b]	-
Maternal age (Years) Mean ± SD	29.80±5.89	23.33±3.21	28.07±4.16	2.142	0.133[b]	-
Maternal Vit. D supplement, N (%)				6.545	0.038[a*]	P1= NA P2=0.037* P3=0 .098
No	5 (100.0%)	3 (100.0%)	14 (50.0%)			
Yes	0 (0.0%)	0 (0.0%)	14 (50.0%)			
Maternal Vit. D Mean ± SD	18.36±3.14	29.80±3.96	28.12±5.50	2.843	0.073[b]	-
Newborn Vit. D Level Mean ± SD	15.76±3.17	15.00±3.62	26.67±1.78	3.940	0.029 [b*]	P1= 0.994 P2=0.034* P3=0.091

*: Significant

Table (4) shows that there was a statistically significant difference regarding age at reaching full enteral feed among the three studied groups, with statistical differences between group (I) and group (III) and group (II) and group (III). Also, it shows a statistically significant difference in furosemide uses and the pair-wise comparison was significantly higher in the group (I) compared to group (III).

Table (4): Comparison of the risk factors of among the studied neonate's group

Variables	Total (n=36)	Group (I) (n=5)	Group (II) (n=3)	Group (III) (n=28)	X^2	P-value	P-value within group
Age at reaching full enteral feed (days), N (%) <14 >14	7 (19.4%) 29 (80.6%)	0 (0.0%) 5 (100.0%)	1 (33.3%) 2 (66.7%)	28 (100.0%) 0 (0.0%)	31.744	<0.001[a*]	P1=0.168 P2<0.001* P3<0.001*
Furosemide Uses, N (%) Yes No	3 (8.3%) 33 (91.7%)	3 (60.0%) 2 (40.0%)	0 (0.0%) 3 (100.0%)	0 (0.0%) 28 (100.0%)	20.291	<0.001[a*]	P1= 0.090 P2<0.001* P3=NA
Caffeine, N (%) Yes No	31 (86.1%) 5 (13.9%)	5 (100.0%) 0 (0.0%)	3 (100.0%) 0 (0.0%)	23 (82.1%) 5 (17.9%)	1.659	0.436	-
Corticosteroides, N (%) Yes No	6 (16.7%) 30 (83.3%)	5(100.0%) 0(0.0%)	0(0.0%) 3(100.0%)	1(3.6%) 27(96.4%)	29.057	<0.001[a*]	P1=0.005* P2<0.001* P3=0.739
Blood or Plasma Transfer, N (%) Blood Plasma Blood and Plasma No	14 (38.9%) 3(8.3%) 10(27.8%) 9(25.0%)	5(100.0%) 0(0.0%) 0(0.0%) 0(0.0%)	0(0.0%) 0(0.0%) 3(100.0%) 0(0.0%)	9(32.1%) 3(10.7%) 7(25.0%) 9(32.1%)	16.824	0.010[a*]	P1=0.005* P2=0.046* P3=0.073
Photo Therapy, N (%) Yes No	14(38.9%) 22(61.1%)	5(100.0%) 0(0.0%)	2(66.7%) 1(33.3%)	7(25.0%) 21(75.0%)	11.104	0.040[a*]	P1= 0.168 P2=0.001* P3=0.131
X-ray, N (%) Grade0 Grade1 Grade2	31 (86.1%) 4(11.1%) 1(2.8%)	0 (0.0%) 4(80.0%) 1(20.0%)	3 (100.0%) 0(0.0%) 0(0.0%)	28 (100.0%) 0(0.0%) 0(0.0%)	36.000	<0.001[a*]	P1=0.018* P2<0.001* P3=NA

*: Significant

The univariate multinomial logistic regression analysis showed that only ALP and PTH were associated with occurrence of osteopenia in neonates (**Table 5).**

Table (5): Predictors of the likelihood of osteopenia in neonates (univariate multinomial logistic regression analysis)

Predictor	Group (I) (N=5)				Group (II) (N=3)				Group (III) (N=28)
	B	COR	95% CI	P value	B	COR	95% CI	P value	
ALP	**1.024**	**2.784**	**2.562-3.026**	**<0.001***	-	-	-	-	R
Phosphorus	-0.725	0.484	0.165-1.425	0.188	-1.144	0.318	0.075-1.351	0.121	R
Vit. D Level	-0.171	0.843	0.701-1.014	0.069	-0.200	0.819	0.635-1.056	0.123	R
Ca	0.270	1.309	0.509-3.370	0.576	-1.105	0.331	0.079-1.395	0.132	R
PTH	**0.170**	**1.186**	**1.016-1.384**	**0.030***	0.049	1.051	0.996-1.108	0.071	R
Albumin	-0.833	0.435	0.112-1.682	0.228	-0.768	0.464	0.090-2.399	0.360	R
Mg	1.335	3.800	0.222-65.140	0.357	-1.133	0.322	0.004-27.356	0.617	R
Maternal Vit. D supplement No Yes	19.100 R	-	-	-	19.100 R	-	-	-	R
Maternal Vit. D	-0.171	0.842	0.709-1.000	0.051	0.022	1.022	0.891-1.173	0.751	R

R= The reference category (Group III). COR=Crude odds ratio. CI=confidence interval. *P*-values: Multinomial logistic regression analysis. *: Significant

Using the statistically significant univariate variables, a multivariate multiple logistic regression analysis was conducted, and ALP was found to be the only factor independently associated with neonatal osteopenia. The goodness of fit of the model was statistically significant **(Table 6).**

Table (6): Predictors of the likelihood of osteopenia in neonates (Multivariate multinomial logistic regression analysis)

Predictor	Group (I) (N=5)			Group (II) (N=3)			Group (III) (N=28)
	OR	95% CI	P-value	OR	95% CI	P-value	
ALP	**2.303**	**1.394-3.805**	**0.001***	-	-	-	R
PTH	2.064	4.725-9.018	0.988	1.730	3.965-7.548	0.991	R
P-value	**<0.001***						
Chi-Square	**44.361**						

DISCUSSION

Metabolic bone disease affects premature infants whose birth weight is less than 1500 grammes and whose gestational age is less than 32 weeks. The disease is characterized by a poor bone matrix, weak skeletal support, and an increased risk of fractures. There are 30 to 70 percent of babies at risk, a multifactorial etiology and an impact on early and late morbidity of the newborns that make this condition important. As well as neonatal rickets and prematurity rickets, it is also known as neonatal metabolic bone disease (MBD) and is an important issue in neonatology where accurate assessment of calcium and phosphate status as well as the 'quality' of bone deposition impede effective management [(15)]. Long-bone radiography (wrist or knee) is recommended by the American Academy of Pediatrics (AAP) to confirm the diagnosis of rickets in preterm infants and to monitor these individuals every 5—6 weeks until the condition is resolved[(16)]. It's still unclear whether radiologic changes correlate with biochemical markers [(14)]. In the current study, the mean GA was 30.97±1.50 weeks, ranged from 28 to 34 weeks. In addition, two patients (5.6%) were aged less than 29 weeks, 13 patients (36.1%) were aged between 29 to 30 weeks, 7 patients (19.4%) were aged between 30 to 31 weeks, and 14 patients (38.9%) were above of 32 weeks. The birth weight (BW) ranged from 950 to 1490 g with a median (IQR) of 1330 (1162.50-1427.50) g, of which 1

infant (2.8%) were <1000 g and 20 patients (55.6%) were males. The majority, 77.8% of prematurity infants were delivered by caesarean section (CS) while 22.2% were delivered by vaginal delivery (VD).

Avila-Alvarez *et al.* [17] included two participating hospitals that delivered 336 premature infants, the average gestational age was 32 weeks, and the average birth weight was 1500 grammes. Mean gestational age (GA) and birth weight (BW) were found to be statistically significant in the population studied 29.9±1.9 weeks and 1207±245 g, respectively.

Regarding the mean serum vitamin D levels, among the preterm infant group with GA ranged from 28 to 34 weeks, the current study found that the mean vitamin D level was 24.18±10.76 ng/mL, ranged from 8.60-46.80 ng/mL. Additionally, the maternal age ranged from 20 to 36 years with a mean of 27.92±4.500 years. Regarding the maternal vitamin D supplement, the current study revealed that, 38.9% of maternal patients received vitamin D supplement with mean serum vitamin D level was 26.91±9.16 ng/mL that ranged from 11.10 to 44.20 ng/mL. These findings agreed with **Angelika *et al.*** [15] and **Abd El Latif *et al.*** [18].

Our findings agreed with **Abd El Latif *et al.*** [18] who observed 7 (21.9%) of the studied preterm infants had evidence of metabolic bone disease of prematurity (MBDP), 3 (9.4%) of them diagnosed by showing osteopenia on radiological examination with Grade 1 Koo's score, and 4 (12.5%) developed biochemical evidence of MBDP (low P level <4.5 mg/dl and high ALP>500 IU/L). Also, 25 infants (78.1%) did not have any markers of the disease. Two out of the three cases with radiological signs had already biochemical evidence of the disease. On other hand, all the 4 cases with biochemical markers of MBDP had no radiological signs of the disease. **Rohana *et al.*** [19], **Lee *et al.*** [20] **and Faienza *et al.*** [21] reported similar results.

However, **Ali *et al.*** [22] in their study of 109 preterm infants who were less than 31 weeks gestation and weighed less than 1500 g BW, found that 51% of the patients had been discharged from the hospital. They found that 8% of the preterm population studied had rib fractures that occurred spontaneously.

Prenatal vitamin D supplementation was statistically significantly ifferent among the study groups. This was in line with what **Koo *et al.*** [23] found that low calcium intake during pregnancy is linked to an increased risk of osteopenia in prematurity, and that providing calcium supplements to pregnant women with low calcium intake improved the total body bone mineral content in term babies.

Preterm infants' BW and GA have a significant negative correlation with both serum ALP levels and radiographic evidence of osteopenia. In line with other studies [24, 25] we found that as BW and GA drop, the risk of osteopenia increases. This study included preterm (32 weeks gestation) neonates with extremely low birth weight (ELBW, <1000 g) in all osteopenic infant groups. Such findings indicate that VLBW and ELBW infants have a high prevalence of osteopenia.

In the current study, measurements of serum ALP level revealed significantly higher value in osteopenic infants compared with non-osteopenic infants, the median of ALP was significantly higher in the group (I) 570.00 IU/L, ranged from 541.50-593.500 IU/L, and in the group (II) 545.00 IU/L, ranged from 520.00-0.00 IU/L compared to group (III) 235.50 IU/L, ranged from 157.00-361.25 IU/L. ALP values for the diagnosis of osteopenia also showed that there was no consistent value at which the evidence of osteopenia could be detected. This study's findings were in agreement with these found by **Abdallah *et al.*** [26] as osteopenia was found in 13.3 percent of the premature infants, while the other 86.7 percent were non-osteopenic, and all of the osteopenic infants were under 1000 grammes of body weight. Compared to serum ALP levels, BW and GA had a significant negative correlation. Osteopenics had significantly higher mean ALP levels than non-osteopenics in both samples. Radiologic evidence of osteopenia was not associated with a constant serum ALP value.

Also, a significant difference was observed in terms of the parathyroid hormone (PTH) concentration among the three studied groups, where the mean of PTH concentration was statistically significantly higher in the group (I) (127.60±18.23) compared to group (III) (48.69±26.31).

This study supports the findings of **Mitchell *et al.*** [24], which state that osteopenia and elevated serum ALP levels continue to exist in very preterm infants.

In our study, the univariate multinomial logistic regression analysis showed that ALP (COR: 2.784; 95% CI: 2.562-3.026; p < 0.001) and PTH (COR: 1.186; 95% CI: 1.016-1.384) were associated with occurrence of osteopenia in neonates. Additionally, using the statistically significant univariate variables, a multivariate multiple logistic regression analysis was conducted, and ALP was found to be the only factor independently associated with neonatal osteopenia (OR = 2.303; 95% CI 1.394–3.805). The goodness of fit of the model was statistically significant. These findings were in accordance with the study of **Moreira *et al.*** [27] where PTH was found to be 71% sensitive and 88% specific for severe MBD when the cutoff point for ALP was set at 660 U l1 and ALP was found to be 29% sensitive and 93% specific. Severe bone disease in newborns was associated with lower birth weights, lower 21-day serum P levels, higher doses of glucocorticoids and caffeine, and a higher incidence of major neonatal morbidities.

Abdallah *et al.* [26] reported 500 IU/L of serum ALP is the best cut-off point for detecting osteopenia, which has 100 percent sensitivity and 80.77 percent accuracy. Researchers agreed with those who reported that serum ALP concentrations >4 times normal adult

levels were considered a marker for osteoporosis in the absence of liver disease and that concentrations >600IU/L were diagnostically sensitive (100 percent) and specific (70 percent) [28].

To the best of our knowledge, this is the first Egyptian study that utilized serial serum ALP and PTH measures correlated with radiological changes for early detection of osteopenic preterm infants. The significant findings in this study add to the existing literature, supporting the role of serum ALP levels as a biomarker for osteopenia of prematurity.

CONCLUSION

Based on the combination of risk factors, biochemical and radiological changes, a diagnosis can be made. One in 10 very preterm infants is diagnosed with MBD by early biochemical criteria (serum ALP and phosphate), despite current nutritional practises.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Alizadeh Taheri P, Sajjadian N, Beyrami B *et al.* (2014):** Prophylactic effect of low dose vitamin D in osteopenia of prematurity: a clinical trial study. Acta Med Iran, 52:671–674.
2. **Gorczyca D, Cebula H (2013):** Osteopenia of prematurity in an extremely low-birth-weight infant. American Journal of Medical Case Reports, 1(1): 12-15.
3. **Wood C, Wood A, Harker C *et al.* (2013):** Bone mineral density and osteoporosis after preterm birth: The role of early life factors and nutrition. International Journal of Endocrinology, 13: 902513.
4. **Rehman M, Narchi H (2015):** Metabolic bone disease in the preterm infant: Current state and future directions. World J Methodol., 5(3):115-121.
5. **Tosun O, Bayat M, Güneş T *et al.* (2011):** Daily physical activity in low-risk preterm infants: Positive impact on bone strength and mid-upper arm circumference. Ann Hum Biol., 38(5):635-9.
6. **Harrison C, Gibson A (2013):** Osteopenia in preterm infants. Arch Dis Child Fetal Neonatal Ed., 98: 272–275.
7. **Carpenter T, Shaw N, Portale A *et al.* (2017):** Rickets. Nat Rev Dis Primers, 3(1):17101.
8. **Greenbaum L (2011):** Rickets and hypervitaminosis D. In: Kliegman RM, Jenson HB, Behrman RH, *et al.* Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Elsverier. Pp. 261-3. https://www.ncbi.nlm.nih.gov/nlmcatalog/101184998
9. **Ross A, Taylor C, Yaktine A *et al.* (2011):** Dietary reference intakes for calcium and vitamin D. The National Academies collection: Reports funded by National Institutes of Health. In: Washington (DC): National Academies Press; PP. 233. https://www.ncbi.nlm.nih.gov/books/NBK56070/
10. **Golden N, Abrams S (2014)** Committee on nutrition. Optimizing bone health in children and adolescents. Pediatrics, 134(4): 1229–1243.
11. **Abrams S (2020):** Vitamin D in preterm and full-term infants. Ann Nutr Metab., 76 (2):6–14.
12. **Abrams S (2013)** Committee on nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. Pediatrics, 131(5): 1676–1683.
13. **Koo W, Gupta J, Nayanar V *et al.* (1982):** Skeletal changes in preterm infants. Arch Dis Child, 57:447–452.
14. **Rustico S, Kelly A, Monk H *et al.* (2015):** Calcitriol treatment in metabolic bone disease of prematurity with elevated parathyroid hormone: a preliminary study. J Clin Transl Endocrinol., 2:14-20.
15. **Angelika D, Etika R, Mapindra M *et al.* (2021):** Associated neonatal and maternal factors of osteopenia of prematurity in low resource setting: A cross-sectional study. Annals of Medicine and Surgery, 64: 235-39.
16. **Shiasi Arani K, Lotfi A, Jahangiri M *et al.* (2015):** Metabolic bone disease in very low-birth-weight neonates. Iranian Journal of Neonatology, 6(2): 7-13.
17. **Avila-Alvarez A, Urisarri A, Fuentes-Carballal J *et al.* (2020):** Metabolic bone disease of prematurity: Risk factors and associated short-term outcomes. Nutrients, 12: 786-92.
18. **Abd El Latif M, Abougabal A, Saad K *et al.* (2018):** Cross-sectional study of osteopenia of prematurity and associated risk factors. Alex J Pediatr., 31:67-75.
19. **Rohana J, Hasmawati J, Zulkifli S (2007):** Risk factors associated with low bone mineral content in very low birth weight infants. Singapore Med J., 48:191–194.
20. **Lee J, Park H, Kim J *et al.* (2017):** Bone mineral density according to dual energy X-ray absorptiometry is associated with serial serum alkaline phosphatase level in extremely low birth weight infants at discharge. Pediatrics & Neonatology, 58(3): 251-257.
21. **Faienza M, D'Amato E, Natale M *et al.* (2019):** Metabolic bone disease of prematurity: diagnosis and management. Front. Pediatr., 12(7):143-47.
22. **Ali E, Rockman-Greenberg C, Moffatt M *et al.* (2018):** Caffeine is a risk factor for osteopenia of prematurity in preterm infants. BMC Pediatr., 18:9-13.
23. **Koo W, Walters J, Esterlitz J *et al.* (1999):** Maternal calcium supple-mentation and fetal bone mineralization. Obstet Gynecol., 94:577–582.
24. **Mitchell M, Rogers P, Hicks D *et al.* (2009):** High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support. BMC Pediatr., 9: 47-51.
25. **Gül Y, Heves K, Elif Ö *et al.* (2014):** Metabolic bone disease of prematurity: report of four cases. J Clin Res Pediatr Endocrinol., 6:111–115.
26. **Abdallah E, Said R, Mosallam D *et al.* (2016):** Serial serum alkaline phosphatase as an early biomarker for osteopenia of prematurity. Medicine (Baltimore), 95(37): 4837-42.
27. **Moreira A, Swischuk L, Malloy M *et al.* (2014):** Parathyroid hormone as a marker for metabolic bone disease of prematurity. Journal of Perinatology, 34:787–791.
28. **Lucas A, Brooke O, Baker B *et al.* (1989):** High alkaline phosphatase activity and growth in preterm neonates. Arch Dis Child, 64:902–909.