Longitudinal Tracking of Dual-Energy X-ray Absorptiometry Bone Measures Over 6 Years in Children and Adolescents: Persistence of Low Bone Mass to Maturity

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Objectives Early assessment of bone mass may be useful for predicting future osteoporosis risk if bone measures “track” during growth. This prospective longitudinal multicenter study examined tracking of bone measures in children and adolescents over 6 years to sexual and skeletal maturity.

Study design A total of 240 healthy male and 293 healthy female patients, ages 6-17 years, underwent yearly evaluations of height, weight, body mass index, skeletal age, Tanner stage, and dual-energy x-ray absorptiometry (DXA) bone measurements of the whole body, spine, hip, and forearm for 6 years. All subjects were sexually and skeletally mature at final follow-up. Correlation was performed between baseline and 6-year follow-up measures, and change in DXA Z-scores was examined for subjects who had baseline Z < −1.5.

Results DXA Z-scores (r = 0.66-0.87) had similar tracking to anthropometric measures (r = 0.64-0.74). Tracking was stronger for bone mineral density compared with bone mineral content and for girls compared with boys. Tracking was weakest during mid- to late puberty but improved when Z-scores were adjusted for height. Almost all subjects with baseline Z < −1.5 had final Z-scores below average, with the majority remaining less than −1.0.

Conclusions Bone status during childhood is a strong predictor of bone status in young adulthood, when peak bone mass is achieved. This suggests that bone mass measurements in children and adolescents may be useful for early identification of individuals at risk for osteoporosis later in life. (J Pediatr 2014; - - - - -).

Due to the difficulties in longitudinally studying subjects from childhood to an elderly age, the contention that senile osteoporosis is the result of inadequate bone acquisition during growth lacks supporting data. This notion is supported, however, by knowledge that the prevalence of osteoporosis is substantially lower in men than women, and in subjects of African-American than European and Asian descent, as the result of sex and racial differences in bone mass that are already present in childhood.1-5 Additional support for this concept comes from studies showing a strong resemblance between mother–daughter bone traits and that this resemblance is present even before the daughters have begun puberty.6,7 If bone loss was indeed the exclusive determinant of late life bone mass, then one would not expect such a strong resemblance in bone traits between girls and mothers.

Peak bone mass is nearly achieved by the end of sexual and skeletal development.8,9 Early assessment of bone mass is only useful if bone measurements “track” during growth, with children who have low bone mass continuing to have low bone mass as they become young adults. We have previously shown that dual-energy x-ray absorptiometry (DXA) bone measures track longitudinally over 3 years during childhood and adolescence.10 The purpose of this prospective longitudinal multicenter study was to examine tracking of DXA bone measures in subjects from the same large pediatric cohort who were followed for 6 years and had reached sexual and skeletal maturity by the final follow-up. We hypothesized that tracking would be maintained over this longer period.

Methods

The study sample derived from the Bone Mineral Density in Childhood Study (BMDCS), a multicenter longitudinal study that examined bone accretion in a

| BMC | Bone mineral content |
| BMD | Bone mineral density (areal) |
| BMDCS | Bone Mineral Density in Childhood Study |
| BMI | Body mass index |
| DXA | Dual-energy x-ray absorptiometry |

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racially diverse cohort of 1554 healthy boys and girls in the
US.11 Subjects were recruited from July 2002 to November
2003 at 5 medical centers across the US. Consent and assent
were obtained from parents/guardians and participants
following institutional review board–approved protocols.
Detailed information about the study participants and proce-
dures has been published previously.11 In brief, the BMDCS
cohort represents healthy children with height, weight, and
body mass index (BMI) between the 3rd and 97th percentile
and no previous or current conditions that might affect bone
acquisition. The subjects were evaluated annually for up to 6
years.

At each visit, height, weight, and BMI were measured, and
Z-scores for sex and age were determined with the use of
normative data from the Centers for Disease Control and
Prevention 2000 growth charts. A pediatrician or pediatric
endocrinologist assessed sexual maturation based on breast
stage in girls and testicular volume in boys using the Tanner
criteria.12 A pediatric radiologist assessed skeletal maturity
on the basis of roentgenograms of the left hand and wrist ac-
cording to the method of Greulich and Pyle.13 DXA measures
were obtained on the same day.

In this work we examine the 533 subjects who completed
the full 6 years of follow-up and were sexually and skeletally
mature at final follow-up. Skeletal maturity was defined as
closure of the long bone physes, which occurs at a skeletal
age of 17 years in boys and 16 years in girls. Of the 1554 sub-
jects in the original BMDCS cohort, 977 completed the year 6
visit, with 533 of these being mature at final follow-up. The
mean ± SD chronological age of the 533 subjects at baseline
was 13.2 ± 1.8 years with a comparable skeletal age (13.5 ±
2.2 years) (Table I). At final follow-up, average
chronological and skeletal age were 19.2 ± 1.8 and 17.7 ±
0.9 years, respectively.

Whole-body, anteroposterior lumbar spine, nondominant
forearm, and left proximal femur DXA scans were performed
with Hologic, Inc (Bedford, Massachusetts) bone densitome-
ters (QDR4500A, QDR4500W, and Delphi A models) and
analyzed with pediatric software (Hologic, version 12.3).
Scanner calibration was described previously.11 The precision
errors were coefficients of variation <1.4% for bone mineral
content (BMC) and <1% for bone mineral density (BMD
[areal]) of the spine and whole body less head, and <1.7% for
BMD of all other sites.14 Standard and height-adjusted
DXA Z-scores were calculated via the appropriate black or
nonblack normative data for sex and age as reported previ-
ously by the BMDCS.11,15,16

### Statistical Analyses

Statistical analyses were conducted using Stata (version 12.0;
StataCorp LP, College Station, Texas). Pearson correlations
were performed between baseline anthropometric and DXA
measures and the same measures 6 years later. Correlations
were calculated by sex and by Tanner stage at baseline. Pear-
son correlations were also used to compare the change in
BMC and BMD Z-scores over 6 years to the change in
Z-scores for anthropometric measures.

To assess further changes over time, we categorized chil-
dren by their DXA Z-scores at baseline (≤−1.5, −1.5 to
1.5, or >1.5) and calculated the mean Z-score by baseline
category for each study year. Cutoffs of −1.5 and +1.5 were
used rather than −2.0 and +2.0 because the subjects were
required to be between the 3rd and 97th percentiles for
height, weight, and BMI, resulting in only a small number

### Table I. Baseline characteristics of the study subjects

<table>
<thead>
<tr>
<th>Developmental characteristics</th>
<th>Male (n = 240)</th>
<th>Female (n = 293)</th>
<th>All subjects (N = 533)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronological age, y</strong></td>
<td>13.7 (1.8)</td>
<td>12.8 (1.7)</td>
<td>13.2 (1.8)</td>
</tr>
<tr>
<td><strong>Skeletal age, y</strong></td>
<td>13.8 (2.3)</td>
<td>13.3 (2.0)</td>
<td>13.5 (2.2)</td>
</tr>
<tr>
<td><strong>Sexual maturation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner 1</td>
<td>24 (10%)</td>
<td>26 (9%)</td>
<td>50 (9%)</td>
</tr>
<tr>
<td>Tanner 2</td>
<td>47 (20%)</td>
<td>45 (15%)</td>
<td>92 (17%)</td>
</tr>
<tr>
<td>Tanner 3</td>
<td>31 (13%)</td>
<td>58 (20%)</td>
<td>89 (17%)</td>
</tr>
<tr>
<td>Tanner 4</td>
<td>48 (20%)</td>
<td>74 (25%)</td>
<td>122 (23%)</td>
</tr>
<tr>
<td>Tanner 5</td>
<td>90 (38%)</td>
<td>90 (31%)</td>
<td>180 (34%)</td>
</tr>
<tr>
<td><strong>Anthropometric characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height Z-score</td>
<td>0.2 (0.8)</td>
<td>0.2 (0.8)</td>
<td>0.2 (0.8)</td>
</tr>
<tr>
<td>Weight Z-score</td>
<td>0.3 (0.8)</td>
<td>0.5 (0.8)</td>
<td>0.4 (0.8)</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>0.3 (0.9)</td>
<td>0.5 (0.8)</td>
<td>0.4 (0.8)</td>
</tr>
<tr>
<td>DXA Z-score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole body less head BMC</td>
<td>0.0 (1.0)</td>
<td>0.2 (0.9)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>Whole body less head BMD</td>
<td>0.1 (1.0)</td>
<td>0.2 (0.9)</td>
<td>0.1 (0.9)</td>
</tr>
<tr>
<td>AP spine BMC</td>
<td>−0.1 (1.0)</td>
<td>0.1 (1.0)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>AP spine BMD</td>
<td>−0.1 (1.0)</td>
<td>0.1 (1.0)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>Hip total BMC</td>
<td>0.0 (1.0)</td>
<td>0.1 (1.0)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>Hip total BMD</td>
<td>0.0 (1.0)</td>
<td>0.1 (1.0)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>Hip neck BMC</td>
<td>0.0 (0.9)</td>
<td>0.1 (0.9)</td>
<td>0.1 (0.9)</td>
</tr>
<tr>
<td>Hip neck BMD</td>
<td>0.0 (1.0)</td>
<td>0.1 (1.0)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>One-third forearm BMC</td>
<td>−0.1 (0.9)</td>
<td>0.1 (0.9)</td>
<td>0.0 (0.9)</td>
</tr>
<tr>
<td>One-third forearm BMD</td>
<td>−0.1 (1.0)</td>
<td>0.1 (1.1)</td>
<td>0.0 (1.1)</td>
</tr>
</tbody>
</table>

AP, anteroposterior.
Continuous variables are shown as mean (SD); categorical variables are n (%).
Baseline Z-scores for anthropometric and DXA bone measures were close to 0 with SDs close to 1 (Table I). The tracking of DXA Z-scores over 6 years (r = 0.66-0.87) was similar in magnitude, or slightly greater, than the tracking of anthropometric measures (Table II). In general, tracking was stronger for BMC than for BMC and for height-adjusted DXA Z-scores compared with unadjusted Z-scores. Tracking also tended to be better for girls compared with boys.

When examined as a function of sexual maturity at baseline, tracking of unadjusted Z-scores was strong before puberty (Tanner 1; boys: r = 0.73-0.89, n = 24, girls: r = 0.83-0.93, n = 26) and after sexual maturity had been achieved (Tanner 5; boys: r = 0.74-0.85, n = 90, girls: r = 0.75-0.89, n = 90). However, tracking was weaker during puberty (Tanner 2-4; boys: r = -0.03 to 0.78, n = 126, girls: r = 0.56-0.88, n = 177), particularly in Tanner stage 3 (boys: r = -0.03 to 0.65, n = 31; girls: r = 0.60-0.75, n = 58) (Figure 1A; available at www.jpeds.com). Tracking generally improved with height adjustment, especially in Tanner stage 3 (Figure 1B).

There was a significant relationship between the change in BMC Z-scores and the change in Z-scores for height (r = 0.50-0.68) and, to a lesser extent, weight (r = 0.38-0.48). A similar, although weaker, relationship was observed for BMD Z-scores (r = 0.31-0.53 for height; r = 0.27-0.48 for weight). Almost all subjects with poor tracking of BMCZ-scores (change exceeding ±1.5) experienced a change in height in the same direction with a median magnitude of change of 0.3-1.7. Similar but weaker trends were observed for BMC Z-scores.

We examined the persistence of values at the tails of the distribution by categorizing children according to their baseline Z-score as low (<−1.5), high (>1.5), or intermediate (−1.5 to 1.5). Although regression towards the mean was observed over time, final Z-scores remained significantly different among subjects in the different baseline groups (Figure 2). Notably, among boys and girls who had initial Z-scores less than −1.5, almost all remained below the mean of normal (Z = 0) and the majority stayed less than −1.0 at final follow-up (Figure 3). This was true for both BMC and BMD, regardless of measurement site and whether Z-scores were adjusted for height (Figure 4; available at www.jpeds.com). Likewise, final values for subjects who had initial Z-scores >1.5 tended to remain above the mean (Figure 3). Only 3.8% of the children crossed from intermediate to low; 12 of 256 girls and 6 of 209 boys. We were not able to identify any characteristics distinguishing the children who crossed Z-score categories.

This study indicates that DXA measures of bone strength track through childhood until the time of skeletal and sexual maturity and this was true in both the axial and appendicular skeleton for both male and female subjects. On average, DXA measures of BMC and BMD during childhood accounted for
approximately 50%-70% of the variation observed 6 years later when subjects were mature. Almost all boys and girls with low bone mass (Z-score < −1.5) became young men and women with values for BMC and BMD less than the mean (Z-score < 0). These results corroborate previous findings indicating that the susceptibility for osteoporosis is present early in life.

Ample data suggest that the amount of bone accrued by skeletal maturity is the main contributor to peak bone mass, which, in turn, is a major determinant of osteoporosis and fractures in elderly subjects. We have also shown recently in the same cohort that bone mass during childhood is a predictor of pediatric fractures. Although the time of life when DXA values reach their peak has been of considerable controversy, most estimates indicate that bone mass does not significantly increase after the third decade. Because the degree of tracking during young adulthood should be comparable or greater than during growth, the findings of our study underscore the potential of these measures to predict bone mineral status in older adulthood. Support for this notion is that the degree of tracking for DXA measures of bone mineral accrual in our large, nationally representative cohort of healthy children was comparable with that of height and weight.

We were not able to identify any characteristics that predicted which subjects would cross Z-score categories, such as changing from low to intermediate or intermediate to low. Changes in bone status may have been related to growth, nutrition, changes in activity, or many other factors. It is important to recognize that although there is strong overall tracking of DXA Z-scores, it is still possible for the bone status of a given individual to worsen or improve.

The large sample of well characterized healthy children representative of the current US population, the relatively long follow-up period until skeletal maturity, and the highly standardized assessments of bone density measured by DXA are strengths of this study. The findings of this 6-year longitudinal study corroborate previous studies with shorter follow-ups suggesting that children retain their bone phenotypes throughout growth. Most studies to date, however, have been constrained by small sample sizes and/or BMD determinations using techniques not widely used in clinical practice. Our results are also consistent with smaller studies of pre- and early pubertal children that were followed for 7 to 8 years. However, the current study is limited to the natural history of bone mineral accrual in healthy children. Studies are needed for children who have chronic medical conditions that may alter bone mineral accrual and cause fluctuations in tracking.
Bone mineral status during childhood is a strong predictor of bone mineral status in the axial and appendicular skeletons in young adulthood. These results suggest that bone mass measurements may be useful for early identification of children at risk for osteoporosis later in life. They also provide a distinct example of how phenotypic traits, like genetic information, could assume a major role in personalized medicine and the customization of health care. Because current treatment for osteoporosis in the elderly does not significantly restore loss of bone, efforts should be directed toward developing preventive measures that increase bone accrual before the completion of skeletal maturity. Studies are needed to establish whether DXA bone measures associated with weaker bones in childhood can be altered as a result of simple nutritional, mechanical, or pharmacologic intervention.

![Figure 3](image-url)

**Figure 3.** Change between baseline and final (6-year) Z-scores for whole body less head BMC subdivided by baseline Z-score: >1.5 (top row), −1.5 to 1.5 (middle row), < −1.5 (bottom row). Similar trends were observed for other DXA bone measures. LH, less head.

References


Appendix

Collaborators in the pediatric endocrine divisions of each Bone Mineral Density in Childhood Study Group clinical center include: Children’s Hospital of Philadelphia: Andrea Kelly, David Langdon, Thomas Moshang, Steve Willi, Lorraine Katz, Charles Stanley, and Craig Alter; Children’s Hospital Los Angeles: Lynda Fisher, Mitchell Geffner, Debra Jeandron, Steven Mittelman, Pisis Pitukcheewanont, and Francine Kaufman; Cincinnati Children’s Hospital Medical Center: Susan Rose, Frank Biro, Peggy Stenger, Debbie Elder, and James Heubi; Columbia University Medical Center-St. Luke’s Hospital: Mary Horlick, Natasha Leibel, and Abeer Hassoun; and Creighton University: Jean-Claude Desmangles.

Data Safety and Monitoring Board members: Clifford Rosen, Ralph D’Agostino, Ingrid Holm, James Reynolds, and Reginald Tsang.

Figure 1. A, Whole body LH BMC and B, whole body LH height-adjusted BMC. Correlation between baseline and final (6-year) Z-scores for whole body less head BMC as a function of baseline Tanner stage. Similar trends were observed for other DXA bone measures.
Figure 4. Final height-adjusted Z-scores for subjects starting with adjusted Z < -1.5 at baseline.