



Osteopenia of Prematurity and its Maternal and Nutrition-Related Factors Among Preterm Infants Admitted to the NICU Department of Afzalipour Medical Center

Bahareh Bahman Bijari^{ID}, Sedighe Salmeei^{ID}, Pedram Niknafs, Zahra Jamali, Hamid Mousavi, Fateme Sabzevari, Zahra Daei, Mohammad Mehdi Bagheri

Department of Pediatrics, Kerman University of Medical Sciences, Kerman, Iran

Abstract

Background: Osteopenia is a relatively common disorder in premature infants. If this disease is not diagnosed and treated promptly, it will lead to impaired growth in infancy. The present study was performed to assess the relationship between osteopenia and neonatal/maternal factors among premature neonates hospitalized in the neonatal intensive care unit (NICU) of Afzalipour Medical Center.

Methods: The present cross-sectional study was performed on 100 premature infants who were admitted to the NICU of Afzalipour Medical Center in Kerman in 2017 and 2018. Alkaline phosphatase was measured in one-month-old infants as a screening criterion for osteopenia and its relation with factors such as birth weight, weight gain, duration of hospitalization, duration of intravenous feeding, type of nutrition, volume of formula, and food supplement consumption was investigated.

Results: Of the total 100 preterm babies, based on the criterion utilized for diagnosis of osteopenia (alkaline phosphatase above 900 units/L), 41 infants had osteopenia of prematurity (41% prevalence). Infants who used breastmilk alone mostly had osteopenia of prematurity. The prevalence of osteopenia was higher among girls compared with boys. The mean length of hospitalization was longer and the total parenteral nutrition venous feeding was longer among neonates with osteopenia compared with other neonates. The mean serum vitamin D levels were significantly lower in mothers of premature neonates with osteopenia compared with others.

Conclusion: Infants who were fed exclusively with breast milk were more vulnerable to osteopenia, and supplements should be considered in these infants.

Keywords: Premature neonates, Osteopenia of prematurity, NICU

Citation: Bahman Bijari B, Salmeei S, Niknafs P, Jamali Z, Mousavi H, Sabzevari F, et al. Osteopenia of prematurity and its maternal and nutrition-related factors among preterm infants admitted to the NICU department of Afzalipour Medical Center. *Journal of Kerman University of Medical Sciences*. 2023;30(6):339–343. doi:10.34172/jkmu.2023.57

Received: May 10, 2023, **Accepted:** August 20, 2023, **ePublished:** December 29, 2023

Introduction

Despite great advances in intensive care for preterm infants, considerable short/long-term complications, including osteopenia of prematurity, still occur in these neonates (1). The prevalence of osteopenia of prematurity, one of the complications of preterm infants, has diminished thanks to improvements in nutritional care. Nevertheless, it still affects around 50% of infants below 1000 g and 23%–32% of neonates less than 1500 g in weight (2). Clinical diagnosis of metabolic diseases of the bone is difficult in the primary stage of the disease. In case of misdiagnosis and delayed treatment, it can lead to developmental disorders, especially inadequate growth of stature, during infancy. Screening this disorder in preterm babies is essential, as pre- and post-natal factors can predispose the baby to osteopenia of prematurity (3).

The clinical symptoms of bone metabolic diseases

include large fontanel, plagiocephaly, relatively nonspecific and late craniotables, and rare generalized hypotonia (4). Osteopenia of prematurity is a cause of post-natal rickets, fractures, and developmental disorders, and can affect the development of the child during infancy and childhood (5). Evidence suggests that osteopenia of prematurity will cause diminished growth of stature even after correcting radiographic and biochemical changes (6). Although breastmilk is an ideal source of nutrition for preterm babies, exclusive use of mother's milk without prescription of calcium and phosphorus supplements increases the incidence of osteopenia of prematurity. Usage of these supplements has caused a clear reduction in fractures and radiographic evidence of osteopenia of prematurity in neonates (7). The present study was conducted to determine the prevalence of osteopenia of prematurity among neonates



hospitalized in the neonatal intensive care unit (NICU), its preventable postnatal factors, and maternal factors such as vitamin D deficiency in mothers.

Materials and Methods

The present cross-sectional study was performed on 100 preterm infants born with gestational ages less than or equal to 34 weeks in 2017 and 2018. These neonates were hospitalized in the NICU of Afzalipour Medical Center, Kerman-Iran, and were chosen through simple nonrandomized or available sampling. The inclusion criterion was the birth of infants with a gestational age less than or equal to 34 weeks. Among the included neonates, those who died before the post-natal age of 4–5 weeks were excluded. The neonates were included in this study after informed consent was acquired from one of their parents.

The required information in this study was collected using a checklist. In this checklist, all required data, including the mother's age, pregnancy age, and vitamin D level around delivery, gender of baby, birth weight and weight gain during the first month, duration of the neonate's hospitalization, method of oral vitamin D administration, calcium and phosphorus consumption by the neonate, amount and type of nutrition, and parenteral nutrition duration were recorded. To investigate the vitamin D level of the mother, her blood sample was taken post-delivery and sent to a standard laboratory for measuring the serum vitamin D level. Measurement of the serum vitamin D level was performed by a typical RIA kit (Martin RJ, FA WM). In this study, the limit of alkaline phosphatase to diagnose osteopenia was 900 units/L according to references (8).

Other information collected by the checklist included the method of consumption of oral supplements, including calcium, phosphorus, and vitamin D, in the next visit at the end of the first month post-delivery, which was asked in person. In cases of delay in referral, the mother was contacted, and the necessary recommendations were given for their visit. Some of the checklist information was asked by phone from the mother, and the neonatal weight was measured and recorded by the one-month neonatal age visit. All of the neonates handled by the researchers were weighed, and other information on the checklist was extracted from the hospital medical records of the neonate and their mothers.

Statistical analysis

The data collected in the study were introduced into SPSS for analysis. Then, quantitative data were described by mean and standard deviation while qualitative data were described by frequency percentage. In this study, to analyze the quantitative variables, independent samples student *t* test was utilized, while for qualitative variables, chi-square and Fisher exact tests were employed. In this

study, to control the confounding variables and specify independent predictors, the logistic regression test was employed. The significance level for all statistical tests utilized was considered 95%, with all *P* values less than 0.05 considered significant.

Results

In the present study, after excluding the neonates with incomplete information or unwilling parents, statistical analysis was performed on 100 preterm babies. Based on the criterion utilized for diagnosis of osteopenia (alkaline phosphatase above 900 units/L), 41 infants had osteopenia of prematurity. Accordingly, the prevalence of osteopenia of prematurity in the tested neonates was 41%. Also, based on double criteria (alkaline phosphatase above 900 units/L and phosphorus level of less than 5.5 mmol/L), 27 infants had osteopenia of prematurity, so the prevalence of osteopenia of prematurity in the tested infants was 27%. In this study, 52 and 48 infants were male and female, respectively. Among the preterm infants with osteopenia in this study, 16 (39%) and 25 (61%) were male and female, respectively, so the prevalence of osteopenia of prematurity was significantly higher in female neonates than in males ($P=0.03$) (Table 1).

In this study, the possible factors affecting the incidence of osteopenia of prematurity, including birth weight, weight gain during the first month, duration of hospitalization, duration of total parenteral nutrition, and the volume of formula consumed, were compared between the infants with and without osteopenia of prematurity. Accordingly, the neonates without osteopenia of prematurity had a larger birth weight, though this difference was not significant ($P=0.06$). In this study, the average weight gain of infants without osteopenia of prematurity was significantly greater than that of the infants with this condition (395.42 g vs. 152.31 g; $P=0.001$). Also, the duration of hospitalization in the NICU was significantly longer for the infants with osteopenia compared to the other infants (25.58 days vs. 15.70 days; $P=0.001$). The average duration of parenteral nutrition as well as the formula consumed were significantly greater in infants with osteopenia of prematurity compared to other infants (Table 2).

In this study, three types of nutrition were used: exclusive nutrition with mother's milk, exclusive nutrition with a formula specially tailored to preterm infants, and simultaneous feeding with mother's milk along with this special formula. None of the infants used breast milk fortifiers. Exclusive breast milk consumption was 28.1%

Table 1. Frequency of osteopenia among neonates according to their gender

	Without osteopenia		With osteopenia		Total		<i>p</i> value
	No.	%	No.	%	No.	%	
Male	36	61	16	39	52	52	0.030
Female	33	39	25	61	48	48	

Table 2. Frequency distribution of premature osteopenia according to neonatal factors

	Without osteopenia		With osteopenia		P value
	Mean	SD	Mean	SD	
Birth weight (g)	1765.76	44.56	1623.17	62.84	0.060
Weight in the first month	2157.54	66.55	1768.78	80.14	0.001
Weight gain in the first month (g)	395.42	32.06	152.31	27.96	0.001
Hospital stay (day)	15.70	1.33	25.58	2.04	0.001
Milk volume (mL)	219.32	24.11	85.19	18.97	0.001
Duration of parenteral nutrition (day)	14.13	1.28	23.97	1.92	0.001

and 71.9% among the infants with and without this condition, respectively. Exclusive nutrition with formula among these infants was 68.75% and 31.25% among the infants with and without this condition, respectively. In this study, 77.7% of infants without osteopenia and 22.3% of other infants were fed with both breast milk and the formula specially designed for preterm infants. The type of nutrition of the infants examined in this study had a significant relationship with the development of osteopenia in these infants ($P < 0.001$).

The method of consumption of vitamin D, calcium, and phosphorus was evaluated. In total, 100% of preterm infants without osteopenia had consumed vitamin D, 88.1% regularly and 11.9% irregularly. On the other hand, 92.7% of infants with osteopenia had consumed vitamin D, while 7.3% had not. Meanwhile, 31.7% and 61% had consumed vitamin D supplements regularly and irregularly, respectively. Based on these results, there was a significant relationship between vitamin D consumption and the prevalence of osteopenia in preterm infants ($P = 0.001$). Among preterm infants without osteopenia, 83.1% had consumed calcium while 16.9% had not. Also, 78% and 5.1% of these infants had consumed calcium supplements regularly and irregularly, respectively. Furthermore, 78% of infants with osteopenia had not consumed calcium supplements, while only 22% had taken those supplements. In these infants, 14.6% and 7.4% had consumed calcium supplements regularly and irregularly, respectively; calcium supplement use was significantly lower in infants with osteopenia of prematurity than in other infants ($P = 0.001$). Similar results were also reported for phosphorus consumption. Among the preterm infants without osteopenia, 81.4% had consumed phosphorus supplements while 18.6% had not. Meanwhile, 76.3% and 5.1% had regular and irregular phosphorus consumption, respectively. Among the infants with osteopenia, 78% had not used phosphorus supplements, while 22% had. In this group, 14.6% and 7.4% had consumed phosphorus supplements regularly and irregularly, respectively. Also, in this study, a significant relationship was observed between the

method of phosphorus consumption and the prevalence of osteopenia in preterm infants ($P = 0.001$; Table 3).

Among the mother-associated factors, age of pregnancy, age of mother, and vitamin D level of mother were examined. Based on the results, there was no significant difference between infants with osteopenia and other infants concerning the mother's age of pregnancy ($P = 0.22$). There was no significant difference regarding the mother's age between the infants with and without osteopenia either ($P = 0.99$). In this study, all studied mothers had vitamin D deficiency. The mean serum vitamin D level of mothers with infants with osteopenia and without osteopenia was 9.90 and 12.72 ng/dL, respectively. Thus, serum vitamin D level was significantly lower in the mothers of infants with osteopenia as compared to other mothers ($P = 0.04$).

In this study, 40%, 47.5%, and 12.5% of the mothers of infants without osteopenia had severe, moderate, and mild vitamin D deficiency, respectively. These values in mothers with infants with osteopenia were 52.5%, 35.6%, and 11.9%, respectively. No significant difference existed between the severity of vitamin D deficiency in the mother and the prevalence of osteopenia ($P = 0.44$; Table 4).

Discussion and Conclusion

The results of this study indicated that gender had a significant relationship with the prevalence of osteopenia. Unlike previous studies and references in which the prevalence of osteopenia was higher in boys, in our study osteopenia was more prevalent in girls. Also, birth weight was lower among infants with osteopenia. A study conducted in 2014 in the United States on extremely low birth weight (ELBW) infants indicated that children with radiographic evidence of bone metabolic diseases were associated with lower birth weight and age of pregnancy compared to the control group (9). After one month, the infants were reweighed, and the weight gain was evaluated after one month. It was observed that there was a significant relationship between infant weight gain during this one month and the prevalence of osteopenia in preterm infants. The duration of hospital stay did not have a significant relationship with the prevalence of osteopenia in preterm infants ($P = 0.001$). The preterm infants with osteopenia had been hospitalized in the NICU for a longer time. The results also showed that there was a significant relationship between the duration of parenteral nutrition and osteopenia of prematurity ($P = 0.001$). In this regard, the infants with osteopenia received parenteral nutrition for a longer time compared to the infants without osteopenia. A study conducted by Viswanathan et al in the United States showed that the duration of parenteral nutrition was longer in preterm infants with radiographic evidence of bone metabolic diseases compared to the control group (9). These results are in line with the findings of the present study.

Table 3. Frequency distribution of premature osteopenia according to supplement usage

		Without osteopenia		With osteopenia		P value
		No.	%	No.	%	
		Vitamin D	Regularly used	52	88.1	
	Irregular used	7	11.9	25	61	
	Not used	0	0	3	7.3	
Calcium	Regularly used	46	78	6	14.6	0.001
	Irregular used	3	5.1	3	7.4	
	Not used	10	16.9	32	78	
Phosphorus	Regularly used	45	76.3	6	14.6	0.001
	Irregular used	3	5.1	3	7.4	
	Not used	11	18.6	32	78	

Considering the manner of consumption of supplements, the time of initiating the supplements, and the type of infant nutrition, i.e., the type of milk consumed, the results indicated that there was a significant relationship between the method of vitamin D consumption and the prevalence of osteopenia in preterm infants. Accordingly, all infants without osteopenia of prematurity had consumed vitamin D, and most of them had regular consumption. However, among the infants with osteopenia, some had not used the supplement, and even among the consumers, most of them had consumed vitamin D irregularly. The results obtained from phosphorus consumption were also similar to those of vitamin D consumption. In a study, Abrams indicated that consumption of calcium, phosphorus, and vitamin D supplements in infants had a positive impact on their bone density, and could play a preventive role in the development of osteopenia in them (1).

In investigating the type of nutrition of the infant based on the type of milk consumed, it was observed that none of them had used breastmilk fortifiers. The results showed that there was a significant relationship between the type of nutrition and the prevalence of osteopenia in preterm infants. In this regard, the infants who used breastmilk alone mostly had osteopenia of prematurity, while most of the infants who exclusively consumed formula tailored to preterm infants or used the combination of breastmilk and this type of formula did not have osteopenia of prematurity. Also, in investigating the volume of formula consumed by infants within 24 hours, the results showed that there is a significant relationship between the volume of formula consumed within 24 hours and the prevalence of osteopenia. In this regard, the infants with osteopenia had consumed less formula within 24 hours. In the study by Valentina, a significant relationship was observed between the consumption of breastmilk alongside breastmilk fortifiers in infants and a reduction in osteopenia in preterm infants, whereby osteopenia was less prevalent in these infants (10).

Table 4. Frequency of osteopenia among neonates according to their maternal serum vitamin D level

	Without osteopenia		With osteopenia		Total		P value
	No.	%	No.	%	No.	%	
Severe	31	52.5	16	40	47	47.5	0.442
Moderate	21	35.6	19	47.5	40	40.4	
Mild	7	11.9	5	12.5	12	12.1	

To investigate the maternal factors affecting osteopenia, age of pregnancy, age of mother, and vitamin D levels of the mothers were evaluated. The results showed that there was no significant relationship between the mother's age and age of pregnancy, and prevalence of osteopenia in preterm infants, and these variables do not affect osteopenia of prematurity. The mothers of neonates with and without osteopenia had vitamin D deficiency, and there was a significant relationship between vitamin D deficiency in mothers and the prevalence of osteopenia of prematurity; vitamin D levels were lower in mothers of neonates with this condition. In examining the severity of vitamin D deficiency in mothers, it was observed that out of all mothers studied, 12.1%, 40.4%, and 47.5% had mild, moderate, and severe vitamin D deficiency, respectively, but there was no significant relationship between the severity of vitamin D deficiency of the mother and the prevalence of osteopenia ($P = 0.442$). In the study by Javid on 198 neonates in England, it was observed that the use of vitamin D supplements by mothers was significantly associated with bone mineral density during childhood, i.e. the concentration of serum 25 hydroxy vitamin D of the mothers was linked to osteopenia in boys at age nine (11).

Acknowledgements

The authors would like to thank the clinical research development unit at Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences for their support and collaboration.

Authors' Contribution

Conceptualization: Sedighe Salmeei.

Data curation: Bahareh Bahman Bijari, Sedighe Salmeei.

Formal analysis: Zahra Jamali.

Funding acquisition: Sedighe Salmeei.

Investigation: Bahareh Bahman Bijari, Sedighe Salmeei.

Methodology: Bahareh Bahman Bijari, Sedighe Salmeei.

Project administration: Sedighe Salmeei.

Resources: Pedram Niknafs.

Software: Hamid Mousavi, Mohammad Mehdi Bagheri.

Supervision: Sedighe Salmeei.

Validation: Bahareh Bahman Bijari, Sedighe Salmeei.

Visualization: Bahareh Bahman Bijari, Sedighe Salmeei.

Writing—original draft: Sedighe Salmeei, Fateme Sabzevari.

Writing—review & editing: Sedighe Salmeei, Zahra Daei.

Competing Interests

No party involved in this article has directly or indirectly received or will receive any financial or non-financial benefits related to this article.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The project protocol was approved by the Ethics Committee of Afzalipour Hospital, Kerman University of Medical Sciences (ethical code: IR.KMU.AH.REC.1397.032). The informed consent form was signed by the participants' parents prior to entering the project. All experimental protocols were carried out in accordance with the Declaration of Helsinki.

Funding

Not applicable.

References

1. Abrams SA. In utero physiology: role in nutrient delivery and fetal development for calcium, phosphorus, and vitamin D. *Am J Clin Nutr.* 2007;85(2):604S-7S. doi: [10.1093/ajcn/85.2.604S](https://doi.org/10.1093/ajcn/85.2.604S).
2. Koo WW. Parenteral nutrition-related bone disease. *JPEN J Parenter Enteral Nutr.* 1992;16(4):386-94. doi: [10.1177/0148607192016004386](https://doi.org/10.1177/0148607192016004386).
3. Fewtrell MS, Cole TJ, Bishop NJ, Lucas A. Neonatal factors predicting childhood height in preterm infants: evidence for a persisting effect of early metabolic bone disease? *J Pediatr.* 2000;137(5):668-73. doi: [10.1067/mpd.2000.108953](https://doi.org/10.1067/mpd.2000.108953).
4. Koo WW, Gupta JM, Nayanar VV, Wilkinson M, Posen S. Skeletal changes in preterm infants. *Arch Dis Child.* 1982;57(6):447-52. doi: [10.1136/adsc.57.6.447](https://doi.org/10.1136/adsc.57.6.447).
5. Faerk J, Peitersen B, Petersen S, Michaelsen KF. Bone mineralisation in premature infants cannot be predicted from serum alkaline phosphatase or serum phosphate. *Arch Dis Child Fetal Neonatal Ed.* 2002;87(2):F133-6. doi: [10.1136/fn.87.2.f133](https://doi.org/10.1136/fn.87.2.f133).
6. Harrison CM, Johnson K, McKechnie E. Osteopenia of prematurity: a national survey and review of practice. *Acta Paediatr.* 2008;97(4):407-13. doi: [10.1111/j.1651-2227.2007.00721.x](https://doi.org/10.1111/j.1651-2227.2007.00721.x).
7. Hung YL, Chen PC, Jeng SF, Hsieh CJ, Peng SS, Yen RF, et al. Serial measurements of serum alkaline phosphatase for early prediction of osteopaenia in preterm infants. *J Paediatr Child Health.* 2011;47(3):134-9. doi: [10.1111/j.1440-1754.2010.01901.x](https://doi.org/10.1111/j.1440-1754.2010.01901.x).
8. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin's Neonatal-Perinatal Medicine, 2-Volume Set: Diseases of the Fetus and Infant. 11th ed. Philadelphia, PA: Elsevier Health Sciences; 2019.
9. Viswanathan S, Khasawneh W, McNelis K, Dykstra C, Amstadt R, Super DM, et al. Metabolic bone disease: a continued challenge in extremely low birth weight infants. *JPEN J Parenter Enteral Nutr.* 2014;38(8):982-90. doi: [10.1177/0148607113499590](https://doi.org/10.1177/0148607113499590).
10. Bozzetti V, Tagliabue P. Metabolic bone disease in preterm newborn: an update on nutritional issues. *Ital J Pediatr.* 2009;35(1):20. doi: [10.1186/1824-7288-35-20](https://doi.org/10.1186/1824-7288-35-20).
11. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet.* 2006;367(9504):36-43. doi: [10.1016/s0140-6736\(06\)67922-1](https://doi.org/10.1016/s0140-6736(06)67922-1).

© 2023 The Author(s); Published by Kerman University of Medical Sciences. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.