Prospective evaluation of growth, nutritional status, and body composition in children with cystic fibrosis

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ABSTRACT
Background: Several cross-sectional studies have shown improvement in the growth of children with cystic fibrosis (CF) because of increased awareness of and more comprehensive care of their special nutritional needs. However, longitudinal data on the nutritional status of these children are rare.

Objective: The objective was to compare changes in growth, body composition, and nutritional status between children with and without CF.

Design: This was a prospective 3-y cohort study of 25 children aged 5–10 y with CF, mild pulmonary disease, and pancreatic insufficiency and of 26 healthy control children. Three methods were used to assess body composition: measurements of skinfold thickness, total body water by deuterium oxide, and total-body electrical conductivity. Growth and body-composition changes over time were analyzed by a longitudinal mixed-effects model.

Results: Growth and body composition changed over time. The boys with CF were slower than that of the control subjects (P = 0.004). The same divergence over time between the boys with and without CF was observed for fat-free mass assessed by skinfold-thickness measurements and total body water (P = 0.008 and 0.02, respectively) and for fat mass assessed by skinfold-thickness measurements and total-body electrical conductivity (P = 0.009 and 0.001, respectively). The differences in the pattern of changes in growth and body composition were less striking for girls.

Conclusions: Despite comprehensive care, the growth of boys with CF was impaired on the basis of height, fat-free mass, and fat mass, when observed longitudinally. Caution should be used when interpreting cross-sectional measurements because they often do not detect suboptimal growth.


KEY WORDS: Body composition, children, cystic fibrosis, deuterium oxide, genotype, growth, longitudinal studies, mixed-effects model, nutritional status, respiratory function tests, total-body electrical conductivity, total body water

INTRODUCTION

Suboptimal growth is frequent in children with cystic fibrosis (CF) and is associated with increased morbidity and mortality (1–6). In the past few decades, the growth of these children has improved because of increased awareness of and more comprehensive care of their special nutritional needs (4, 7). Many children with CF have achieved growth above the third percentile and appear to have normal growth when weight and height are measured cross-sectionally (3). These apparent achievements might, however, be misleading in evaluations of individual children over time. Even when final height is above the third percentile, there still may be a growth deficit relative to the individual genetic potential for height. Furthermore, weight is a composite value of the 2 major body components: fat-free mass (FFM) and fat mass (FM). Therefore, the separate observation of changes in these 2 body compartments may provide more information on the growth patterns of children with CF.

To evaluate growth more fully, investigators have recommended the use of several methods of body-composition assessment (8, 9). Furthermore, prospective examinations of the changes in body composition provide insight into the mechanisms that underlie body-composition deficits in CF. In the current study, changes in FFM and FM were evaluated prospectively by using 3 different methods. At the initiation of this longitudinal study of preadolescent children, FFM and FM were similar by design in both groups (10).

The purpose of this study was to characterize over 3 y the longitudinal changes in body composition and growth of clinically stable prepubertal children with CF, mild pulmonary disease, and pancreatic insufficiency, and to compare these changes with those observed in healthy control children. The influence of age and sex on these changes was also examined.

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2 Supported by The Cystic Fibrosis Foundation, the Nutrition Center, and the General Clinical Research Center (RR-00240) of The Children’s Hospital of Philadelphia.

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Received July 6, 1999.

Accepted for publication January 13, 2000.
SUBJECTS AND METHODS

Subjects

Twenty-five subjects (12 boys and 13 girls) aged 5–10 y with CF were recruited from the Cystic Fibrosis Center at The Children’s Hospital of Philadelphia. The diagnosis of CF was based on clinical signs and on sodium and chloride values > 60 mmol/L as measured in duplicate quantitative pilocarpine iontophoresis sweat tests. At baseline, all subjects with CF were prepubertal and pancreatic insufficient, with mild pulmonary disease, ie, a forced expiratory volume at 1 s (FEV₁) > 60% as measured by standard methods. All subjects had adequate growth status on the basis of a screening definition of height and weight above the third percentile. The subjects had no other chronic disorders and were not taking medications known to affect growth or nutritional status. Twenty-six healthy prepubertal children (15 boys and 11 girls), similar to the children with CF in age, sex, and weight, were recruited from hospital and community sources. Subjects were evaluated annually 4 times over 3 y and were not taking medications known to affect growth or body composition.

RESULTS

Statistical analysis

Weights and heights were compared with National Center for Health Statistics reference standards (22), and z scores (SD scores) were calculated with the ANTHROPOMETRIC SOFTWARE PROGRAM (version 3.1, 1988; Centers for Disease Control and Prevention, Atlanta). Means and CIs for growth and body-composition measures were calculated by group and sex at each time point and plotted to examine time trends. Baseline group comparisons were made by using a two-sample t test. Comparisons of the changes between groups from the beginning to the end of the study were made by using a two-sample t test when the distribution was normal and by using Wilcoxon’s rank-sum test when the distribution was not normal.

Comparisons of body-composition methods for individual measurements were described by using a Spearman’s rho correlation coefficient and by calculating the mean differences between methods. All reported P values are two-tailed and values ≤ 0.05 were considered significant. The longitudinal mixed-effects model of Laird and Ware (23) was used to examine longitudinal trends. This approach allows analysis of the linear association between repeated measurements of an outcome variable and both time and other explanatory variables such as CF group and control group. The data from all subjects were included in the analysis, even when some subjects did not have a complete set of measurements. Therefore, this analysis was more likely to detect differences undetected by simple comparison of differences between groups. A random effect was included in each model to account for within-subject random variability. The models examined changes over time in growth and body composition, and whether patterns of change were different between the CF and control groups. Parameter estimates, as in regression analysis, indicate the contribution of the independent variable to the model. For example, the parameter estimate for the time variable estimates the rate of change in the dependent variable over time. Boys and girls were analyzed separately because of the expected sex differences in growth and body composition. Statistical evaluation was conducted by using STATA 5.0 (STATA Corp, College Station, TX).

Anthropometric and body-composition evaluations

Weight, height, midupper arm circumference, and skinfold thickness (SFT) at the triceps, biceps, subscapular, and suprailiac sites were measured in triplicate by using standard methods (12). One well-trained anthropometrist conducted the evaluation in the first year; a second well-trained anthropometrist conducted the evaluation in subsequent years. Pubertal development was scored according to Tanner (13). The average of the genital and pubic hair development scores was used in the analysis.

Upper arm muscle area was calculated from anthropometric measures (14). FFM and FM were measured by using several methods of body-composition assessment because no single method is recognized as optimal for children with CF. First, FFM and FM were computed from SFT measurements at 4 sites with the use of age- and sex-appropriate prediction equations (15, 16). Total body water (TBW) was measured by the deuterium oxide (2H2O) dilution method (17). A baseline urine sample was obtained and then 2H2O was administered orally 1.5 h after consumption of a standardized evening meal. The dose (0.14 g 2H2O/kg estimated total body water) was of 99.8 or 99.9 atom percent deuterium (Aldrich Chemical, Milwaukee). Urine was collected overnight and pooled with the first urine sample of the morning. The volume and deuterium concentration of the pooled sample were used to estimate isotope losses during the equilibration period. The second morning urine sample was collected and analyzed to calculate TBW. Urinary 2H2O isotopic abundance was measured by isotope ratio mass spectroscopy (18) (Nuclide 6-60; State College, PA) by 1 of 2 laboratories (Global Geochemistry Corporation, Canoga Park, CA, or Metabolic Solutions, Merrimack, NH). Agreement between laboratories was established by analyzing duplicate samples. FFM and FM were derived from TBW by using a hydration factor of 75.3% for prepubertal children (19).

Body composition was also determined by total-body electrical conductivity (TOBEC) (HA-2; EmScan, Springfield, IL). The TOBEC instrument contains a low-energy electromagnetic field through which the subject moves on a gantry table. Changes in the energy field are caused by the conductivity of the water and electrolytes in the FFM (8, 20, 21). These measured changes are used to determine FFM and FM on the basis of age-appropriate calibration equations.

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visit. However, because of occasional equipment or protocol failure, not all methods were used for each subject at each study visit. There were 182 sets of SFT measurements, 181 TBW measurements, and 173 TOBEC measurements of body composition. One subject with CF and one control subject were seen only once. The sample sizes for each measurement at each visit. There were 182 sets of SFT measurements, 181 TBW measurements, and 173 TOBEC measurements of body composition methods for each individual FFM measurement was consistent between the results of the different body-composition methods. For CF and control subjects, regardless of the body-composition-assessment method used. The changes in FFM determined by TBW, TOBEC, and SFT are presented in Table 2 and Figure 2. Analysis of the longitudinal data for boys showed that initial age, time, and time-by-group interaction contributed significantly to changes in FFM determined by TBW (P < 0.001, P < 0.001, and P = 0.02, respectively) and SFT (P < 0.001, P < 0.001, and P = 0.008, respectively), but only initial age (P < 0.001) and time (P < 0.001) contributed significantly to the model using TOBEC for FFM assessment. In girls, only initial age and time contributed to the model in all 3 methods of FFM assessment (all P-values < 0.001). However, when the alternative statistical model for TOBEC measurement was used, which did not include children with CF at baseline, the time-by-group interaction term was significant in girls (P = 0.043). Upper arm muscle area was not significantly different between CF and control subjects at baseline. Longitudinal changes in upper arm muscle area were significantly explained by time in boys and by time and initial age in girls, but changes in upper arm muscle area were not significantly different between the CF and control groups. Changes in FM were also analyzed to evaluate energy stores. At baseline, FM determined by TBW was significantly lower in boys with CF than in control boys (P = 0.004; Figure 3). There were no significant differences in girls. Similar results were observed in boys when TOBEC (P = 0.01) and SFT (P = 0.04) were used. In boys, the time-by-group interaction term predicted changes in FM determined by TOBEC (P = 0.001) and SFT (P = 0.009) only. In girls, the time-by-group interaction term contributed negatively to the model of FM changes when
determined by TBW \((P = 0.05)\), indicating that girls with CF gained more fat over time than did the control girls. Because puberty began in 9 of the 24 girls during the study, a secondary analysis was conducted in girls to introduce any detectable pubertal changes (Tanner stage 2) as a dichotomous variable to fit a model, assuming a change point at initiation of puberty. This variable contributed significantly to every model \((\text{all } P \text{ values } < 0.01)\), but the results reported above remained essentially the same with only a few exceptions. After inclusion of pubertal changes in the model, initial age contributed to the model of WAZ scores \((P = 0.012)\), the group-by-time interaction term was no longer significant in the model of HAZ scores, the group-by-time interaction term was no longer significant in the model of FM by TBW, and initial age was no longer significant in the model of FM by TOBEC. Because only 2 of the 27 boys showed detectable signs of pubertal changes, no similar analysis was conducted in boys. Because of the observed differences in results between the sexes, a separate secondary analysis also was performed with use of a sex-by-time interaction term to compare changes in WAZ scores, HAZ scores, FFM, and FM between boys and girls with CF. Only changes in FM were significantly different between the sexes, with girls having more FM than boys, as determined by TBW \((P = 0.02)\), TOBEC

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>CF group ((n = 21))</th>
<th>Control group ((n = 23))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>8.1 ± 0.7(^2)</td>
<td>10.4 ± 0.8</td>
</tr>
<tr>
<td>Girls</td>
<td>10.7 ± 1.4</td>
<td>9.5 ± 0.9</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>15.2 ± 0.7(^3)</td>
<td>18.7 ± 0.6</td>
</tr>
<tr>
<td>Girls</td>
<td>16.4 ± 1.0</td>
<td>18.1 ± 1.1</td>
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<tr>
<td><strong>FFM (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBW</td>
<td>6.9 ± 2.0(^4)</td>
<td>8.9 ± 2.6</td>
</tr>
<tr>
<td>Boys</td>
<td>8.0 ± 1.1</td>
<td>8.0 ± 1.1</td>
</tr>
<tr>
<td>Girls</td>
<td>6.2 ± 1.5</td>
<td>6.7 ± 2.3</td>
</tr>
<tr>
<td><strong>SFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>7.2 ± 2.0</td>
<td>8.4 ± 2.0</td>
</tr>
<tr>
<td>Girls</td>
<td>7.8 ± 0.7</td>
<td>7.3 ± 0.7</td>
</tr>
<tr>
<td><strong>FM (kg)</strong></td>
<td></td>
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<tr>
<td>TBW</td>
<td>1.2 ± 1.2</td>
<td>1.5 ± 1.9</td>
</tr>
<tr>
<td>Boys</td>
<td>2.8 ± 0.8</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Girls</td>
<td>1.5 ± 1.0</td>
<td>3.0 ± 1.9</td>
</tr>
<tr>
<td>TOBEC</td>
<td>2.9 ± 1.6</td>
<td>2.9 ± 1.5</td>
</tr>
<tr>
<td><strong>SFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>0.9 ± 0.6</td>
<td>1.7 ± 1.5</td>
</tr>
<tr>
<td>Girls</td>
<td>2.9 ± 0.8</td>
<td>2.2 ± 0.6</td>
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<tr>
<td><strong>Percentage fat (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>TBW</td>
<td>1.5 ± 1.4</td>
<td>-0.4 ± 1.2</td>
</tr>
<tr>
<td>Boys</td>
<td>2.2 ± 7.0</td>
<td>-0.7 ± 5.9</td>
</tr>
<tr>
<td>Girls</td>
<td>1.5 ± 3.6</td>
<td>3.1 ± 4.4</td>
</tr>
<tr>
<td>TOBEC</td>
<td>3.6 ± 4.0</td>
<td>2.6 ± 3.4</td>
</tr>
<tr>
<td><strong>SFT</strong></td>
<td>-0.8 ± 0.6</td>
<td>-0.4 ± 0.8</td>
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<td>Boys</td>
<td>3.0 ± 1.5</td>
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<td>Girls</td>
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</tbody>
</table>

\(^1\)± SD. CF, cystic fibrosis; TOBEC, total-body electrical conductivity; TBW, total body water; SFT, skinfold thickness.

\(^2\)Significantly different from the control group: \(^7P = 0.05, ^7P = 0.0008, ^7P = 0.02.\)
in the present study, the use of several methods of body-composition assessment in research settings may be more reliable for describing the longitudinal changes in body composition of children with CF (9).

This study was designed to assess longitudinal changes in growth, body composition, energy expenditure, and pulmonary function in children with adequate growth status and mild pulmonary symptoms of CF (34). Control subjects were therefore selected at baseline to be similar in age and weight to the children with CF, explaining the initial similarities between the 2 groups, except for HAZ scores in boys. The decrease in WAZ scores with time in boys and girls in both groups may have resulted from impairments in nutritional status in the children with CF, but was not easily explained in the control children. In boys, greater differences in HAZ scores over time were observed between the CF and control groups. This finding emphasizes the fact that even when cross-sectional anthropometric indexes are comparable between CF and control groups, CF subjects may suffer a delay in statural growth, a phenomenon best observed in longitudinal studies.

Similarly, by design, total weight and FFM were comparable at baseline between the 2 groups. However, boys with CF gained less FFM than did control boys over the 3 y of the study. The present study suggests that the girls with CF and the control girls had similar increases in FFM during the entire study period. When the TOBEC determinations over the first year for girls with CF were not included in the analysis, this interaction term became significantly negative, suggesting that subjects with CF

DISCUSSION

The body-mass compartments of the children with CF, mild pulmonary symptoms, and pancreatic insufficiency did not change as did those of the control subjects when observed prospectively over several years. Previous cross-sectional studies showed that adults and children with CF have deficits in both FFM and FM as early as 5 wk of age (24–28). Furthermore, in a prospective study, Farrell et al (29) showed higher growth rates on the basis of weight and height assessments in children in whom CF was diagnosed at birth than in children in whom CF was diagnosed later in life (0–7 y). Similar results were observed in infants and young children (25, 30). However, prospective changes in the body composition of older children with CF have not been documented. Body-composition assessment in children with CF may be complicated by the characteristics of the disease (31, 32). Hydrodensitometry, usually referred to as the optimal method for measuring body composition in healthy adult subjects, may be unreliable in adults and children with CF (8, 33). Except for hydrodensitometry, different methods of body-composition assessment have been shown to correlate well with each other, but absolute FFM and FM values may vary between methods. The present study showed consistency between methods for FFM, but not for assessments of FM in individuals. Therefore, as

\[ P = 0.004 \], and SFT \( (P < 0.001) \). The different CF genotypes did not contribute significantly to any of the models for change in weight, height, FFM, and FM for this group of children with CF and pancreatic insufficiency.
gained more FFM than did control girls. This result should, however, be interpreted with caution. The growth deficiency in FFM observed in boys with CF might reflect the energy deficit experienced by these children because no dietary protein deficiency was observed (35).

The dietary data at the initiation of this study suggest that the children with CF had normal growth with energy intakes that were higher than those of the control subjects, yet lower than the recommended intakes for children with CF (35). The present longitudinal study showed that dietary intakes at this level were likely insufficient to ensure normal growth over the 4 y of follow-up. Unlike FFM, upper arm muscle area did not differ significantly between the CF and control groups. This difference emphasizes the limitation of change in upper arm muscle area as an indicator of FFM changes. In an evaluation of fat stores, and thus of cumulative energy stores over the 3 y of the study, boys with CF gained significantly less FM than did control boys and girls with CF. This difference is explained by the relative energy deficit in boys with CF. The sex difference in FM change was unexpected because boys usually have a better survival rate than do girls. This result suggests a possible interaction between sex, growth, and survival that should be investigated. An alternative explanation is that sex differences in FM are unrelated to survival.

Although the absolute differences between the children with CF and the control children were small, they were thought to be clinically significant for the following reasons. First, follow-up was limited to 3 y and the observed growth deficits likely were cumulative over childhood. Second, by design, the control group was selected to be of similar weight to the children with CF at baseline. Therefore, the control group might have been genetically smaller than the general population, thus underestimating the growth deficit observed in the children with CF. Third, the group of children with CF was selected to have only mild pulmonary symptoms; therefore, it can be speculated that in a more representative group of children with CF, the growth deficit over 3 y would have been larger than the one observed in the present study. The agreement between the results of the longitudinal analyses obtained with the 3 methods of body-composition assessment further supports the conclusions of this study. CF genotype group was not associated with body-composition changes, in contrast with the changes in pulmonary function observed in some studies (36). A larger sample in each genotype group as well as inclusion of subjects without pancreatic insufficiency may, however, be necessary to detect such differences.

In conclusion, the results of this longitudinal study indicate that children with CF do not grow at an optimal rate on the basis of the growth rates observed in the group of healthy control subjects, despite comprehensive care that includes nutrition education. The boys with CF tended to gain less FFM and less FM than did control boys, and less FM than did girls with CF. Therefore, cross-sectional assessments of children with CF need to be interpreted with caution and optimal nutritional and overall clinical care can only be evaluated after careful longitudinal observations of appropriate growth over several years. It is recommended that better surveillance of growth and body composition should be conducted in children with CF by using standard protocols, accurate equipment, and well-trained observers, to allow earlier recognition and treatment of suboptimal growth.

We thank the children and their families who took part in the study as well as the staff of the Cystic Fibrosis Center and General Clinical Research Center for their assistance.

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