Peripheral Quantitative Computed Tomography (pQCT) Bone Measurements in Children With Cystic Fibrosis

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Summary. Background: Individuals with cystic fibrosis (CF) have low bone density and increased fracture risk. Methods: Cross-sectional study investigating whole body bone mineral content (WBBMC), bone geometry and strength in 12 children with CF compared to 23 age- and sex-matched controls with and without adjusting for age, height, and body composition. Results: CF group had lower WBBMC than controls ($P=0.007$) with larger differences at older ages (age-by-group, $P=0.08$). CF group had decreased height ($P=0.006$), a trend of lower lean mass per height ($P=0.08$), and no difference in relationship between WBBMC and lean mass compared to controls ($P=0.65$). Periosteal and endosteal circumferences were smaller in CF (each, $P=0.02$). Positive relationships of cortical area and bone strength with age were attenuated with CF (group-by-age; each, $P<0.01$). Conclusion: Children with CF have similar WBBMC relative to lean mass as controls. Cortical bone area and bone strength were less in CF group compared to controls, with greater differences in older children. 

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Key words: DXA; bone size; bone strength; cystic fibrosis; whole body bone mineral content.

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INTRODUCTION

Cystic fibrosis (CF) patients are at risk for nutritional deficiencies and chronic illness resulting in low body weight and attenuated linear growth. Compared to healthy children, children with CF have reduced weight and length at, or shortly after, birth and throughout infancy.1,2 They are oftentimes below the national average in both height and weight for the duration of their childhood.3

Individuals with CF have been documented to have low bone mineral density (BMD)4 and increased fracture rate as early as adolescence.5 Although the etiologies involved are not fully understood and have not been elucidated, a popular theory is decreased nutrient absorption in patients with CF results in vitamin D and calcium deficiencies. This malnutrition exacerbates secondary disease outcomes and is thought to contribute to the impaired bone metabolism and mineralization.6 Another potential consideration is children with CF may have reduced vigorous physical activity compared to healthy children,7 which may further decrease muscular gain and periosteal expansion.8,9 As these children move into adulthood, bone complications worsen, and fracture rates, including vertebral fractures, are higher than those without the disease.10

Dual energy X-ray absorptiometry (DXA) is the current clinical gold standard to diagnose low areal BMD (aBMD) and there has been recent development of a 4-step algorithm for investigating whole body bone mineral content (WB BMC) in relation to height and total body lean mass in children with chronic diseases.11,12 In addition, DXA-based testing does not account for bone size that may be useful in determining bone strength. Peripheral quantitative computed tomography (pQCT) is a technology that is able to measure bone size, as well as

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determine the volumetric bone mineral density (vBMD) and estimate bone strength. Accordingly, the purpose of this paper was to examine WB BMC using the 4-step algorithm and to investigate vBMD and geometric bone properties of children with CF compared with healthy sex-and age-matched controls.

METHODS

Subjects

Twelve participants aged 7–18 years with CF were a convenience sample recruited from a Pediatric Cystic Fibrosis Center or during the South Dakota Annual Cystic Fibrosis Day event held at Sanford Children’s Specialty Clinic. For each participant diagnosed with CF, two sex- and age-matched controls (within 2 years of age) were randomly selected from a current database of children in the same geographic region. Inclusion criteria for cases included an age between 5 and 18 years, documented elevation of sweat chloride concentrations, and willingness or parent or guardian to sign informed consent. Controls with chronic diseases or receiving medications known to influence calcium or bone metabolism (cancer, major gastrointestinal disease, diabetes mellitus; oral steroids, anticonvulsants, immunosuppressants) were excluded. Because all participants were minors, a parent or legal guardian signed the informed consent document and verbal assent was obtained from the child. South Dakota State University and University of South Dakota Institutional Review Boards approved the study protocol.

Procedures

Study personnel completed a medical questionnaire, including medication history and usage, with each child and guardian. Participants were weighed to 0.1 kg on a digital scale (Seca Model 770, Hamburg, Germany) and measured without shoes on a stadiometer (Seca Model 225, Hamburg, Germany) to the nearest 0.5 cm. Three-day dietary records were obtained and analyzed using Nutritionist V software (First Data Bank, San Bruno, CA). Pubertal development was assessed for children with CF using the Tanner self-report of pubic hair for males and breast development for females. A testicular examination was not performed. Body composition and bone measurements of the whole body were performed using a Hologic QDR 4500 (Bedford, MA version 12.3). Measurements of the left distal radius were obtained using a Norland-Stratec XCT2000 densitometer (Pforzheim, Germany). Arm length was measured from the elbow to the ulnar styloid process where a scout view was taken to identify the most distal aspect of the radius. Cross-sectional slices were obtained at the 4% and 20% of the measured arm length from the distal radius using a voxel size of 0.4 mm and a scan speed of 30 mm/s with a one-block rotation. The slices were analyzed using ContMode 2, Peel Mode 2, and a threshold of 400 mg/cm³ to obtain trabecular vBMD (4% site only). Cortical vBMD at the 4% site was not determined due to partial volume effects with small cortical thicknesses. Cortical bone at the 20% site was identified using CortMode 1 with a density threshold of 280 mg/cm³ for polar stress strain index (pSSI) and a threshold of 710 mg/cm³ for all other bone outcomes. Cortical thicknesses and perosteal and endosteal circumferences were calculated using the circular ring procedure. The polar stress strain index (pSSI) at the 20%, a measure of torsional bone strength, is based on structural and material properties obtained by pQCT.

Statistical Analysis

All statistical analyses were performed using SAS® statistical software (SAS® Institute, Cary, NC). Group differences were identified utilizing a mixed model approach. In order to account for matching, an identification variable for the matched case and its two controls was entered into the model as a random effect. Covariates included were age, lean mass, fat mass, and height. The significance of the group-by-age and group-by-height interaction terms were determined to identify whether the relationships between the bone measurements and age or height were similar between groups while adjusting for lean mass and fat mass. Bone measurements included whole body BMC by DXA and cortical BMC (mg/mm), cortical vBMD (mg/cm³), cortical area (mm²), cortical thickness (mm), periosteal circumference (mm), endosteal circumference (mm), and pSSI (mm³) at the 20% site and trabecular vBMD at the 4% site by pQCT.

RESULTS

Twelve (5 male) children with CF aged 7–18 years were enrolled. Mean (± sem) percent-predicted forced expiratory volume (FEV1) was 87.1 ± 5.5%. Nine of the children were receiving enzymes and 3 were not. Eight of the children had the F508del mutation, 2 were not identified and 2 had not had CF genetic testing. One child with CF (female, aged 12 years) was receiving insulin for CF-related diabetes. None of the other children with CF had evidence of glucose intolerance and none of the children were receiving glucocorticoids. Six children with CF were Tanner stage 1, three were Tanner stages 2 or 3, and three were Tanner stages 4 or 5.

Anthropometric and nutrient intake data for CF and control children are given in Table 1. Although the two groups were age-matched within 2 years of age all the control children were older than children with CF resulting in a statistically significant age difference, with a mean difference of 0.8 years (range 0–1.9). Children with CF weighed less (weight Z-score, $P = 0.001$) and were shorter
TABLE 1—Anthropometric Measurements and Nutrient Intakes by Disease Status

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>Controls</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (male)</td>
<td>12 (5)</td>
<td>23 (10)</td>
<td>—</td>
</tr>
<tr>
<td>Age (year)</td>
<td>11.8 ± 0.9</td>
<td>12.4 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Anthropometrics**

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>Controls</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>36.1 ± 4.8</td>
<td>49.2 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight z-score</td>
<td>-0.35 ± 0.30</td>
<td>0.50 ± 0.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>143.8 ± 4.9</td>
<td>152.7 ± 4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height z-score</td>
<td>-0.64 ± 0.33</td>
<td>0.18 ± 0.27</td>
<td>0.02</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>28.8 ± 3.8</td>
<td>36.8 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>6.6 ± 1.4</td>
<td>11.4 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Body fat</td>
<td>18.0 ± 1.8</td>
<td>22.4 ± 1.6</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Nutrient intake**

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>Controls</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/day)</td>
<td>1016 ± 216</td>
<td>1118 ± 145</td>
<td>0.66</td>
</tr>
<tr>
<td>Vitamin D (IU/day)</td>
<td>586 ± 97</td>
<td>235 ± 59</td>
<td>0.007</td>
</tr>
<tr>
<td>Total energy (kcals/day)</td>
<td>4548 ± 1309</td>
<td>1988 ± 813</td>
<td>0.11</td>
</tr>
</tbody>
</table>

DP values from paired analysis using mixed models.

(height Z-score, P = 0.02) than their age- and sex-matched controls. Nutrient intakes were similar, except for a greater vitamin D intake among children with CF (P = 0.007).

**Four-Step Algorithm for Investigating Whole Body BMC**

The relationships, defined in the 4-step algorithm, between WB BMC and age, height and age, lean mass and height, and BMC and lean mass for children with and without CF are shown in Figure 1. Children with CF had lower BMC than control children (P = 0.007), and the relationship between BMC and age was slightly attenuated in children with CF with the difference between children with CF and controls becoming larger at older ages (Panel A: age-by-group interaction, P = 0.08). Panel B shows the decreased height among children with CF at all ages (group differences, P = 0.006). There was a trend for children with CF to have lower lean mass at a given height compared to control children, but this was not statistically significant (Panel C, P = 0.08). The similar relationship between whole body BMC and lean mass for children with and without CF is shown in Panel D (group differences, P = 0.65).

**Peripheral Quantitative Computed Tomography (pQCT)**

Children with CF had smaller periosteal and endosteal circumferences at the 20% distal radius than control children, both before and after adjusting for age, lean mass, fat mass, and height (Table 2). Children with CF were found to have greater cortical thickness and cortical vBMD than control children after adjusting for age, lean mass, fat mass, and height, and the group-by-age interaction was significant for both cortical area (P = 0.01) and pSSI.

Fig. 1. A 4-step algorithm was used to evaluate whole body BMC in children with CF. (A) Children with CF had lower WB BMC than control children (P = 0.007), and the age-by-group interaction was borderline significant (P = 0.08). (B) Height among children with CF was lower at all ages compared to control children (P = 0.006). (C) Lean mass tended to be lower at a given height among children with CF compared to control children (P = 0.08). (D) There was no difference in the relationship between WB BMC and lean mass for children with and without CF (P = 0.65). —X— represent children with CF and —O— represent control children.
indicating that the positive relationship between the bone measures and age was attenuated among children with CF (Fig. 2A and B, respectively). Similar results were observed if the group-by-height interaction term was included rather than the group-by-age interaction (data not shown). Inclusion of sex in the analysis did not alter any of the results. Trabecular vBMD was not different between groups either before or after adjusting for age, weight, and height (Table 2).

### DISCUSSION

Our finding of decreased weight and height among children with CF compared to control children is not surprising and has been reported previously.\(^1\) These results concur with others who have acknowledged the importance of body size and composition, specifically height and lean mass, when measuring BMC or aBMD in children and adolescents with CF and in short stunted individuals in general.\(^1\) We also found that lean mass for height and whole body BMC for lean mass did not differ between children with and without CF, a finding similar to Brodie and coworkers.\(^12\)

Although we did not find differences in whole body BMC between children with and without CF, we did find deficits in cortical bone measures by pQCT. Children with CF had thicker and denser cortical bone than controls, but this did not compensate for the smaller bone size which compromised the bone strength in children with CF. Our finding of a smaller periosteal circumference, combined with the slightly less lean mass for a given height, in children with CF compared to control children is consistent with bone effects resulting from possible decreased physical activity levels in children with CF. We previously observed in a randomized exercise trial an increase in periosteal circumference among preschoolers randomized to gross motor activity than those randomized to fine motor activity.\(^20\) Unfortunately we did not collect physical activity information to determine whether levels differed between CF and control children or whether activity levels were associated with lean mass or periosteal circumference in this population.

### TABLE 2—Mean pQCT Bone Measurements\(^1\) by Disease Status

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>Control</th>
<th>P-Value</th>
<th>Least square means(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF</td>
<td>Control</td>
<td></td>
<td>CF</td>
</tr>
<tr>
<td>Cortical area</td>
<td>50.8 ± 5.6</td>
<td>62.5 ± 5.1</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>2.00 ± 0.12</td>
<td>2.04 ± 0.11</td>
<td>NS</td>
<td>2.14 ± 0.07</td>
</tr>
<tr>
<td>Periosteal circ.</td>
<td>31 ± 2</td>
<td>36 ± 1</td>
<td>0.03</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>Endosteal circ.</td>
<td>19 ± 1</td>
<td>23 ± 1</td>
<td>0.003</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Cortical vBMD</td>
<td>1081 ± 18</td>
<td>1062 ± 14</td>
<td>NS</td>
<td>1091 ± 15</td>
</tr>
<tr>
<td>pSSI</td>
<td>132 ± 20</td>
<td>201 ± 23</td>
<td>0.07</td>
<td>—</td>
</tr>
<tr>
<td>Trab vBMD</td>
<td>233 ± 7</td>
<td>236 ± 7</td>
<td>NS</td>
<td>230 ± 11</td>
</tr>
</tbody>
</table>

Data are means ± sem.
Circ., circumference; vBMD, volumetric bone mineral density; pSSI, polar stress-strain index; trab, trabecular.

\(^1\)All measures except 4% trabecular vBMD were obtained at the 20% distal radius site.

\(^2\)Least square means ± sem adjusting for age, lean mass, fat mass, and height.

\(^3\)Significance stated is for the age-by-group interaction that was also included in the model for this outcome variable. Marginal means not reported due to significant interaction, see Figure 2 for results.

\(P = 0.004\) indicating that the positive relationship between the bone measures and age was attenuated among children with CF (Fig. 2A and B, respectively). Similar results were observed if the group-by-height interaction term was included rather than the group-by-age interaction (data not shown). Inclusion of sex in the analysis did not alter any of the results. Trabecular vBMD was not different between groups either before or after adjusting for age, weight, and height (Table 2).

**Fig. 2.** Cortical area (A) and pSSI (B) by age for children with CF (---X---) and age- and sex-matched control children (—O—). The relationship between cortical area and age and between pSSI and age were attenuated among children with CF compared to controls (group-by-age interaction: \(P = 0.01\) and \(P = 0.004\) respectively).

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It can be speculated that the group-by-age and group-by-height interactions that were observed with cortical area and pSSI may be due to a delayed pubertal status among children with CF. Slowed pubertal growth is common among adolescents with CF. During early puberty there is significant expansion of the periosteum due to the increases in growth hormone and insulin-like growth factor-I. Because periosteal circumference and cortical area are major contributors to pSSI, any changes that occur at the periosteal site are amplified in the pSSI. Children who are younger or shorter are more likely to be prepubertal and therefore have similar measures of bone strength. We speculate that at older ages and taller heights the control children were more advanced in pubertal development than the children with CF and therefore have greater cortical area and bone strength. Unfortunately we did not have Tanner stages on the control children to test this hypothesis.

Brookes and coworkers finding of larger bone deficits in post-pubertal children with CF compared to prepubertal children with CF are consistent with our results. Histomorphometric data suggest that adult patients with CF have lower cortical and trabecular bone mass, with low bone turnover and significant decreases in bone formation at the cellular level compared with healthy controls. Putman and colleagues reported that young adults with CF have smaller bone area and lower vBMD at the radius and tibia and have compromised bone microarchitecture at these two sites based on HR-pQCT results. We did not find differences in vBMD in our young pediatric population. These findings support the conclusion that the deficits in bone mass in patients with CF is due to suboptimal bone mass accrual throughout their childhood that becomes more apparent with increasing age.

Factors that may contribute to the delay in puberty that can occur with CF include poor nutritional status due to energy and nutrient malabsorption. Individuals with CF in our study consumed twice the daily calories (although not statistically different) and vitamin D as the controls. Calcium intake was not different between groups. It has been proposed that the skeletal deficits that occur with this disease are due to deficiencies in calcium or vitamin D or both. We did not measure biological indicators of these nutrients, but previous reports relating BMD with vitamin D status in patients with CF have not supported the hypothesis that bone deficits are a result of vitamin D deficiency. In an Australian study by Buntain et al., adolescents and adults with CF who were vitamin D sufficient also had BMD deficits, and the recent study by Brookes et al. found similar serum 25-hydroxyvitamin D levels that were not different between the CF and control groups.

In conclusion, our data support the previous finding that children with CF have similar whole body BMC relative to lean mass as sex- and age-matched healthy children. Our pQCT results indicate that older children with CF have smaller periosteal circumference and cortical area leading to greater deficits in bone strength (pSSI) than younger children with CF. Combined with deficits seen in lean mass as these children age, strategies that focus on increasing lean mass during growth may prove to be beneficial. Future focus for research includes identifying methods for increasing physical activity in children with CF to test for effects on increasing lean mass and bone size.

ACKNOWLEDGMENTS

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