Prediction Models for Evaluation of Total-Body Bone Mass With Dual-Energy X-Ray Absorptiometry Among Children and Adolescents

Mary Horlick, MD*‡; Jack Wang, MS*; Richard N. Pierson, Jr., MD*; and John C. Thornton, PhD*

ABSTRACT. Objective. The performance of dual-energy x-ray absorptiometry (DXA) in identifying children with decreased bone mass is increasing, but there is no consensus regarding how to interpret the results. The World Health Organization diagnostic categories for normal, osteopenia, and osteoporosis, based on T scores, are not applicable to children and adolescents who have not yet reached peak bone mass. The pediatric reference standards provided by DXA manufacturers have been questioned. Bone mineral density determined with DXA is “areal” density (a 2-dimensional measurement of a 3-dimensional structure), and its misleading nature among growing and maturing children is well recognized. Few published pediatric reference values for bone mineral density measured with DXA include factors that are known to affect the results besides age and gender. Our objective was to develop an algorithm for the evaluation of bone mass among children that included known determinants of bone mass and of its measurement with DXA.

Methods. Height, weight, pubertal status, and total-body bone mineral content, total-body bone area, and total-body bone mineral density measured with DXA were recorded for an ethnically diverse group of healthy pediatric subjects (n = 1218; age: 6–18 years). Prediction models for bone measurements were developed and validated with healthy pediatric subjects and then applied to children with medical disorders.

Results. There was a significant gender effect, as well as an interaction between gender and ethnicity. Separate models were developed for log total-body bone mineral content, log total-body bone area, and 1/total-body bone mineral density for girls and boys. The variability explained for each measurement increased from level 1, including age and ethnicity (76–86%), to level 2, including age, ethnicity, height, and weight (84–97%), and to level 3, including age, ethnicity, height, weight, and bone area (89–99%). Pubertal stage was an additional significant predictor of bone measurements but increased the explained variability by only 0.1% with height and weight in the models. The values predicted with each model were not different from measured values for the validation group but were different for patients with medical disorders. We propose an algorithm for evaluation of bone measurements that follows levels 1 to 3. Our findings suggest that application of this algorithm to well-characterized groups of pediatric patients could identify disease-specific features of DXA results. We recommend this approach as a basis for consensus regarding the clinical evaluation of pediatric bone mass, and we suggest that it could lead to meaningful classification of pediatric bone disorders, investigation of pathophysiologic processes, and development of appropriate interventions. Pediatrics 2004;114:e337–e345. URL: http://www.pediatrics.org/cgi/content/full/114/3/e337; pediatrics, bone mass, bone mineral density, ethnicity, dual-energy x-ray absorptiometry, algorithm.

Conclusions. These models, including known determinants of bone mass and of bone measurements with DXA, provide an evaluation of pediatric bone mass that proceeds in steps from level 1 to level 3. The outcomes were different for patients at risk for compromised bone mass, compared with healthy children, with specific patterns for each medical disorder. We propose an algorithm for evaluation of bone measurements that follows levels 1 to 3. Our findings suggest that application of this algorithm to well-characterized groups of pediatric patients could identify disease-specific features of DXA results. We recommend this approach as a basis for consensus regarding the clinical evaluation of pediatric bone mass, and we suggest that it could lead to meaningful classification of pediatric bone disorders, investigation of pathophysiologic processes, and development of appropriate interventions. Pediatrics 2004;114:e337–e345. URL: http://www.pediatrics.org/cgi/content/full/114/3/e337; pediatrics, bone mass, bone mineral density, ethnicity, dual-energy x-ray absorptiometry, algorithm.

ABBREVIATIONS. DXA, dual-energy x-ray absorptiometry; TBBMC, total-body bone mineral content; TBBMD, total-body bone mineral density; TBBBA, total-body bone area.

Achievement of optimal peak bone mineral mass is recognized as the best means of preventing osteoporosis in adulthood, which is a major public health problem.1,2 A recent meta-analysis characterized clinical decisions regarding the treatment of osteoporosis among adults as “complex, challenging, and fraught with uncertainty.”3 Prevention of this debilitating and painful condition is preferable and is especially important for a population with anticipated greater longevity.4 Because childhood and adolescence are the critical life periods for bone mineral accrual, a reliable method of identifying pediatric patients with skeletal compromise is essential for the development of prevention strategies.1,2 The ideal method for measuring pediatric bone mass should be safe, readily available, and easily performed for children of all ages. The measurement results should unambiguously identify individuals out of the normal range and should clearly gauge the efficacy of intervention. Dual-energy x-ray absorptiometry (DXA) satisfies the first set of requirements, but the interpretation of pediatric DXA results is controversial.5–8

The World Health Organization diagnostic categories for normal density, osteopenia, and osteoporosis based on T scores are not applicable to children and adolescents who have not yet reached peak bone mass. The pediatric reference standards provided by

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DXA manufacturers have been questioned. The misleading nature of areal bone mineral density measurements with DXA (bone mass for projected bone area, i.e., a 2-dimensional measurement of a 3-dimensional structure) among growing and maturing children has been recognized for years. Although several sets of pediatric reference values for DXA bone density measurements have been published, few include factors that are known to affect bone measurements besides age and gender, and there is no consensus regarding how to identify children with decreased bone mass. To compound this dilemma, the Food and Drug Administration has approved the use of DXA scans for bone mineral density measurements among children, and pediatricians are increasingly aware of the importance of evaluating bone mass among patients with frequent fractures or medical conditions known to affect bone. Therefore, radiologists are confronted with evaluating DXA scans for children without appropriate guidelines, and they interpret them using either T scores (leading to inappropriate diagnoses of osteoporosis) or z scores from the manufacturers’ questionable databases.

Total-body bone mineral content (TBBMC) measured with DXA, a validated measure of bone mineral mass, has been proposed as the best outcome measure for bone mass status during growth and maturation. We propose an algorithm for the interpretation of total-body DXA measurements that is based on prediction models for TBBMC, as well as for total-body bone area (TBBA) and total-body bone mineral density (TBBMD), developed with total-body DXA scans for 1218 healthy pediatric volunteers.

**METHODS**

**Subjects**

Volunteers (578 female subjects and 640 male subjects; age: 6–18 years) were recruited in New York City through local newspaper notices, announcements at schools and after-school centers, and word of mouth. Ethnicity was established on the basis of consistent Asian (n = 356), black (n = 279), Hispanic (n = 176), or white (n = 308) backgrounds for all 4 grandparents, as determined with a questionnaire. Subjects who did not meet these criteria were classified as other (n = 99). There were no height or weight restrictions for entry into the study. A medical history obtained from the parent or guardian and a physical examination performed at the time of the study visit confirmed normal health status. Pubertal stage was assessed, with the criteria described by Tanner, by the study physician or nurse for younger subjects and by self-assessment for subjects 11 to 12 years of age and older.

The results for 1218 subjects were used to create the prediction models. The models were validated with results from 65 scans of 54 new and follow-up subjects (age: 4–18 years). The results for a convenience sample of 39 pediatric patients with medical disorders (age: 5–19 years) were obtained either from volunteer body composition studies or from DXA scans requested for clinical reasons by the patients’ physicians.

Consent was obtained from each volunteer’s parent or guardian, and assent was obtained from each volunteer. Parental consent to use the results of the clinical DXA scans was obtained. The institutional review board of St. Luke’s-Roosevelt Hospital Center approved all studies.

### TABLE 1. Descriptive Statistics for Demographic and Bone Measurements for the Study Population (n = 1218)

<table>
<thead>
<tr>
<th>PS*</th>
<th>n</th>
<th>Age, y</th>
<th>Height, cm</th>
<th>Height, z Score†</th>
<th>Weight, kg</th>
<th>Weight, z Score†</th>
<th>TBBMC, g</th>
<th>TBBA, cm²</th>
<th>TBBMD, g/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All girls</td>
<td>578</td>
<td>11.4 ± 3.4</td>
<td>147 ± 16</td>
<td>147 ± 16</td>
<td>0.08 ± 1.07</td>
<td>45.8 ± 17.7</td>
<td>0.43 ± 1.11</td>
<td>1674 ± 643</td>
<td>1629 ± 414</td>
</tr>
<tr>
<td>1</td>
<td>214</td>
<td>8.0 ± 1.5</td>
<td>129 ± 10</td>
<td>0.09 ± 0.97</td>
<td>29.9 ± 9.1</td>
<td>0.19 ± 1.09</td>
<td>1054 ± 254</td>
<td>1210 ± 205</td>
<td>0.862 ± 0.070</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>10.5 ± 1.2</td>
<td>147 ± 7</td>
<td>0.35 ± 1.02</td>
<td>43.0 ± 9.8</td>
<td>0.50 ± 1.23</td>
<td>1443 ± 254</td>
<td>1536 ± 178</td>
<td>0.934 ± 0.070</td>
</tr>
<tr>
<td>3</td>
<td>99</td>
<td>12.3 ± 2.1</td>
<td>155 ± 8</td>
<td>0.35 ± 1.11</td>
<td>51.4 ± 12.2</td>
<td>0.56 ± 1.05</td>
<td>1887 ± 387</td>
<td>1818 ± 233</td>
<td>1.030 ± 0.097</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>14.5 ± 1.9</td>
<td>160 ± 7</td>
<td>0.38 ± 1.20</td>
<td>75.8 ± 11.9</td>
<td>0.42 ± 1.11</td>
<td>2201 ± 362</td>
<td>1966 ± 220</td>
<td>1.114 ± 0.081</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>15.4 ± 1.7</td>
<td>163 ± 7</td>
<td>0.19 ± 0.93</td>
<td>65.9 ± 15.1</td>
<td>0.85 ± 0.94</td>
<td>2485 ± 421</td>
<td>2101 ± 216</td>
<td>1.176 ± 0.097</td>
</tr>
<tr>
<td>All boys</td>
<td>640</td>
<td>11.6 ± 3.5</td>
<td>152 ± 20</td>
<td>0.22 ± 1.00</td>
<td>49.0 ± 19.6</td>
<td>0.55 ± 1.08</td>
<td>1882 ± 826</td>
<td>1784 ± 530</td>
<td>1.013 ± 0.152</td>
</tr>
<tr>
<td>1</td>
<td>122</td>
<td>8.0 ± 1.5</td>
<td>132 ± 10</td>
<td>0.23 ± 0.98</td>
<td>31.9 ± 10.0</td>
<td>0.54 ± 1.11</td>
<td>1140 ± 278</td>
<td>1277 ± 232</td>
<td>0.884 ± 0.066</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>11.0 ± 1.4</td>
<td>148 ± 9</td>
<td>0.25 ± 1.03</td>
<td>45.6 ± 12.9</td>
<td>0.62 ± 1.07</td>
<td>1585 ± 358</td>
<td>1626 ± 245</td>
<td>0.966 ± 0.083</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>13.5 ± 1.8</td>
<td>164 ± 11</td>
<td>0.25 ± 1.00</td>
<td>59.1 ± 15.5</td>
<td>0.58 ± 1.10</td>
<td>2233 ± 559</td>
<td>2068 ± 322</td>
<td>1.066 ± 0.112</td>
</tr>
<tr>
<td>4</td>
<td>98</td>
<td>15.0 ± 1.7</td>
<td>169 ± 10</td>
<td>0.02 ± 1.03</td>
<td>63.9 ± 15.4</td>
<td>0.37 ± 1.13</td>
<td>2581 ± 551</td>
<td>2261 ± 312</td>
<td>1.130 ± 0.104</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>16.0 ± 1.5</td>
<td>175 ± 7</td>
<td>0.33 ± 0.95</td>
<td>70.1 ± 12.0</td>
<td>0.59 ± 0.82</td>
<td>3083 ± 511</td>
<td>2490 ± 253</td>
<td>1.231 ± 0.100</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* PS indicates pubertal stage.

† z scores for height and weight for age were based on Centers for Disease Control and Prevention 2000 growth curves.

### TABLE 2. Variables Included in Regression Models for DXA Bone Measurements for Each Gender

<table>
<thead>
<tr>
<th>Level</th>
<th>Dependent Variable</th>
<th>Independent Variables</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBBMC*†</td>
<td>Age, Ethnicity, Height, Weight, TBBA, TBBMD†</td>
<td>0.847</td>
<td>0.813</td>
</tr>
<tr>
<td>2</td>
<td>TBBMC*†</td>
<td>Age, Ethnicity, Height, Weight, TBBA</td>
<td>0.858</td>
<td>0.819</td>
</tr>
<tr>
<td>3</td>
<td>TBBMC*†</td>
<td>Age, Ethnicity, Height, Weight, TBBA</td>
<td>0.759</td>
<td>0.757</td>
</tr>
</tbody>
</table>

P < .00001 for all models.

* log TBBMC was used for analysis.

† log TBBA was used for analysis.

‡ 1/TBBMD was used for analysis.
Measurement Methods

Body weight was measured to the nearest 0.1 kg with a balance-beam scale (Weight Tronix, New York, NY), and height was measured to the nearest 0.1 cm with a wall-mounted stadiometer (Holtain, Crosswell, Wales). Measurements of TBBMC (grams), TBBA (square centimeters), and TBBMD (grams per square centimeter) were obtained with DXA (Lunar DPX and DPX-L, pediatric software version 3.8G; Lunar Corp, Madison, WI). An anthropomorphic spine phantom composed of calcium hydroxyapatite embedded in a Lucite block (17.5 × 15 × 17.5 cm) was scanned, for quality control, on each working day before subject evaluation. The phantom was also scanned immediately before and after all DXA system manufacturer maintenance visits. The measured phantom bone mineral density was stable throughout the study period, at 1.166 to 1.196 g/cm². The coefficient of variation for repeated TBBMD measurements among adult subjects in our laboratory is 0.5%.

Statistical Analyses

Descriptive statistics were calculated for each variable and are reported as the mean and SD. Three sets of independent variables were used to develop models for TBBMC, TBBA, and TBBMD, with regression techniques.29 The first set of independent variables (level 1) included gender, ethnicity, and age, the second set (level 2) included gender, ethnicity, height, and weight, and the third set (level 3) included gender, ethnicity, age, weight, and bone area; boys: $r^2 = 0.987$; girls: $r^2 = 0.985$.

Fig 1. Measured versus predicted log TBBMC for 1218 healthy subjects (age: 6–18 years; 640 boys and 578 girls). A, Level 1 (age and ethnicity; boys: $r^2 = 0.847$; girls: $r^2 = 0.813$); B, level 2 (age, ethnicity, height, and weight; boys: $r^2 = 0.959$; girls: $r^2 = 0.956$); C, level 3 (age, ethnicity, height, weight, and bone area; boys: $r^2 = 0.987$; girls: $r^2 = 0.985$).
height, and TBBA. Nonlinear models were investigated. The BoxCox family of transformations was used to determine whether the dependent variable should be transformed and to identify the type of transformation to be used. Transformations of the independent variables, products, and powers were also considered. The backward elimination technique was used to identify a minimal subset of the independent variables required to model the dependent variable. Residual analyses were performed to evaluate the ability of the model to describe the data. The models were also evaluated with a comparison of the predicted values obtained from the model with the measured values for a set of new and follow-up studies (these data were not included in the data used to develop the models). A paired t-test was used to test the hypothesis that the mean predicted value was equal to the mean measured value. Separate analyses were performed for each variable.

All statistical calculations were performed with the Stata statistical software package (version 6) for personal computers (Stata Corp, College Station, TX). The level of significance for all statistical tests was .05.

RESULTS

Descriptive statistics for demographic data and bone measurements for the study group are presented in Table 1. There was a significant gender effect for all 3 dependent variables. Therefore, separate regression models were developed for log TBBMC, log TBBA, and 1/TBBMD for girls and boys (Table 2). Plots of measured versus predicted values for log TBBMC for girls and boys with the models for level 1 (age and ethnicity), level 2 (age, ethnicity, height, and weight), and level 3 (age, ethnicity, height, weight, and bone area) are presented in Fig 1. Examples of the prediction equations (level 3 for log TBBMC and 1/TBBMD) are presented in Table 3.

There was significant interaction between gender and ethnicity. The “other” ethnic group appears in the models (Table 3) but, because these subjects represented a variety of backgrounds that were not the same for girls and boys, the statistical differences identified are not reported as ethnic effects. Pairwise comparisons between ethnic groups for the 3 bone measurements at all levels are presented in Table 4. For both boys and girls, the major difference at level 3 (with height, weight, and bone area in the models) for log TBBMC and 1/TBBMD was between black subjects and all others. The most ethnic differences for girls were at level 2 for log TBBA and for boys were at level 1 for all 3 bone variables and at level 2 for log TBBMC. For girls only, there were interactions between ethnicity and age at levels 1 and 2 for TBBA, between ethnicity and weight at level 2 for log TBBA and 1/TBBMD, and between ethnicity and height at level 2 for 1/TBBMD. For boys, the ethnic effect involved significant differences in intercepts at levels 1 and 2 for all 3 dependent variables, but there were no interactions between ethnicity and other independent variables.

At levels 2 and 3, with height and weight in the models, there was a significant effect of weight of >35 kg (level 3 in Table 3). This is the cutoff value for the use of pediatric or adult scan mode, according to the manufacturer’s instructions. The intercepts differed at levels 2 and 3 for all bone measurements for both girls and boys with weights of >35 kg. There were interactions between weight of >35 kg and both TBBA and weight for both girls and boys.

Pubertal stage was also a significant independent determinant, but its addition to the models resulted in little change in $r^2$ or SE of the estimate when body size variables were included (Table 5). For example, the $r^2$ value increased from 0.987 for level 3 for log TBBMC for boys to 0.988 with the addition of puber-

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TABLE 3. Level 3 Prediction Equations for Log TBBMC and 1/TBBMD

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Weight of ≥35 kg</th>
<th>Weight of &lt;35 kg</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log TBBMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female ($r^2 = 0.99$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4.153</td>
<td>4.173</td>
<td>Intercept + 0.088 age - 0.008 age$^2$ + 0.0002 age$^3$ - 0.071 log weight (kg) + 0.005 height (cm) - 0.516 log TBBA</td>
</tr>
<tr>
<td>Black</td>
<td>4.109</td>
<td>4.130</td>
<td>Intercept + 0.088 age - 0.008 age$^2$ + 0.0002 age$^3$ - 0.071 log weight (kg) + 0.005 height (cm) - 0.516 log TBBA</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.130</td>
<td>4.151</td>
<td>Intercept + 0.088 age - 0.008 age$^2$ + 0.0002 age$^3$ - 0.071 log weight (kg) + 0.005 height (cm) - 0.516 log TBBA</td>
</tr>
<tr>
<td>White</td>
<td>4.145</td>
<td>4.165</td>
<td>Intercept + 0.088 age - 0.008 age$^2$ + 0.0002 age$^3$ - 0.071 log weight (kg) + 0.005 height (cm) - 0.516 log TBBA</td>
</tr>
<tr>
<td>Male ($r^2 = 0.89$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4.362</td>
<td>4.114</td>
<td>Weight of ≥35 kg: intercept + 0.023 age - 0.001 age$^2$ + 0.003 height (cm) - 0.491 log TBBA - 0.074 log weight (kg)</td>
</tr>
<tr>
<td>Black</td>
<td>4.343</td>
<td>4.095</td>
<td>Weight of ≥35 kg: intercept + 0.023 age - 0.001 age$^2$ + 0.003 height (cm) - 0.491 log TBBA - 0.074 log weight (kg)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.356</td>
<td>4.109</td>
<td>Weight of ≥35 kg: intercept + 0.023 age - 0.001 age$^2$ + 0.003 height (cm) - 0.491 log TBBA - 0.074 log weight (kg)</td>
</tr>
<tr>
<td>Other</td>
<td>4.370</td>
<td>4.123</td>
<td>Weight of ≥35 kg: intercept + 0.023 age - 0.001 age$^2$ + 0.003 height (cm) - 0.491 log TBBA - 0.074 log weight (kg)</td>
</tr>
<tr>
<td>White</td>
<td>4.369</td>
<td>4.121</td>
<td>Weight of ≥35 kg: intercept + 0.023 age - 0.001 age$^2$ + 0.003 height (cm) - 0.491 log TBBA - 0.074 log weight (kg)</td>
</tr>
</tbody>
</table>

---
The final models were tested with 54 subjects who underwent 65 scans (age: 4–18 years), and the predicted values were not different from the measured values (log TBBMC: $P = .6412$ at level 3; log TBBA: $P = .3214$ at level 2; 1/TBBMD: $P = .6430$ at level 3). For 39 patients with medical disorders known to affect bone mass, however, the differences between predicted and measured values were significant (Table 7), with a different z score pattern for each disorder.

### DISCUSSION

These prediction models adjust for the effects of body and bone size on total-body bone measurements for gender and ethnicity at a given age. Serial application of levels 1 to 3 allows evaluation of the contributions of height and weight and then bone size (estimated as 2-dimensional bone area with DXA) to total-body bone mass for an individual, compared with the expected effects of these variables on bone mass among healthy subjects of the same gender, age, and race. If adjustment for these variables results in appropriate values for the patient’s reference group, then intrinsic bone mass compromise is unlikely. However, if adjustment yields lower-than-expected values, then a deficit in bone mineral mass is suggested. The pediatrician’s clinical approach to a patient whose results are consistent with small body size or small bones would differ from that for a patient with low bone mass that is independent of body and bone size. An algorithm for the evaluation of bone mass among pediatric patients with the use of levels 1 to 3 for TBBMC is presented in Fig 2.

The application of this approach to a small convenience sample of pediatric patients yielded results that were significantly lower than those for the healthy population, with a different pattern of z scores for each diagnosis (Table 7). This suggests that use of this algorithm for DXA bone measurements among well-characterized clinical groups may reveal disease-specific features of bone mass compromise.

The problematic nature of measuring “areal” bone mineral density by DXA among growing children has been addressed in several ways. Previous prediction models for total-body DXA bone parameters have included the same independent variables as in this study, but none have combined them all. For example, Molgaard et al suggested a 3-step approach to check for short bones (height for age), narrow bones (TBBA for height), and light bones (TBBMC for TBBA). However, age was an additional significant contributor in all of our models and in previous work of others, so that TBBA for a given height and TBBMC for a given TBBMD varied with age. A recent article proposed determination of "possible osteopenia" on the basis of TBBMC or TBBMD for age and height for age, followed by differentiation of "primary, secondary, or mixed bone defects" on the basis of the ratio of TBBMC to total-body lean mass, as assessed with DXA. Although this approach may contribute to an understanding of the cause of decreased bone mass,
TABLE 7. z Scores for TBBMC, TBBA, and TBBMD for 39 Pediatric Patients With Medical Disorders

<table>
<thead>
<tr>
<th>n</th>
<th>Age, y</th>
<th>Level 1‡</th>
<th>Level 2†</th>
<th>Level 3¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TBBMC</td>
<td>TBBA</td>
<td>TBBMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>15.1 ± 2.8</td>
<td>-2.4 ± 1.6§</td>
<td>-2.1 ± 1.6§</td>
<td>-2.9 ± 1.8§</td>
</tr>
<tr>
<td>9</td>
<td>9.6 ± 3.7</td>
<td>-1.2 ± 1.1§</td>
<td>-1.1 ± 1.2§</td>
<td>-1.3 ± 1.3§</td>
</tr>
<tr>
<td>7</td>
<td>14.1 ± 1.8</td>
<td>-1.8 ± 1.5§</td>
<td>-1.6 ± 1.5§</td>
<td>-1.8 ± 1.5§</td>
</tr>
<tr>
<td>13</td>
<td>12.1 ± 4.2</td>
<td>0.7 ± 1.2</td>
<td>-0.4 ± 1.1</td>
<td>-1.1 ± 1.4§</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* z score for age, gender, and ethnicity.
† z score for age, gender, ethnicity, height, and weight.
‡ z score for age, gender, ethnicity, height, weight, and bone area.
§ p < .05, compared with z score of 0.

TABLE 6. Predicted Values for Log TBBMC at Levels 1 to 3 With Models With and Without Pubertal Stage (n = 58)

<table>
<thead>
<tr>
<th>Level</th>
<th>Measured TBBMC, g*</th>
<th>Predicted With PS, g†</th>
<th>Predicted Without PS, g‡</th>
<th>Predicted With PS – Predicted Without PS, g (% of Measured TBBMC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1451</td>
<td>1477</td>
<td>1459</td>
<td>18 (1.2%)</td>
</tr>
<tr>
<td>2</td>
<td>1451</td>
<td>1423</td>
<td>1425</td>
<td>-2 (0.1%)</td>
</tr>
<tr>
<td>3</td>
<td>1451</td>
<td>1456</td>
<td>1458</td>
<td>-2 (0.1%)</td>
</tr>
</tbody>
</table>

PS indicates pubertal stage.
* Mean measured value for 58 subjects of known pubertal stage whose results were not used to develop models for levels 1 to 3.
† Mean predicted value; value is the antilogarithm of the mean value for log TBBMC.
‡ Mean measured value for 58 subjects of known pubertal stage whose results were not used to develop models for levels 1 to 3.
§ Mean predicted value; value is the antilogarithm of the mean value for log TBBMC.

it does not advance the clinical definition of decreased bone mass or pediatric osteopenia.

Another approach to addressing the limitations of areal bone mineral density measurements is to estimate volumetric density (bone mineral apparent density), ie, bone mineral content assessed with DXA divided by volume calculated with formulas from the 2 dimensions of bone measured with DXA.²⁸,³¹,³² Nevill et al¹³ recently questioned the underlying assumption of estimated bone mineral apparent density, which is that bone size is the only confounding variable. Their models for the bone mineral content of L2-L4 vertebrae among healthy adolescents suggested that the effects of gender, age, body size, and maturation must be included for appropriate assessment of bone mass acquisition. This is what we have attempted to do. However, there is no overall consensus regarding the interpretation of pediatric DXA results.²⁴ Indeed, 1 group of investigators used different approaches to DXA in each of 3 recent reports on different pediatric clinical groups, making comparisons of findings for each group difficult.¹⁷,¹⁸,³⁵

The observed small contribution of pubertal stage to the explanation of the variability in bone results or the prediction of bone measurements with these models (Tables 5 and 6) may seem surprising, given the relationship of pubertal hormones to growth and bone mass accrual. We suggest that this is attributable in large part to the cross-sectional study design and does not negate the importance of puberty for achievement of optimal peak bone mass. The subjects were healthy and had normal pubertal timing; therefore, the gender, ethnicity, age, and body and bone size variables contained much of the “pubertal” information, and pubertal stage itself added little additional explanatory information for the variability in DXA results, as evident in Tables 5 and 6. As noted by Tanner and Whitehouse,³⁰ literature dating back to the 19th century demonstrates the fallacy of using cross-sectional data to evaluate changes associated with puberty. Longitudinal studies with serial pubertal examinations may identify the specific contributions of puberty to bone measurements with DXA.

The wide range of body sizes at each stage of puberty means that the known overestimation of bone density with DXA for large individuals and the underestimation for small individuals would not be addressed with adjustment for pubertal stage alone, without body size variables. A practical advantage of prediction models without pubertal stage is that the variables used are all routinely obtained in bone density assessment units (age, gender, ethnicity, height, and weight) or from the scanner output (bone area), whereas pubertal stage is not. We suggest that serial z scores based on these models from a cross-sectional healthy reference population can indicate an individual child’s “catch up” in bone mass, much as pediatricians use changes in height z scores for age and gender (ie, not pubertal stage), based on the cross-sectional Centers for Disease Control and Prevention 2000 growth curves,³⁰ to monitor catch-up growth in stature.

Although the specific models for levels 1 to 3 in this study are applicable only to total-body scans with the scanner model used in this project, the principle used to develop the models is applicable to all scanners and sites, if specific scanner characteristics are taken into account.²⁵,³⁷ For example, the difference in prediction models for subjects ≥35 kg and <35 kg reflects the cutoff point between pediatric and adult scan modes, which is unique to this scanner and manufacturer. There is a difference in absolute values between scans performed in pediatric
Level 1
Age, sex, and ethnicity

Level 2
Age, sex, ethnicity, height, and weight

Level 3
Age, sex, ethnicity, height, weight, and bone area

Fig 2. Algorithm for assessment of TBBMC. The full algorithm includes z scores for TBBA and TBBMD.

and adult modes for the same individual; therefore, we recommend that 2 scans be performed at the visit at which a patient first meets the criteria for the adult mode, ie, 1 in pediatric mode and 1 in adult mode, so that the absolute values can be compared as needed. Our models account for this, and z scores for scans in pediatric mode can thus be compared with subsequent z scores for scans in adult mode. For clinical application, these models and models for other scanners and sites could be incorporated into software programs that would yield z scores in a clear, straightforward, algorithm format.

The primary goals of pediatric bone mass measurement are identification of groups of children at risk for not achieving adequate peak bone mass and identification of individuals at risk for morbidity during childhood and adolescence. Our objective was to develop an evaluation in steps that could separate the influence of factors known to affect DXA measurements from actual compromise in bone mass, while avoiding overcorrection that might mask clinically significant deficits in bone mass. Application of this approach to total-body scans for a convenience sample of clinical patients (Table 7; Fig 2) revealed different patterns of z scores for the 3 levels of evaluation for each clinical group. For example, for children with fractures, the mean z scores for TBBMC and TBBA for age, gender, and ethnicity (level 1) were normal, but values decreased with adjustment for body size (level 2) and this decrease persisted with additional adjustment for bone area (level 3). The mean z scores for the other groups were all low at level 1; scores increased at level 2 for patients with celiac disease and at level 3 for patients with sickle cell disease but remained low for patients with Crohn’s disease. This was a convenience sample of patients, but the findings suggest that consistent application of this algorithm to well-characterized clinical groups of patients could identify disease-specific features of DXA results, including bone measurement characteristics and threshold values for bone fragility. This is what has been missing in pediatric bone mass assessments to date, namely, the relationship of bone measurements to clinical outcomes.

Candidate clinical groups deserving characterization with these methods include children with symptoms such as repeated fractures or with medical conditions or treatments known to affect growth and bone mineral accrual. Because there is a strong genetic influence on bone mass, children with a family history of osteoporosis may also be candidates.

Pediatricians currently try to enhance the modifiable factors that affect bone mineral accrual, such as calcium intake, vitamin D status, and weight-bearing conditions.
exercise, for children at risk for bone mass compromise, but there is a need for specific intervention trials with uniform outcome criteria and monitoring strategies including clinical outcomes. We suggest that the approach presented in this study could provide the basis for consensus regarding clinical evaluation of pediatric bone mass and could lead to meaningful classification of pediatric bone disorders, investigation of pathophysiologic processes, and development of appropriate interventions to be used in clinical trials.

Consistent interpretation of pediatric scan results could also lead to the use of DXA data to assess geometric features associated with bone strength, for example, as well as bone mass, and could suggest strategies to enhance the bone health of children at risk. This endeavor is consistent with the major goals of pediatric medicine, namely, treatment of children and prevention of adult disease.

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REFERENCES


Prediction Models for Evaluation of Total-Body Bone Mass With Dual-Energy X-Ray Absorptiometry Among Children and Adolescents
Mary Horlick, Jack Wang, Richard N. Pierson, Jr. and John C. Thornton
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