Clinical-laboratory findings of bone metabolism in healthy premature and full-term neonates: preliminary results

Charalampos Dokos1
Christos Taikalidis1
Kyriakoula Manaridou1
Paraskevi Karayianni1
Ioannis Kyrkos2
Israel Roussos3

1 2nd Neonatal Clinic, Papageorgiou University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
2 3rd Orthopaedic Clinic, Papageorgiou University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
3 2nd Pediatric Clinic, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Address for correspondence:
Charalampos Dokos
2nd Neonatal Clinic, Papageorgiou Hospital, Medical School Aristotle University of Thessaloniki, Thessaloniki, Greece
Phone: +35 797735079
E-mail: dokos1984@yahoo.gr

Summary

Premature infants are a major risk group for bone metabolic disorders. The purpose of this study is to clarify certain aspects of bone metabolism in healthy premature and full-term neonates. Forty neonates (20 preterm and 20 full-term) were the material of the study. For each neonate demographic data (gender, gestational week) and anthropometric data (body weight) were recorded. Blood samples were collected and biochemical markers of bone metabolism (serum ALP, Ca, P, Mg) were immediately estimated. According to the results there is a statistically significant difference in average ALP of preterm neonates compared to full term neonates. Slightly higher values of Ca, P, Mg occurred in premature neonates while there was a statistically significant difference in the weeks of gestation and body weights between the two groups. It is typical in premature neonates the decrease in levels of ALP by the gestation week seems to positively affect P and Mg levels in preterm neonates. Conclusively from our study’s results arises that the week of gestation and not so much the body weight influence the alterations of bone biochemical biomarkers in healthy premature newborns. It seems that very premature neonates have high levels of serum ALP in decompensation of lower levels of Mg and P from all the newborns in this study. Therefore in very premature neonates, it is recommended to estimate serum ALP, Mg and P for assessment of bone turnover.

KEY WORDS: bone metabolism; premature neonates; alkaline phosphatase; magnesium; phosphorus; calcium.

Introduction

Bone regeneration is a dynamic bone growth process which involves the intense deposition of minerals such as hydroxyapatite [Ca10(PO4)6(OH)2], and the bone resorption of bone tissue mediated by osteoclasts. The main factors that affect bone regeneration have not been fully clarified. It is well known that premature infants are high risk group for metabolic bone diseases such as rickets, osteopenia, etc. (1). According to several studies, the factors that have been implicated for bone metabolic disorders in premature infants include the lack of calcium and phosphorus, especially in the third semester of pregnancy, metabolic disorders of vitamin D3 in the placenta, intrauterine growth retardation, chorioamnionitis and extended drug treatment (especially diuretics) (1-6). The elucidation of the pathogenesis of disorders of bone metabolism is very important also the investigation of clinical and laboratory alterations that have direct or indirect relation with bone regeneration mechanisms and infant prematurity. Although there are several guidelines for preventing, screening and treating this high risk group for bone metabolic disorders, there is still lack of evidence and consensus (7, 8).

For the first time we investigate clinical and laboratory findings of bone metabolism in healthy premature and full term infants of our intensive care unit.

Material and methods

We examined forty neonates (20 preterm gestational age < 34 weeks and 20 full-term) who were hospitalized in the 2nd Neonatal Clinic Papageorgiou General Hospital, from 2011 to 2015. A prerequisite was the absence of pathological conditions and any medications that will directly affect bone mass in accordance with the criteria by Beyers et al. (9). Some of the strict inclusion criteria included any pregnancy disease such as chorionamnionits or viral infection, genetic syndromes, bone metabolic and rheumatological disorders, maternal smoking and alcohol, extensive use of antibiotics, diuretic, surfactants, corticosteroids, bronchopulmonary dysplasia, intraventricular hemorrhage and cholestasis.

The diet was the same for all infants. For every newborn it is recorded demographic data (sex, gestational week) and anthropometric data (body weight). Double blood samples after birth were collected and directly measured the biochemical markers of bone turnover, such as alkaline phosphatase (ALP, IU / ml), calcium (Ca, mg / dL), phosphorus (P, mg / dL) and magnesium (Mg, mg / dL) serum. The study was approved by the local ethics committee, and informed parental consent was obtained in all cases.

The statistical analysis was performed with SPSS statistical program (version 13.0) and Microsoft Excel (Windows Office 2003). It is calculated for each variable the mean and standard deviation (SD - Standard Deviation). We applied the t-test (t-test for paired observations) between the two groups of infants.
Also the Levene test was applied to test whether the differences in variations in the sample have emerged due to random sampling. Statistical significance was considered the p-value <0.05.

Results

In the group of premature babies, the ratio of male to female was 2:3 as opposed to full-term infants where male are predominant (7:3). The body weight, the biochemical parameters and the mean gestational week are demonstrated in Table 1. There is a significance difference in average serum ALP between premature than full-term infants (Figure 1). Slightly elevated values of Ca, P and Mg are observed in premature newborns (Figure 2). According to the statistical processing of data by Levene test, a statistically significant difference in gestational week is observed between the two groups, while according to the t-test, significant difference have gestational weeks, body weight and ALP (Table 2).

We observed a decline in ALP level with gestational age in preterm infants (inclination l = -18.568) and the fall of the enzyme activity with the increased body weight in the same group (Figures 3, 4). From the graphical representations relating serum Ca levels with body weight and gestational week in preterm neonates there were no significant alterations to observe (constant inclination) (Figures 5, 6). The gestational week seems to affect positively P levels in premature infants, in contrast with the constant metal concentration and body weight (Figures 7, 8). Finally it is observed an escalation of serum Mg level both on the body weight and gestational week (inclination l = 0.04) in preterm neonates (Figures 9, 10).

Discussion

Research concerning bone mineral metabolism is particularly important in high risk groups such as preterm neonates. Bone reconstruction is a silent process, especially in premature infants, so verification of reliable bone turnover markers is essential. So far few are the studies concerning healthy prema-

ture newborns and bone metabolism; therefore it is essential to investigate both preterm and full-term newborns. According to our results, the ALP mean level is significantly higher in premature infants compared to full-term but in normal range of values. Bone regeneration is a dynamic process that reflects upon ALP activity. Studies have shown that neonatal serum ALP is 90% of bone origin (1, 10, 11). The results of our study show a statistically significant difference of the mean values of ALP activity of the two groups. Crofton PM et al. have not identified a statistically significant difference of ALP between preterm and full-term neonates, but a difference in the

| Table 1 - Body weight, gestational week, sex ratio and biochemical parameters in premature and full-term neonates. Values are expressed in mean ± SD. |
|---------------------------------|------------------|------------------|
| Sex ratio (Male:Female)         | 2:3              | 7:3              |
| Body weight (gr)                | 1391 ± 471,5     | 3142 ± 421,14    |
| Gestational week                | 30,9 ± 2,98      | 38,2 ± 1,36      |
| Alkaline phosphatase (mg/dL)    | 262,3 ± 156,75   | 173,85 ± 58,2    |
| Calcium (mg/dL)                 | 8,97 ± 2,11      | 8,9 ± 0,79       |
| Phosphorus (mg/dL)              | 6,05 ± 1,09      | 5,97 ± 1,17      |
| Magnesium (mg/dL)               | 2,03 ± 0,44      | 2,02 ± 0,23      |

Figure 1 - Mean ALP activity in premature and full-term infants.
mean values (10). The difference of ALP activity between the
two study groups may be due to the dynamics of bone growth
that occurred after birth. It seems that the gestational week
plays an essential role in the ALP activity in preterm and full-
term infants, implicating those very premature infants are in
high risk for bone metabolic diseases with high mean values of
ALP (12-14).

Furthermore the differences between the mean concentrations
of Ca, P and Mg between the two study groups are rather
small. It seems that there is a certain increasing trend of Mg
and P levels in relation with gestational week in premature
neonates. Taking account that 60% of the total Mg concentra-
tion in the newborn is bone origin and the statistical significant
difference in average gestational week between the two

Clinical Cases in Mineral and Bone Metabolism 2017; 14(2):167-172
groups, it seems that the gestational week influence more than the body weight the alterations of the biochemical parameters of bone metabolism in preterm and full-term neonates. The differences in the mean levels of ALP and P in both groups agree with the results of previous studies, but in this study we have not observed significant difference in serum Ca levels (15). It

Figure 4 - Correlation of ALP activity and gestational week in premature neonates.

Figure 5 - Correlation of serum calcium concentration and body weight in premature neonates.

Figure 6 - Correlation of serum calcium concentration and gestational week in premature neonates.
must be emphasized that there are certain limitations in the use of these biochemical markers of bone metabolism. For example the concentration of serum P is correlated with the P concentrations in bone tissue. However serum Ca levels may be affected by other systemic metabolic disorders such as hypophosphatemia (6, 14). Our study clarifies the potential role of
gestational week in healthy premature infants on the final concentration in serum of certain metals mainly of Mg and P. In a study of 108 premature newborns, Faerk et al. argue that the high levels of ALP may be associated with high levels of serum P. According to their results there is no correlation between ALP and P with the total bone mineral density in premature neonates. It seems that the ALP acts as a carrier of P on the membrane of osteocytes, if there is a sufficient concentration of P in the body. Certainly a sufficient amount of Ca is needed to maintain the ratio of Ca:P in the creation of bone tissue. Therefore the physiological activity of the enzyme reflects the normal deposition rate of hydroxyapatite. However the reduced enzyme activity reflects to a certain deposition rate where the ratio of Ca level of the transmembrane vesicles with the P levels of bone tissue is always steady (15). Although in the current literature there are studies that suggest that ALP is not a reliable biochemical biomarker of bone metabolism in premature neonates (15-17), however it used until nowadays to identify premature infants with bone metabolic disorders (1, 6, 11, 18).

We concluded that gestational week and less the body weight is a factor in the assessment of biochemical markers of bone metabolism in healthy premature neonates. Alterations of basic metal concentrations and ALP which are observed in premature infants are not only due to reduced intake of nutrients. Very premature infants have significantly higher levels of serum ALP from full-term neonates with very small difference in serum metal concentrations. It seems that very premature healthy neonates have high serum ALP with lower serum levels of Mg and P. For this reason it is recommended the controlling of serum ALP, Mg and P for the assessment of bone metabolism status in premature neonates.

References