Increments in Whole Body Bone Mineral Content Associated With Weight and Length in Pre-Term and Full-Term Infants During the First 6 Months of Life

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Background. The objective of the present study was to assess bone mineral content (BMC) of the whole skeleton in pre-term and full-term healthy infants and the factors influencing BMC, such as bone area, birth weight, birth length, current weight, current length, gender, and gestational age.

Methods. Forty-eight healthy full-term infants and 34 healthy premature infants fed predominantly with intact human milk were studied. BMC was measured monthly with dual energy X-ray absorptiometry (DEXA). At the same time, length and weight were measured and registered. Pre-term infants were studied at 60-day intervals.

Results. For both full-term and pre-term infants, BMC increased during the first months of life. However, the values of pre-term infants never reached the values of full-term infants, even after correcting for age and weight. For both full-term and pre-term infants, BMC was significantly correlated at the second month with birth weight ($r = 0.901$), birth length ($r = 0.860$), gestational age ($r = 0.803$), bone area ($r = 0.960$), current weight ($r = 0.920$), and current length ($r = 0.840, p < 0.001$ for all correlation coefficients). Multivariate analysis revealed that bone area was the most important factor in predicting BMC.

Conclusions. Pre-term children have lower BMC than full-term children. The main factor explaining this apparent osteopenia is bone area. Pre-term children have a higher daily mineralization rate than full-term children, but this catch-up mineralization is not enough to reach BMC levels seen in full-term children. © 2001 IMSS. Published by Elsevier Science Inc.

Key Words: Bone mineral content, Bone area, Bone densitometry, Dual-energy X-ray absorptiometry, Full-term infants, Pre-term infants.

Introduction

Bone growing and maturation are key elements of normal child growth and development. By the last gestational trimester, the fetus accumulates 80% of the bone calcium, phosphate, and magnesium present at the time of birth. Premature children, especially those with very low weight (<1500 g), show lower skeletal mineralization level than full-term infants (1) and a higher risk for metabolic bone disease, including delayed longitudinal growth, osteopenia, and rickets (2,3). The incidence of metabolic bone disease among premature infants with birth weight <1000 g is up to 60%; it is negatively related to gestational age and directly related to disorders such as bronchopulmonary dysplasia and diuretic therapy (4,5).

Bone mineral content (BMC) is a measure of bone calcification. Bone mineral density (BMD) represents the ratio between BMC (g) and bone area (BA) (cm$^2$) measured during scanning. The latter index is not considered useful to assess true bone density in children because it may lead to size-related artifacts (6,7). Instead, indexes BMC for BA,
BA for length, and length for age have been recommended for clinical evaluation of patients with low BMC (7). For studying bone mineralization at early stages of life, plain X-ray films of the long bones are not useful, because bone loss can only be detected when it is >40% (8,9). Single photon absorptiometry and dual photon absorptiometry have been used to assess BMC at radius, humerus, and spine. Quantitative computed tomography scans are useful to assess the density of all bones, but the radiation dose that they deliver is too high for children (9–12). Dual energy X-ray absorptiometry (DEXA) is currently the most extensively employed method for measuring BMC in children because it delivers a low radiation dose, and the time required for the procedure is short (13,14). There are previous reports from cross-sectional studies on BMC of premature and full-term children using DEXA (15–17).

The reported prematurity rate in the urban area of Mexico City is 11.0–11.7%, and 9.8–10.0% of premature infants have low weight for gestational age (18,19). Despite these high prematurity indices, there is no published information from Mexico concerning skeletal mineralization in pre- and full-term infants.

The objective of the present study was to assess BMC of the whole skeleton in pre-indices and full-term healthy infants and the factors influencing it, such as bone area, birth weight, birth length, current weight, current length, gender, and gestational age.

Patients and Methods

Infants born at a tertiary-level care facility in Mexico City were included in the study upon receiving informed consent from parents. The protocol was approved by the local Ethics and Research Committee (October 7, 1995). Forty-eight full-term healthy infants and 34 pre-term infants who were predominantly breast-fed were studied. BMC was measured monthly for full-term infants during the first 5 months of extrauterine life and bimonthly for pre-term infants during the first 6 months of extrauterine life. Weight and length were assessed and registered at the same time. Data were available for only 37 full-term children in the first month, 35 in the second, 29 in the third, 18 in the fourth, and 16 in the fifth month of the 48 full-term children included in the study. The number of examinations per child ranged from one to five. Infants with five, four, three, two, and one examination during the study were 1, 16, 18, 7, and 6, respectively. Data were available for only 25 pre-term children in the second month, 27 in the fourth, and 26 in the sixth month of the 34 pre-term children studied. The number of examinations per child ranged from one to three. Infants with three, two, and one examinations during the study were 17, 12, and five children, respectively.

BMC was measured by a DEXA apparatus QDR-1500 (Hologic, Waltham, MA, USA) with an integrated software Infant Whole Body version 5.67P (Hologic) suitable for pediatric use. The energy for one of the beams is 70 kV and for the other, 140 kV. Radiation dose is 0.1 mRem. BMC of peripheral and axial skeleton is calculated as grams of calcium hydroxyapatite. The apparatus was calibrated daily against a synthetic calcium hydroxyapatite spine phantom. BMC showed a 2% variation coefficient with this apparatus, using the phantom for repeated measurements.

An infant pad was placed on the scanning table with the head of the child at the marked start line, assuring that the position was the same for all subjects. The study was carried out with the infants sleeping without sedation. The infants were placed lying on their backs and were restrained with a cotton blanket. Each infant underwent scanning only once for each scheduled visit. To induce sleep, infants were fed a few minutes prior to the study. When image quality was poor due to movements of the infant or to other causes, the measurement at that time-point was not included for analysis.

Weight was measured with a Kiltron Arizona electronic scale with 12-kg capacity and length with a Holtein-type infantometer. Gestational age was determined by the date of the mother’s last menstrual period and confirmed by ultrasonographic anthropometric measurements and Ballard examination (20). Corrected age (CA) was calculated by the following formula: CA = chronological age − (40 − gestational age at birth time). Individual daily increase of BMC corrected by body weight (∆BMC/BW/d) was calculated by the following formula:

$$\Delta \text{BMC}/\text{BW}/d = \Delta \text{BMC}(g)/\Delta \text{day} \times \text{sum of the two body weights(kg)}/2.$$  

Statistics. Differences between groups were assessed by Student t test or Mann-Whitney U test as applicable. Pearson r correlation coefficients were calculated between birth weight and BMC, birth length and BMC, and gestational age and BMC. Partial multiple correlation coefficients were calculated for BMC, BA, and current length and weight, correcting by group (full-term and pre-term). Two models of multivariate analysis were carried out by logistic regression, including and not including bone area in the model, to disclose the most important factors determining BMC. Differences were considered as significant with p values <0.05. All calculations were done with the statistical software package SPSS for Windows version 8.0 (SPSS, Chicago, IL, USA).

| Table 1. Baseline characteristics of the studied children |
|-------------|-------------|
| Term/N | Pre-term |
| n | 48 | 34 |
| Gender (F/M) | 22/26 | 18/16 |
| Birth weight (g) | 3,195 ± 323 | 1,294 ± 167.52 |
| Birth length (cm) | 50.4 ± 1.7 | 38.7 ± 2.7 |
| Gestational age (week) | 39 ± 0.9 | 30 ± 2.6 |
| Weight <10th percentile | 3 | 12 |

*According to Naeye (21). Data are expressed as mean ± standard deviation.
Results

Baseline characteristics of the infants are shown in Table 1. In Table 2, weight, length, BMC, bone area, and BMC adjusted for weight and length and Δ BMC/BW/d from the first through the fifth month of full-term children are shown.

BMC/weight ratio was stable in full-term infants for the entire follow-up period. Δ BMC/BW/d in full-term infants was higher during the first 2 months (0.16 ± 0.04 g/kg/d) and in the following months stabilized at approximately 0.09 g/kg/d.

Weight, length, bone area, BMC unadjusted and adjusted for weight and length, and Δ BMC/BW/d of pre-term infants considering the corrected age are shown in Table 3. There were significant differences of all these values among the second, fourth, and sixth months.

BMC and BA were significantly higher for full-term infants than for pre-term infants even after correcting for age. BMC/weight and BMC/length also showed statistically significant differences between full-term and pre-term children. When considering children of similar body weight, Δ BMC/BW/d was higher for pre-term than for full-term children. In the pre-term children weighing 5,742 ± 732 g, Δ BMC/BW/d was significantly higher (0.12 ± 0.02 g/kg/d) than in full-term children with similar body weight (5,976 ± 614 g) (0.095 ± 0.04 g/kg/d) (Tables 2 and 3). The relation of BMC and bone area for both full-term and pre-term children is shown in Figure 1. On the other hand, BMC was not related to gender.

Pooling together full-term and pre-term children, at the second month there was a significant bivariate correlation of BMC with birth weight \( r = 0.901, \ p < 0.001 \), BMC with birth length \( r = 0.860, \ p < 0.001 \), and BMC with gestational age \( r = 0.803, \ p < 0.001 \). A partial multiple correlation of BMC, weight, length, and bone area controlled by group is shown in Table 4. The highest correlation was found between BMC and BA, although the correlation was also significant between each pair of variables. Additionally, two logistic regression models were calculated considering both full- and pre-term infants. In the first model, current weight, current length, birth weight, and birth length were considered as predicting factors for BMC. In this model, current weight was the most important factor for predicting BMC. In the second model, when BA was added it became the most significant predictor of BMC (Table 5).

Discussion

In the present study, pre-term children had lower BMC than full-term children of the same postnatal age, as reported previously (1–3). This difference persisted even after correction for gestational age at time of birth. Atkinson et al. also

<table>
<thead>
<tr>
<th>Months</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>33 ± 4</td>
<td>63 ± 4</td>
<td>94 ± 11</td>
<td>126 ± 10</td>
<td>147 ± 6</td>
</tr>
<tr>
<td>n</td>
<td>37</td>
<td>35</td>
<td>29</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>4,220 ± 485</td>
<td>5,265 ± 618</td>
<td>5,976 ± 614</td>
<td>6,657 ± 752</td>
<td>7,016 ± 694</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>54.4 ± 1.8</td>
<td>58.1 ± 2.3</td>
<td>60.1 ± 2.0</td>
<td>63.0 ± 2.0</td>
<td>63.7 ± 2.3</td>
</tr>
<tr>
<td>BMC (g)</td>
<td>82.6 ± 11.9</td>
<td>103.8 ± 16.0</td>
<td>111.0 ± 15.1</td>
<td>129.3 ± 17.7</td>
<td>134.0 ± 20.0</td>
</tr>
<tr>
<td>Bone area (cm²)</td>
<td>377.71 ± 36.60</td>
<td>437.24 ± 61.84</td>
<td>467.65 ± 39.29</td>
<td>499.26 ± 43.31</td>
<td>521.01 ± 46.0</td>
</tr>
<tr>
<td>BMC/weight (g/kg)</td>
<td>19.5 ± 1.4</td>
<td>19.8 ± 2.0</td>
<td>18.6 ± 1.7</td>
<td>19.4 ± 1.0</td>
<td>19.2 ± 2.0</td>
</tr>
<tr>
<td>BMC/length (g/cm)</td>
<td>1.51 ± 0.18</td>
<td>1.78 ± 0.23</td>
<td>1.85 ± 0.23</td>
<td>2.05 ± 0.23</td>
<td>2.11 ± 0.29</td>
</tr>
<tr>
<td>Δ BMC/BW/day (g/kg/d)</td>
<td>—</td>
<td>0.16 ± 0.07 (24)</td>
<td>0.095 ± 0.04 (24)</td>
<td>0.096 ± 0.03 (14)</td>
<td>0.084 ± 0.03 (12)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. BMC: bone mineral content, BW: body weight. "p < 0.05 vs. each other; "p < 0.05 vs. second month. The number of children with a paired measurement with respect to the baseline is shown within parentheses.
The regression equation for full-term children was $y = 0.953x + 0.357$, $r^2 = 0.908$, $p < 0.001$. The regression equation for pre-term children was $y = 0.981x + 0.299$, $r^2 = 0.962$, $p < 0.001$.

reported that pre-term children show lower BMC than full-term children at the same gestational age, but the differences disappear when BMC is corrected for weight (22). However, in the present study the difference of BMC between full- and pre-term children persists even after correcting by weight (Tables 2 and 3); nonetheless, the gap tends to narrow as the children’s ages increase. Additionally, when BMC is plotted against BA the points display similar regression lines for both pre- and full-term children (Figure 1). This suggests that the apparent bone mineral deficit frequently reported in pre-term children is mainly the result of postnatal growth restriction.

BMC/weight ratio was stable at approximately 19.5 g/kg during the entire follow-up period in full-term children (Table 2), but in pre-term children it increased significantly from 14 g/kg at month 2 to 17 g/kg at month 6 (Table 3). These data suggest an important spontaneous post-discharge, catch-up mineralization in pre-term children.

Postnatal BMC increased throughout the follow-up period in both groups. Our values are similar to those reported in previous cross-sectional studies (16,17,23–25). The growth rate of the premature children while hospitalized was similar to the growth rate reported for other premature children (26).

For full-term children, body weight corresponds to the 50th percentile to month 4, but declines to the 25th percentile at month 5 when U.S. reference values (27) are considered, suggesting that individuals lost to follow-up were those with higher values of BMC and/or body weight. When Mexican reference values are considered (28), the weight values of our full-term children’s sample correspond to the 50–75th percentiles. The number of studied full-term children decreased progressively throughout the months of follow-up because their parents were less willing to bring them to the hospital because they appeared healthy. Full-term children also have higher neuropsychologic development; thus, it is more difficult to keep them immobilized to perform the study. This incomplete follow-up is a methodologic limitation of the present study.

It has been reported that premature children small for their gestational age (SGA) have lower BMC than premature children with adequate weight for their gestational age (AGA) (29,30). In contrast, we did not find BMC differences in SGA and AGA children (data not shown).

The index BMC/BA, commonly known as bone mineral density (BMD), is not in fact a density, because it only considers a bidimensional BA. The calculation of a true density would require the consideration of (tridimensional) bone depth, not available in DEXA scanning (7). Therefore, we do not report the results of BMD.

When analyzed univariately, BMC shows a high degree of correlation with bone area, length, and weight. If these variables are analyzed in a multivariate logistic regression without including BA in the model, the only significant predictor for BMC is current weight. When BA is introduced into the model, it becomes the most important predictor for BMC followed by current weight (Table 5). The interpretation of the high univariate association of length and weight to BMC and the lesser importance of these variables when analyzed together with BA in a multivariate regression model is that length and weight are strongly related to BA. In turn, the strong association of BA to BMC explains the majority of the association of length and weight to BMC. According to our data, gestational age exerts a significant effect on BMC as previously demonstrated (31). Additionally, as previously reported (25,32), we did not find gender differences of BMC. However, there is at least one report of gender-related differences of BMC and BMD (33).

BA and weight were the most important factors for BMC both for pre-term and full-term children during the first months of life. A similar observation of newborns aged 1–2 weeks has been reported (25).

In summary, we confirmed that pre-term children have lower BMC than full-term children. The main factor explaining this apparent osteopenia is BA. Pre-term children have a higher daily mineralization rate than full-term children; however, this catch-up mineralization is not sufficient to reach BMC levels observed in full-term children because pre-term children have persistent growth deficit reflected by lower BA. Gender does not appear to affect BMC and BMD in pre- or full-term children.

Table 4. Partial correlation coefficients corrected by group (full- and pre-term)

<table>
<thead>
<tr>
<th></th>
<th>Bone area</th>
<th>Length</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMC</td>
<td>0.96*</td>
<td>0.84*</td>
<td>0.92*</td>
</tr>
<tr>
<td>Weight</td>
<td>0.94*</td>
<td>0.92*</td>
<td>—</td>
</tr>
<tr>
<td>Length</td>
<td>0.90*</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*p <0.001.
Table 5. Logistic regression models including and not including bone area as a predictive factor for BMC, considering both full- and pre-term infants

<table>
<thead>
<tr>
<th></th>
<th>Without bone area</th>
<th>With bone area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p</td>
<td>OR 95% CI p</td>
</tr>
<tr>
<td>Bone area</td>
<td>NA</td>
<td>1.070</td>
</tr>
<tr>
<td>Current weight</td>
<td>1.004 NA</td>
<td>1.025–1.118 0.002</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1.000 0.999–1.003</td>
<td>1.000</td>
</tr>
<tr>
<td>Current length</td>
<td>1.030 0.792–1.339</td>
<td>0.990</td>
</tr>
<tr>
<td>Birth length</td>
<td>1.118 0.825–1.515</td>
<td>1.127</td>
</tr>
</tbody>
</table>

NA = not applicable, OR = odds ratio, 95% CI = 95% confidence interval.

Acknowledgments

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