

Assessment of the place of tubular reabsorption of phosphorus in the diagnosis of osteopenia of prematurity

Duygu Besnili Acar¹, Sultan Kavuncuoğlu², Merih Çetinkaya², Ercüment Petmezci³, Mesut Dursun⁴, Orhan Korkmaz⁵, Emel Kayrak Altuncu⁶

¹Department of Pediatrics, Silivri Penal Institution Public Hospital, İstanbul, Turkey

²Neonatal Intensive Care Unit, Kanuni Sultan Süleyman Education and Research Hospital, İstanbul, Turkey

³Pediatric Intensive Care Unit, Çukurova University Faculty of Medicine, Adana, Turkey

⁴Neonatal Intensive Care Unit, Çukurova University Faculty of Medicine, İstanbul, Turkey

⁵Department of Radiology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

⁶Neonatal Intensive Care Unit, Private Emsey Hospital, İstanbul, Turkey

Abstract

Aim: In this study, we aimed to investigate the utility of tubular reabsorption of phosphorus in the diagnosis of osteopenia of prematurity in addition to biochemical markers.

Material and Methods: Premature babies with a gestational age of ≤ 32 weeks and/or a birth weight of ≤ 1500 g who were hospitalized in the neonatal intensive care unit between June 2009 and March 2011 were included in the study. These babies were evaluated at the 40th gestational week and serum calcium, phosphorus, alkaline phosphatase, urea, creatinine, urinary calcium and phosphorus levels were measured and tubular reabsorption of phosphorus was determined. The subjects who had bone graphy findings and/or an alkaline phosphatase level of >400 IU/L and a phosphorus value of <3.5 mg/dL were considered osteopenic. The levels of tubular reabsorption of phosphorus of the osteopenic patients were compared with the ones of the non-osteopenic patients. The study was initiated after obtaining ethics committee approval (date: 04.29.2009/213).

Results: During the study period, a total of 698 premature babies were hospitalized in our neonatology unit. A diagnosis of osteopenia of prematurity was made in 24 of 190 subjects who met the study criteria. The level of tubular reabsorption of phosphorus was compared with the serum calcium, phosphorus and alkaline phosphatase levels measured at the 40th gestational week and alkaline phosphatase was found to be significantly increased in the group with a high tubular reabsorption of phosphorus ($\geq 95\%$). When the subjects with a phosphorus level of <3.5 mg/dL and an alkaline phosphatase level of >499 IU were compared with the newborns who were found to have a tubular reabsorption of phosphorus of $\geq 95\%$ for the objective of evaluating the specificity and sensitivity of tubular reabsorption of phosphorus, the sensitivity, specificity, positive predictive value and negative predictive value of tubular reabsorption of phosphorus in the diagnosis of osteopenia were found to be 27%, 82%, 17% and 89%, respectively. When the osteopenic and non-osteopenic patients were compared in terms of the levels of tubular reabsorption of phosphorus, no statistically significant difference was found.

Conclusions: It was thought that it was not appropriate to use tubular reabsorption of phosphorus alone in the diagnosis of osteopenia of prematurity. (Türk Ped Arş 2015; 50: 45-50)

Keywords: Biochemical markers, osteopenia of prematurity, tubular reabsorption of phosphorus

Introduction

Keeping very low birth weight (VLBW) infants alive with advances in neonatal intensive care units have made various diseases a current issue and osteopenia of prematurity is one of these diseases.

The incidence of osteopenia of prematurity has been reported to be 20-30% in infants below 1500 g and 50-60% in infants below 1000 g (1, 2).

Various biochemical variables and radiological investigations are used in the diagnosis of osteopenia

of prematurity. In addition to the traditional markers showing bone turnover [serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP)], methods including dual energy X-ray absorptiometry (DEXA), Quantitative Computerized tomography (QCT), Single Photon Absorptiometry (SPA) and Dual Photon Absorptiometry (DPA) and measurement of bone ultrasound velocity using quantitative ultrasonography device (QUA) can be used in the diagnosis of osteopenia (3-5). Studies related with the levels of bone and collagen markers including bone specific ALP (B-ALP), type I collagen C terminal propeptide (PICP), type III procollagen, N terminal propeptide (P3NP), type I collagen terminal te-

Address for Correspondence: Duygu Besnili Acar, Department of Pediatrics, Silivri Penal Institution Public Hospital, İstanbul, Turkey.
E-mail: dbesnili@hotmail.com

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lo peptide (ICTP) and pyridolin (Pyd) and deoxypyridolin which are catabolites of collagen are being conducted (6, 7).

In premature babies, absorption of P is better compared to absorption of Ca and the level depends on intake with diet. Almost all absorption takes place in the jejunum. Decreased serum P level stimulates 1α hydroxylase activity in the kidney and causes to formation of vitamin 1-25 OH D and absorption of P in the intestines. The kidneys are the main regulator of P balance. Ninety % of P in the plasma is filtered in the glomerules and 85% of the ultrafiltrate is reabsorbed. Very low birth weight babies have a lower P threshold value compared to term babies. Therefore, urinary excretion continues even in the presence of a low P level (8, 9). In addition, percentage of renal tubular reabsorption is considered directive in showing the sufficiency of P supplement, since P is not bound in plasma as Ca (10). The normal range of tubular reabsorption of phosphorus (TRP) is 78-91% and a value above 95% is a significant marker showing insufficient P supplement (10).

In our study, the utility of TRP in addition to other methods in the diagnosis of osteopenia of prematurity was evaluated.

Material and Methods

This study was conducted prospectively with preterm babies who were born below the gestational age of 32 weeks according to the revised Ballard score (11) and/or with a birth weight below 1 500 g, between June 2009 and March 2011 in the Turkish Republic Ministry of Health Bakırköy Women's and Children's Education and Research Hospital and who were internalized in the Neonatal Intensive Care Unit. The babies who had anomaly, who were lost during the study and who did not come for the 40th gestational week (GW) visit were excluded from the study. The study was initiated after obtaining approval from the ethics committee (date: 29.04.2009, number: 213).

A diagnosis of osteopenia was made in the patients who had findings on femur graphy or who were found to have a P value of <3.5 mg/dL and a ALP value of >400 IU/L at the 40th gestational week. The tests were performed in the biochemistry laboratory of our hospital using Roche-Hitachi 917/modular P analyzers device and Microtech- 3 000 spectrophotometer device.

Tubular phosphorus reabsorption was calculated according to the following formula and by studying as defined (12).

$$[1 - (\text{urinary phosphorus} / \text{urinary creatinine} \times \text{serum creatinine} / \text{serum phosphorus})] \times 100$$

The threshold value for tubular phosphorus reabsorption was considered 78-91% and values above 95% were compared with the other markers in terms of presence of osteopenia. In statistical evaluation, the sensitivity, specificity and predictive values of TRP were calculated.

Femur graphies (Siemens seldix 550) obtained for radiological assessment of bone mineralization were interpreted by the same radiologist. In classification, the radiological change scale in osteopenia of prematurity developed by Koo et al. (13) was used.

24 patients who had osteopenia of prematurity were compared with the patients who did not have osteopenia in terms of gestational week, birth weight, height and head circumference, mode of delivery, APGAR score, gender, sepsis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), acute renal failure (ARF), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), neonatal jaundice (NJ), hospitalization time in the NICU, time of total parenteral nutrition (TPN) and use of aminophylline and steroid.

Leukocytosis, leukopenia, thrombocytopenia and increased CRP in the first 30 days of life which is due bacterial infections is defined as neonatal sepsis (14). Respiratory distress syndrome is characterized with cyanosis, retractions, tachypnea (>60/min), and uniform reticular appearance and air bronchograms on lung graphy observed in the first 48-96 hours of life or for a longer period (15). Patent ductus arteriosus is a ductal opening of >1.4 mm and/or a left atrium/aortic arcus diameter (LA/AO) of >1.4 on echocardiography (ECHO) (16). Acute renal failure is defined as a serum creatinine level above 1.5 mg/dL in the infant in the presence of a normal maternal serum creatinine value or more than 0,3mg/dL increase in the serum creatinine value during the follow-up (17). Persistence of oxygen dependence at the 36th GW and oxygen requirement for at least 28 days is defined as BPD (18). Necrotizing enterocolitis is a severe gastrointestinal disease characterized with partial or complete ischemia in the intestines which is observed commonly in preterm babies (19).

The picture which occurs as a result of bilirubin accumulation in the tissues because of incomplete maturation of the liver and inability to remove bilirubin adequately from the body is defined as NJ (20).

Statistical analysis

In this study, statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In assessment of the data, descriptive statistical methods (mean, standard deviation), independent T test in comparison of double groups and chi-square and Fisher exact tests in comparison of quantitative data were used. A p value of <0.05 was considered significant.

Results

A total of 698 preterm babies were internalized in the secondary and tertiary neonatal intensive care unit between June 2009 and March 2011 and 190 patients who met the study criteria were evaluated. A diagnosis of osteopenia of prematurity was made in 24 patients. In the osteopenic group, the mean GW was found to be 29.04 ± 2.1 weeks, the mean birth weight was found to be 1074.58 ± 277.83 g and the mean head circumference was found to be 26.54 ± 3.12 cm and was significantly lower compared to the non-osteopenic group ($p < 0.05$). It was observed that the mode of delivery, gender and the APGAR score at the 5th minute had no effect on osteopenia (Table 1).

When the groups were compared in terms of the risk factors for osteopenia of prematurity, RDS was found

with a higher rate, the time of total parenteral nutrition was longer, neonatal jaundice was less frequent, cholestasis was more common, use of steroid and aminopjylline was more common and the hospitalization time in the neonatal intensive care unit was longer in the osteopenic group. No significant difference was observed between the groups in terms of intraventricular hemorrhage, ARF, PDA, NEC and BPD (Table 2).

When Ca, P, ALP levels of the patients measured at the 40th week were compared with TRP, it was observed that ALP was correlated with TRP (Table 3). However, no statistically significant difference was found between the TRP values of the osteopenic and non-osteopenic groups ($p = 0.4$) (Table 4).

When the patients whose phosphorus levels were found to be < 3.5 mg/dL and ALP levels were found to be > 400 IU were compared with the preterm babies whose TRP values were found to be ≥ 95 in order to evaluate the sensitivity and specificity of tubular phosphorus reabsorption, TRP was found to have a sensitivity of 27%, a specificity of 82%, a positive predictive value (PPV) of 17% and a negative predictive value (NPV) of 89% in the diagnosis of osteopenia (Table 5).

Discussion

One of the important problems of VLBW preterm babies who are kept alive in neonatal intensive care units is osteopenia of prematurity. In the etiology of the dis-

Table 1. Demographic properties

		Osteopenic group (n=24)	Normal group (n:166)	p
Gestational week		29.04 ± 2.1^a	30.19 ± 2.46^a	0.032*
Birth weight (g)		1074.58 ± 277.83^a	1223.34 ± 269.66^a	0.013*
Birth height (cm)		37.33 ± 4.61^a	37.91 ± 3.25^a	0.443
Birth head circumference (cm)		26.54 ± 3.12^a	27.63 ± 2.2^a	0.034*
Mode of delivery	NSD	29.17% (n: 7)	18.67% (n: 31)	0.23
	C/S	70.83% (n: 17)	81.33% (n: 135)	
Gender	Male	54.3% (n:13)	48.9% (n:81)	0.55
	Female	45.6% (n:11)	51.02% (n:85)	
APGAR score at the 5 th minute		8.29 ± 1.3^a	7.78 ± 1.44^a	0.105

NSD: normal spontaneous delivery; C/S: cesarean section;

^amean \pm SD

Table 2. Risk factors for osteopenia

	Osteopenic group (n:24)		Normal group (n:166)		p
Respiratory distress syndrome	(n:18)	79.17%	(n:83)	50.00%	0.007
Neonatal jaundice	(n:21)	91.67%	(n:111)	67.47%	0.015
Hospitaizaiton in ICU	(n:20)	83.33%	(n:107)	64.46%	0.066
Total parenteral nutrition time (days)	29.71±20.01 ^a		18.09±12.72 ^a		0.0001
Use of steroid	(n:7)	29.17%	(n:24)	14.46%	0.068
Use of aminophylline	(n:22)	91.67%	(n:103)	62.05%	0.004
Bronchopulmonary dysplasia	(n:7)	29.17%	(n:36)	21.69%	0.413
Sepsis	(n:15)	62.50%	(n:87)	52.41%	0.354
Necrotizing enterocolitis	(n:4)	16.67%	(n:23)	13.86%	0.712
Acute renal failure	(n:5)	20.83%	(n:23)	13.86%	0.367
Patent ductus arteriosus	(n:1)	4.17%	(n:17)	10.2%	0.342
Intraventricular hemorrhage	(n:5)	20.83%	(n:29)	17.4%	0.688

^amean±SD**Table 3. Comparison of the serum calcium, phosphorus, aljkalene phosphatase levels at the 40th gestational week with tubular phosphorus reabsorption**

	Tubular phosphorus reabsorption		
	<95% (n:168)		p
	mean±SD ^a	mean±SD ^a	
Calcium (mg/dL)	9.52±0.47	9.42±0.37	0.366
Phosphorus (mg/dL)	5.66±1.20	5.25±1.26	0.136
Alkalene phosphatase (IU)	449.19±187.71	592.32±237.22	0.001

^amean±SD**Table 4. Comparison of the osteopenic and non-osteopenic groups in terms of tubular phosphorus reabsorption**

	Osteopenic group (n:24)		Normal group (n:166)		p
	n	%	n	%	
TRP≥95%	4	16.7	18	10.8	
TRP<95%	20	83.3	148	89.2	0.405

TRP: tubular reabsorption of phosphorus

ease, insufficient bone stores of Ca and P in the intra-uterine period, drugs used during the neonatal period (steroids, diuretics etc.), delayed initiation of enteral feeding and inadequate enteral feeding and long-term immobility have been defined as the main risk factors (21). Although many preterm babies do not have signs of osteopenia, radiological rickets and non-traumatic fractures are observed in a small group (21).

It has been reported that use of serum P levels in combination with ALP, increases the sensitivity of screen-

Table 5. Evaluation of tubular reabsorption of phosphorus (TRP) according to the results of phosphorus and alkalene phosphatase

		TRP					
		≥95%		<95%		Total	
		n	%	n	%	n	%
P and ALP	p<3.5 mg/dL and ALP>400IU	6	3.2	29	15.3	35	18.4
	p>3.5mg/dL and ALP<400IU	16	8.4	139	73.2	155	81.6
Total		22	11.6	168	88.4	190	100

Sensitivity

27.27

Specificity

82.74

Positive predictive value

17.14

Negative predictive value

89.68

Accuracy

76.32

ALP: alkalene phosphatase; P: phosphorus

ing and contributes to specifying preterm babies who carry a risk for osteopenia (22-24). Backstrom et al. (25) reported that a serum ALP value above 900 U/L was related with low bone mineral density, its sensitivity was 88% and specificity was 71% and a serum P level of <5,5 mg/dL was related with low bone mineral density and its sensitivity was 96% and specificity was 50%. Glass et al. (26) reported that an ALP value of >900 IU/l had a sensitivity of 100% in the diagnosis of osteopenia and combination of an ALP value of >800 IU/dL and a P value of <3.5 mg/dL defined severe osteopenia. In our study, we used decreased P and increased ALP in combination in defining osteopenia.

In a meta-analysis published by Harrison et al. (10) in 2008, it was reported that TRP percentage was the best indicator in showing the adequacy of P supplement and if TRP was >95%, P supplement was insufficient; these authors recommended that TRP level should be studied in cases where the ALP value is >500IU/L and P value is <1.8 mmol/L. In another study conducted with 30 AGA and 34 SGA VLBW preterm babies, it was shown that serum P and Ca levels were insufficient in determining bone mineral loss in the early period and it was found that TRP was increased in both groups in preterm babies who developed bone mineral loss (27). Çakır et al. (28) found a positive correlation between the urinary deoxypyridinoline level which is one of the markers of bone destruction and TRP in 39 preterm and 20 term babies who were started to be fed in the first five days postnatally and proposed that TRP could be used in the diagnosis of osteopenia of prematurity. In our study, no statistically significant difference was found between the patients who were and were not found to have osteopenia in terms of TRP values, though TRP was found to be compatible with increased ALP. In addition, TRP was found to have a lower sensitivity and specificity compared to P and ALP. We could not find any study related with sensitivity and specificity of TRP in determining osteopenia in the literature.

There are studies reporting that the diagnosis of osteopenia can be made more definitely by bone mineral density measurement or histological examination (29, 30). However, preterm babies are not appropriate for histological examination. Single-photon absorptiometry (SPA), Dual-photon absorptiometry (DPA), Dual-energy x-ray absorptiometry (DEXA), Quantitative Computed tomography (QTC) may be used for measurement of bone mineral density. Determining minor defects in bone mineral density by DEXA is a considerably sensitive method, but its use is limited because of low availability and lack of a threshold value for preterm babies. Since the above-mentioned bone mineral density measurement methods are not available in our hospital, we could not use these methods.

Koo et al. (13) reported that they found radiographic changes in more than 30% of the VLBW preterm babies who had osteopenia of prematurity. McIntosh N et al. (2) reported that they found radiographic changes in more than 57% of the VLBW babies in whom osteopenia of prematurity was defined. In our study, femur graphs were obtained when the patients completed the 40th GW; stage 1 osteopenia was found in 22 patients and stage 2 osteopenia was found in 2 patients.

Conclusively, the place of TRP in the diagnosis of osteopenia of prematurity was evaluated in our study and it was found that it was not sufficient alone in making the diagnosis because of low sensitivity and specificity, though it was found to be correlated with ALP. There is no new publication in this area in the literature. Convenient and accessible methods with high sensitivity and specificity which may be used in the diagnosis of osteopenia of prematurity which is one of the important problems of preterm babies are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Gynaecology and Pediatrics Training and Research Hospital (29.04.2009/213).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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