Diagnostic and Interventional Imaging (2017) xxx, xxx—xxx

ORIGINAL ARTICLE /*Pediatric imaging*

Metabolic bone disease in preterm infants: Relationship between radiologic grading in the wrist and serum biochemical markers

S.K. You[a], J.E. Lee[a,*], S.M. Lee[b], H.-H. Cho[c]

[a] *Department of Radiology, Chungnam National University Hospital, 282 Munhwa-ro, Jung-gu, Daejeon 35015, Republic of Korea*
[b] *Department of Radiology, Kyungpook National University Medical Center, 807 Hoguk-ro, Buk-gu, Daegu 41404, Republic of Korea*
[c] *Department of Radiology, Ewha Womans University Mokdong Hospital, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Republic of Korea*

KEYWORDS
Preterm infant;
Metabolic bone disease;
Wrist;
Radiographs;
Alkaline phosphatase

Abstract
Purpose: To assess the relationship between radiographic findings of metabolic bone disease (MBD) and serum biochemical markers in preterm infants.
Materials and methods: A total of 159 preterm infants were included in this study. Two readers reviewed the wrist radiography for grading according to MBD severity. We recorded the levels of alkaline phosphatase (ALP) and phosphorous (P) immediately after birth, on the same day of the first wrist radiography (ALP-s, P-s), the highest/lowest ALP/P levels before the first wrist radiography (ALP-hb/P-lb) and during follow-up (ALP-h/P-l). For analysis, the patients were first subdivided into 4 groups according to MBD severity, and were then divided into 2 groups according to MBD presence or absence.
Results: Of the 159 patients, 94, 39, 19, and 7 infants were classified into grades 0,1, 2, and 3. Analysis according to severity showed that ALP-s, ALP-hb, and ALP-h differed between grades 0—1 and 2—3 (all $P < 0.001$); P-lb differed between grades 0 and 2 ($P = 0.001$); and P-l differed between grades 0 and 2 or 3 ($P < 0.001$ or $P = 0.001$). Moreover, ALP-s, ALP-hb, ALP-h, P-s, P-lb, and P-l differed according to the presence or absence of MBD ($P < 0.001$). ALP-h showed the largest area under the curve value (0.752, 95% confidence interval = 0.676—0.828, $P < 0.001$). The optimal cut-off value of ALP-h was 473.5 U/L. The sensitivity and specificity were 81.5% and 47.9%. ALP-h was measured at 6.9 ± 5.3 weeks after birth.
Conclusion: Taking the wrist radiography with reference to an ALP level measured at around 6.9 weeks after birth could be helpful for screening of MBD in preterm infants, unless a fracture is clinically suspected.

* Corresponding author.
E-mail address: leeje290@gmail.com (J.E. Lee).

http://dx.doi.org/10.1016/j.diii.2017.06.008

Please cite this article in press as: You SK, et al. Metabolic bone disease in preterm infants: Relationship between radiologic grading in the wrist and serum biochemical markers. Diagnostic and Interventional Imaging (2017), http://dx.doi.org/10.1016/j.diii.2017.06.008

Preterm and low birth weight (LBW) infants are at an increased risk of developing metabolic bone disease (MBD) [1,2]. The prevalence of MBD in preterm infants with very low birth weight (VLBW, < 1500 g) and extremely low birth weight (ELBW, < 1000 g) was estimated at 20—30% and 50—60%, respectively, in 1996 [3]. The fetus absorbs calcium and phosphorus (P) mainly during the third trimester of pregnancy; therefore, preterm infants lose the opportunity to store minerals [4,5]. The frequency of MBD has increased correspondingly with an increase in the survival rate of preterm infants [6—8]. Even when the radiologic signs of MBD and biochemical markers are corrected, MBD can still have a negative influence on the linear growth of affected infants [9]. Therefore, the early detection and prevention of MBD in neonatal intensive care units is now a critical consideration. However, there is a lack of consensus on the definition, screening, and treatment of MBD [6,10]. The definition of MBD varies, as patients can present with osteopenia, osteoporosis, rickets, and fractures [8,11]. High levels of alkaline phosphatase (ALP) and low levels of P have been commonly used as serum biochemical markers for the detection of MBD [6,8,12,13]. In addition to these biochemical markers, radiological findings are commonly used for the diagnosis of MBD. The American Academy of Pediatrics recommends carrying out long-bone (wrist or knee) radiography to confirm the diagnosis of rickets in preterm infants and to follow-up these individuals at 5—6-week intervals until it is resolved [10]. However, the relationship between radiologic changes and biochemical markers is under debate [11,14—16].

The aim of this study was to evaluate the relationship between wrist radiographs and levels of ALP or P, the standard biochemical markers for MBD screening. We also assessed the optimal timing of wrist radiographs and evaluated the optimal cut-off values of biochemical markers to predict MBD.

Materials and methods

Patients

This study was approved by the institutional review board of our institution. A retrospective review of clinical, biochemical, and radiological information was performed from records of infants born at less than 37 weeks of gestational age in the neonatal intensive care unit of our institution between January 2014 and September 2016. We excluded 3 of the 162 patients, including 2 patients with congenital hypothyroidism and 1 patient with jejunal atresia. The characteristics of the remaining patient cohort were as follows: boy/girl, 90/69; mean gestational age, 29.5 ± 2.4 (SD) weeks; mean birth weight, 1214.8 ± 315.5 g. Of the 159 patients included in the study, 34 (21.4%) were ELBW infants and 98 (61.6%) were VLBW infants.

Biochemical analysis

According to the routine protocol of our institution, all preterm infants in the neonatal intensive care unit were measured for standard biochemistry parameters (serum ALP and P) weekly or bi-weekly until discharge. We recorded the following levels of ALP and P: the first measurements after birth, levels on the same day of the first wrist radiography (ALP-s, P-s; if these data were not recorded on the same day, the levels recorded closest to that day were used instead), the highest ALP level before the first radiography (ALP-hb) and during the serial follow-up (ALP-h), and the lowest P level before the first wrist radiography (P-lb) and during the serial follow-up period (P-l).

Radiological grading

The first and serial bilateral wrist radiography were retrospectively reviewed independently by two board-certified pediatric radiologists (S.K.Y. and S.M.L, each with 7 years of experience) who were blinded to the clinical findings. The presence of MBD was graded on the basis of the wrist radiography according to previous studies (Fig. 1) [16,17] as follows: grade 0, normal epiphysis of the radius or ulna; grade 1, loss of the dense white line, increased submetaphyseal lucency, and/or thinning of the cortex; grade 2, irregularity, fraying, splaying, and/or cupping of the metaphysis; and grade 3, fractures with grade 2. The inter-observer reliability was assessed using the intra-class correlation coefficient (ICC). The ICC was 0.94 (95% confidence interval [CI] = 0.92—0.96, $P < 0.001$), showing good inter-observer reliability between the two readers. The most severe grade recording during the serial follow-up period was determined in consensus by two radiologists for analysis. In the first analysis, we compared the biochemistry values for each of the four grades. For the second analysis, the patients were divided into two groups according to the presence or absence of radiographic changes.

Statistical analyses

All data were analyzed using IBM SPSS Statistics for Windows (Version 21.0., IBM Corp., Armonk, NY, USA). Statistical significance was defined as $P < 0.05$. The mean and standard deviation were calculated for the clinical and demographic data of each group. In the first analysis, the biochemistry results were compared among the four radiological grades using one-way analysis of variance (ANOVA) with a Tukey multiple-comparison post-hoc test. In the second analysis, the results were compared between two groups according to the presence and absence of radiographic changes using the Student *t*-test. A receiver operator characteristic (ROC) curve was constructed to determine the optimal cut-off values of the biochemical markers for the detection of MBD.

Results

In total, 159 preterm infants were included in this study. Based on the wrist radiography, 94, 39, 19, and 7 infants were classified into grades 0, 1, 2, and 3, respectively. The demographic data for the patients classified into each of the grades are summarized in Table 1. The gestational age, birth weight, and days of hospitalization were significantly different among the four grades (Table 1). ALP-s, ALP-hb, and ALP-h significantly differed between grades 0/1 and 2/3 (Table 2). P-lb and P-l significantly differed between grades 0 and 2, and between grades 0 and 2/3 (Table 2). Whisker

Please cite this article in press as: You SK, et al. Metabolic bone disease in preterm infants: Relationship between radiologic grading in the wrist and serum biochemical markers. Diagnostic and Interventional Imaging (2017), http://dx.doi.org/10.1016/j.diii.2017.06.008