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Deficits in Bone Mineral Content in Children and Adolescents with Cystic Fibrosis Are Related to Height Deficits

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Abstract

Objective—Despite reports of decreased bone density, children with mild to moderate cystic fibrosis (CF)-associated pulmonary disease do not have increased fracture rates. Short stature and delayed puberty complicate interpretations of bone mineral status in many children with chronic diseases. This study sought to characterize bone mineral content (BMC) in children with CF and determine its relationship to growth, body composition, and disease severity.

Design—Dual energy x-ray absorptiometry measurements of whole body BMC (WB-BMC), spine BMC (Sp-BMC), and lean body mass (LBM) were converted to Z-scores in 82 CF and 322 healthy children. Effects of growth, body composition, and CF-disease characteristics upon BMC were determined using linear regression.

Results—Children with CF had lower weight, height (HT), BMI, and LBM-Z. Females with CF had lower ($p < 0.001$) WB-BMC-Z (-1.1 ± 1.1) and Sp-BMC-Z (-0.9 ± 1.1) than controls. Following adjustment for HT-Z, deficits were absent. Males with CF had lower ($p < 0.001$) WB-BMC-Z (-1.3 ± 0.9) and Sp-BMC-Z (-0.9 ± 1.3). Following adjustment for HT-Z, WB-BMC-Z deficits were attenuated and Sp-BMC-Z deficits absent. HT-Z, LBM-Z, and pulmonary function had independent effects upon WB-BMC-Z and Sp-BMC-Z.

Conclusion—BMC deficits are related to altered body size, reduced LBM, and pulmonary function in children with CF. Interventions targeting improved growth, muscle mass, and pulmonary function may benefit bone health in CF.

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Keywords

bone density; bone mineral content; cystic fibrosis; DXA; children

INTRODUCTION

Cystic Fibrosis (CF) poses numerous threats to optimal bone mineral accrual during childhood and adolescence and thus, to the attainment of optimal peak bone mass. Chronic nutritional deficits including caloric deprivation and poor vitamin D, vitamin K, calcium, and essential fatty acid status (1) may jeopardize bone health. Muscle mass plays an important role in achieving and maintaining bone health via direct mechanical force on bone (2); thus, decreased muscle mass, common in CF (3,4), may also compromise bone health. Reduced physical activity, chronic inflammation, and glucocorticoid medication use further threaten bone health in CF (5). Delayed puberty is accompanied by delayed sex hormone related bone mineral accrual and relative short stature compared to gender and age-matched controls without pubertal delay. Thus, delayed sexual maturation and altered body composition complicate interpretations of bone health and may have long-term implications for bone mineral accrual and achieving optimal peak bone mass.

Despite these issues, the reports on bone health in patients with CF are conflicting. Increased fracture rates were reported in adults with CF with end-stage lung disease referred for lung transplantation (6) and in female children and adolescents (7). Increased fracture rates, however, were not seen in children and adolescents with mild to moderate CF who were compared to healthy children using current control fracture rate data (8). Additionally, both normal and compromised bone mineral content (BMC) have been reported in the pediatric and adult populations with CF (9–13). The potential reasons for the divergent results are numerous and include study differences in 1) disease severity, 2) measurement techniques, 3) reference data, and 4) analytic techniques for adjusting for CF-related impaired growth and maturation. The 2006 CF Foundation Registry highlighted the importance of accurately defining and adequately addressing bone health and found nearly 5% of adolescents had bone disorders and that the prevalence approaches 30% in older population with CF (14).

The impact of impaired growth and maturation on bone health assessment is a particularly important issue for children and adolescents with CF. Although bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) is an established modality for osteoporosis assessment in adults (15), DXA measurements are highly influenced by bone size. In the setting of CF in which short stature, delayed puberty, and delayed and decreased peak height velocity are common (16,17), DXA BMD may over-estimate bone mineral deficits. DXA areal-BMD measurements are two-dimensional and fail to take into account the depth and thickness of bone. Measurements of the spine by computed tomography in children demonstrated that DXA spine BMC was more accurate than DXA areal-BMD. In a study using peripheral quantitative computed tomography (pQCT), DXA-derived whole body BMC (WB-BMC) measures adjusted for subject height correlated best with pQCT-derived cortical BMC, cortical dimensions, and strength (18). Others have suggested that the adequacy of BMC relative to muscle mass (which is influenced by height) be determined to improve our understanding of bone health (2).

Given the many issues surrounding adjustment for stature, body composition, and puberty in children and adolescents, this study was designed to assess WB-BMC and spine BMC (Sp-BMC) adjusted for height and lean mass in children and adolescents with mild to moderate CF. A large healthy comparison group was used so that the effects of growth, body composition, and puberty on BMC could be optimally assessed. The goals of the study were to assess the

BMC status in children with mild to moderate pulmonary manifestations of CF, (2) to determine the impact of growth, body composition, and maturation on BMC, and (3) to assess the relationship of CF-disease characteristics to BMC.

MATERIALS AND METHODS

Subjects

Individuals with CF and pancreatic insufficiency, age 8–18 y, cared for at the Cystic Fibrosis Centers at The Children's Hospital of Philadelphia, Hershey Medical Center, or the Hospital of the University of Pennsylvania, were recruited. Diagnosis was established by sweat test and/or genotype. The diagnosis of pancreatic insufficiency was determined at the home CF center based on clinical or laboratory values including 72-hour fecal fat analyses with <93% absorption or stool trypsin concentration <80 μ g/g. Inclusion criteria included forced expiratory volume in one second (FEV₁) > 40%. Exclusion criteria included known diabetes, cirrhosis or portal hypertension, history of lung transplant, and other medical condition not associated with CF that potentially affect growth or bone health.

Healthy subjects (age 5–18 y) were recruited to participate in a study to develop contemporary reference data for growth, body composition, and bone measurements from pediatric practices affiliated with The Children's Hospital of Philadelphia and through regional newspaper advertisements. Subjects in the comparison group were excluded for chronic medical conditions or use of medications known to affect growth, nutritional status, dietary intake, pubertal development, or bone health. For the purposes of this study, only Caucasian subjects 8 y of age and older were included in the comparison group in order to be comparable to the CF sample in terms of race (90% Caucasian) and age range.

The protocol was approved by the Institutional Review Boards at The Children's Hospital of Philadelphia, Hospital of the University of Pennsylvania, and Hershey Medical Center. Informed consent was obtained from young adult participants (age 18 y) and from parents/guardians of participants (age <18 y). Assent was obtained from participants age <18 y.

CF Characteristics

Following recruitment, medical records were reviewed and interviews conducted with subjects with CF to collect data on genotype, nutritional supplement use, feeding tube supplementation, age of menarche, sputum colonization with *Burkholderia cepacia* (*B. cepacia*) or methicillin-resistant *Staphylococcus aureus* (MRSA), and pattern of oral and/or inhaled glucocorticoid use. If genotype was not recorded in the medical record, a blood sample was obtained and analyzed for CF genotype (Genzyme Genetics Laboratory, Westborough, MA). CF genotype was categorized as homozygous for Δ F508 mutation (the most common CF mutation), heterozygous for Δ F508, or other variants.

Anthropometry and Pubertal Development

Weight was measured to the nearest 0.1 kg using a digital scale (Scaltronix, White Plains, NY, USA). Height was measured to the nearest 0.1 cm using a stadiometer (Holtain, Crymch, UK). Age- and gender-specific standard deviation scores (Z-scores) for weight (WT-Z), height (HT-Z), and body mass index (BMI-Z) were calculated using current reference data (Centers for Disease Control and Prevention 2000 growth charts for the United States (19)).

Puberty status was ascertained using a validated self-assessment questionnaire (20,21) to categorize Tanner stages (TS) of pubic hair distribution in both sexes, and genital development for boys and breast development for girls (22). Breast stage development in girls and genital development in boys were used in the analyses.

Hand-wrist radiographs were obtained in participants with CF who showed evidence of growth in the previous year for determination of bone age (BA). BA was assessed by one reader (JIS) using a left-hand radiograph and using the Tanner-Whitehouse III method (23). Z-scores for BA were calculated for subjects age <16 y using the Tanner-Whitehouse III software.

DXA, Pulmonary Function, Calcium, Vitamin D and PTH

Spine and whole body DXA scans were performed (Hologic Delphi, Bedford, MA, USA) using a fan beam array, and analyzed using the Discovery software version 12.3. Measurements were obtained using standard positioning techniques, and whole body scans were analyzed to generate estimates of WB-BMC (g), lean body mass (LBM, kg), and fat mass (FM, kg). Lumbar spine scans were analyzed to estimate Sp-BMC (g). The instrument was calibrated daily with a hydroxyapatite phantom. The *in vitro* CV was <0.6%; the *in vivo* CV was <1%.

For subjects with CF, pulmonary status was evaluated by standard pulmonary function methods. FEV₁ was reported as the percentage of predicted value (FEV₁%) based upon prediction equations of Wang and Hankinson (24,25). Forced vital capacity (FVC) was reported as percentage of predicted value (FVC%). Blood samples were analyzed for intact PTH (pg/mL) (Clinical Laboratory of The Children's Hospital of Philadelphia) and 25-hydroxy vitamin D [25-(OH)-D] (Medical University of South Carolina, Dr. Bruce Hollis).

Dietary intake of calcium and vitamin D was determined from 3-day food records obtained on two weekdays and one weekend day. Subjects with CF and their families were provided with verbal and written instructions, food scales, and diet diaries and were instructed to weigh and record all food that was eaten in a three-day period. For the healthy comparison group, three 24-hour recalls were conducted by telephone in the two weeks following the study visits. All diet records were analyzed using the Nutrition Data System (University of Minnesota, Minneapolis, MN). Information about dietary supplements was obtained by interview.

Statistical Analyses

Means, standard deviations, and ranges were used to summarize continuous variables, and proportions were used for categorical variables. The CF and healthy comparison groups were compared using t-tests or the Wilcoxon rank-sum test, depending upon normalcy of the data using Stata 9 (Stata Corp., College Station, TX). Two-sided tests of hypotheses were used, and a $p < 0.05$ was considered statistically significant.

Data from the healthy comparison group were used to derive reference curves of LBM, FM, WB-BMC, and Sp-BMC relative to age and sex using the "LMS" method (26). This technique accounts for the non-linearity, heteroscedasticity, and skewness of these measures in growing children across this age range, and the technique was used to create the US growth charts. Based on the reference curves generated by this technique, LBM, FM, WB-BMC, and Sp-BMC were converted to age- and sex-specific standard deviation scores (Z) for both the CF and healthy subjects.

The primary outcomes were WB-BMC-Z and Sp-BMC-Z. In order to adjust for body size, HT-Z was used in multivariable models. The analyses were stratified by sex, employing a multi-stage approach to assess effects of puberty, HT-Z, and LBM-Z upon BMC-Z in the two groups. The outcome was represented as the BMC-Z deficit adjusted for the covariates for subjects with CF compared to the healthy comparison group. The fit of each model was assessed through the adjusted R² value. The regression models were assessed further through graphical checks, the Shapiro-Wilk test of normality of the residuals, and the Cook-Weisberg test for heteroscedasticity.

To assess the impact of CF-specific effects upon bone health, multivariable linear regression was employed to identify clinical factors important for BMC-Z using stepwise regression and bootstrap analysis with 999 iterations. HT-Z was entered into all the models tested to account for the differences in size between the CF and healthy comparison groups. Sex, age, puberty status (pubertal vs prepubertal), FM-Z, LBM-Z, FEV₁, genotype, tube feed use, nutritional supplement use, glucocorticoid use (percent of visits in which inhaled glucocorticoids were prescribed; percent of visits in which oral glucocorticoids were prescribed), *B. cepacia* status, MRSA status, serum iPTH, serum 25-OH-D, and calcium intake (mg/day).

RESULTS

Subject Characteristics and Body Composition

Characteristics for subjects with CF (n=82) and the healthy comparison group (n=322) are summarized in Table 1. The pubertal stages were well-represented in both groups, and mean age at each TS was not different between the groups. As is typical for healthy US children, mean BMI-Z was >0 for the reference group, indicating the increase in relative weight in the US population compared to the CDC reference curves (19). WT-Z, HT-Z, BMI-Z, LBM-Z, and FM-Z were all significantly lower in subjects with CF than the comparison group. No differences in WT-Z, HT-Z, BMI-Z, LBM-Z, and FM-Z were observed between males and females with CF, nor between pre-pubertal (TS1) and pubertal (TS2 to 5) subjects with CF (data not shown).

BA (n=59) was delayed (p=0.001) among children with CF; the mean ($\pm$ SD) BA-Z was -0.6 ± 1.0 (range: -3.1 to 1.2). In general, children with CF had mild pulmonary disease (FEV₁% = 84 ± 19 ; FVC% = 93 ± 13). As expected in pancreatic insufficient subjects with CF, 83% were homozygous or heterozygous for the $\Delta F508$ mutation. Sputum was colonized with MRSA in three subjects and *B. cepacia* in four subjects. Nutritional support was common; as recommended, all subjects reported routine vitamin supplementation; 43% reported regular oral nutritional supplement use, and 8% reported feeding tube use.

Information regarding glucocorticoid use was available for at least one year of records in over 90% of subjects (Table 1). The average time interval for which glucocorticoid use was available was 2.8 y (range: 0–3), and the average number of CF clinic visits during that time interval was 15.5 (range: 1–59). Oral glucocorticoids were prescribed at 42% of visits. As is common in CF, nearly 50% of subjects had 25-(OH)-D concentrations in the insufficient range (< 20 ng/mL) and nearly 90% had levels below the target range of 30 ng/mL (27). 25-(OH)-D were higher in the May to October interval (24.4 ± 5.3 ng/mL, n=20) than the November to April interval (19.4 ± 6.2 ng/mL, n=36), p=0.003, showing the expected seasonal effect.

BMC

Bone and body composition measures are shown in Table 2; overall, bone area, WB-BMC, Sp-BMC, LBM, and FM were lower in subjects with CF. Sex-specific distributions of WB-BMC and Sp-BMC relative to age in both the healthy comparison group and subjects with CF are shown in Figure 1. Figures A and B illustrate that subjects with CF had lower WB-BMC and Sp-BMC. However, as previously noted, children with CF tend to be shorter and have less LBM, both of which impact BMC. To address these issues, a series of linear regression models was employed to assess WB-BMC-Z and Sp-BMC-Z in CF compared with the healthy comparison group. Analyses were stratified by sex.

Whole Body and Spine Assessment

Females with CF had significant deficits (-0.9 ; 95% CI: -1.2 to -0.5 , p < 0.001) in WB-BMC-Z compared with the healthy comparison group. As shown in Table 3, these deficits were no

longer statistically significant following adjustment for HT-Z, $p=0.11$. Similarly, males with CF had significant deficits (-1.1 , 95% CI: -1.2 to -0.7 , $p<0.001$) in WB-BMC-Z compared with the healthy comparison group. These deficits persisted after adjustment for HT-Z ($p=0.009$) but not after inclusion of LBM-Z in the model ($p=0.154$) (see Table 3). Puberty was not significantly associated with WB-BMC-Z even when HT-Z was not included in the model.

For Sp-BMC-Z, females with CF displayed significant deficits (-0.8 , 95% CI: -1.1 to -0.4 , $p<0.001$) (Table 3). Likewise, Sp-BMC deficits were present in males with CF (Sp-BMC-Z = -0.9 , 95% CI, -1.3 to -0.6 , $p<0.001$). In both sexes, Sp-BMC deficits were no longer significant following adjustment for HT-Z. Puberty stage had no effect upon Sp-BMC-Z even when HT-Z was not included in the model.

CF-Specific Factors and Bone Health

Bootstrap analysis revealed several factors that were independently associated WB-BMC-Z and Sp-BMC-Z (Table 4). HT-Z and LBM-Z were positively associated with both WB-BMC-Z and Sp-BMC-Z. Highlighting the importance of pulmonary health, FEV₁ was positively associated with WB-BMC-Z and Sp-BMC-Z after adjustment for other clinical factors.

DISCUSSION

Inadequate bone mineral accrual during growth and development poses two threats: first, the childhood risk of fracture and second, now that people with CF live much longer (14), the life-long risk and serious consequences of osteoporosis. Long-bone fractures are common during childhood; however, we have shown previously that children with CF were not at increased risk for fracture when compared to a geographically and temporally similar group of healthy children (8). However, for children with CF, the life-long threat of fracture is a particular concern since the accumulation of disease processes related to inflammation, malnutrition, and reduced physical activity may accelerate the onset of osteoporosis later in life. As the life expectancy of people with CF continues to increase (14), long-term bone health becomes an ever-important concern. Therefore, determining whether currently typical bone mineral accrual during growth and development is adequate for patients with CF is essential to insuring that the timing and nature of screening, prevention, and intervention plans will be most effective.

Interpretation of DXA bone mineral status is difficult in pediatric patients with chronic diseases due to their altered body sizes and body compositions. These alterations are a particular concern for children with CF, since the magnitude of growth failure varies as a function of age, sex, and disease severity and often worsens during the peripubertal years (28–31). In order to quantify these effects, we compared subjects with CF to a healthy comparison group of similar age, puberty status, ethnicity and geographic region. Multivariable techniques were used to adjust for age and sex appropriate skeletal size (height) and body composition (LBM). This adjustment was particularly important since BMC, growth, and body composition measures were converted to sex-specific standard deviation scores using a statistical technique that accounts for the non-linear age-related changes and variability that are known to occur across the age range of the children with CF. Spine and whole body BMC were assessed since the spine is a site comprised predominantly of trabecular bone and the whole body predominantly cortical bone (32). Our findings showed significant deficits in age- and sex-adjusted WB-BMC and Sp-BMC in subjects with CF. These deficits were largely explained by shorter stature, as demonstrated by the adjustment for HT-Z fully explaining the WB-BMC deficits in females and the Sp-BMC deficits in both sexes. Moreover, deficits in WB-BMC in males were attenuated by adjustment for HT-Z and were absent after adjustment for LBM-Z. These findings highlight the impact of growth and body composition upon bone health, and suggest that bone deficits in children with mild to moderate CF were largely attributable to altered growth. One important caveat is that, although BMC deficits were not statistically significant

when adjusted for the shorter stature, bones of similar BMC but differing size may not be equally strong (33) and equally resistant to fracture.

Considerable progress has been made in the treatment of CF. The CF Foundation Registry has documented improvement in life expectancy, pulmonary function, and BMI over the past three decades, yet suboptimal growth and nutrition persist (30,34) as evidenced by the low WT-Z and HT-Z in our subjects with CF and in the CF Registry. The importance of height and bone strength was underscored by the finding that HT-Z independently influenced WB-BMC and Sp-BMC. Ongoing nutritional issues, prolonged glucocorticoid use, and chronic inflammation may contribute to height deficits that persist despite improvements in pulmonary status in children with CF; these same factors threaten bone health. Currently, no consensus exists as to how to account for short stature in DXA measurements. Pediatric recommendations established by the International Society for Clinical Densitometry (35) state that height should be considered in the clinical interpretation of bone mineral status. However, this recommendation has not been implemented in all clinical and research settings. This issue is particularly problematic since short stature may be related to disease severity (36) and bone health is likely to be more compromised in children with more severe disease. The results of our study demonstrated that HT-Z, LBM-Z, and FEV₁% were significant, independent predictors of bone mineral status among children with CF and relatively mild lung disease. Thus, while clinicians caring for children with CF must consider DXA results in light of height, they cannot be completely reassured by concomitant short stature. Additional factors such as fracture history, glucocorticoid use, and pace of pubertal maturation must be considered.

Decreased HT-Z can result from delayed sexual maturation. Ht-Z is sensitive to maturational differences in peripubertal ages, so the effect of HT-Z on both WB and Sp-BMC may reflect the combined effects of smaller body size and pubertal delay. Puberty also has a pronounced effect on bone mineral accrual. Hypogonadotropic hypogonadism and delayed puberty cause low bone mineral status during adolescence with lingering effects into adulthood (37). In our sample, short stature and low BMC for age were not attributable to significantly delayed puberty, as puberty status of children with CF was similar to that of the healthy comparison group overall. While we cannot conclude that pubertal delay is not present based upon the small sample size in this study, the slight BA delay suggests that the timing of puberty in children with CF may lag somewhat behind that of the healthy comparison group. Pubertal delay was expected in CF based upon studies primarily from the 1970s and 1980s (16,17,43–47). The present study echoes more recent findings of Buntain et al. (10) who found no evidence of clinical pubertal delay in US subjects with mild to moderate CF pulmonary disease. Improved overall health status in children and adolescents with CF may be accompanied by both normalization of puberty and bone health. Whether the two are interrelated or independent manifestations of CF status is not clear.

Lean mass plays an important role in bone accretion and long-term bone health by maintaining mechanical forces on bone (48–51). Subjects with CF had significantly lower age-adjusted LBM-Z than the healthy comparison group, and in pubertal males WB-BMC deficits persisted after adjustment for height but not after adjustment for LBM. The evolution of decreased LBM and its contribution to BMC deficits are likely complex. LBM deficits not only play a causal role in BMC deficits, but also LBM and BMC deficits both reflect disease severity. Subjects with worse pulmonary status are likely to be less physically active and more nutritionally compromised, both of which can negatively impact LBM. We found that LBM independently predicted WB-BMC-Z and Sp-BMC-Z even after adjustment for height and other clinical factors including FEV₁. These findings suggest that in subjects with compromised bone health, efforts to improve BMC through LBM-improving interventions, such as physical activity and nutritional strategies, may be helpful.

Our results differ from the study of Bianchi *et al.* who studied 136 subjects with CF (age 3–24 y) compared to 410 healthy Italian subjects (2–25 y) in whom longitudinal data were available for 80 individuals with CF. In addition to having a wider age range, this study used a different approach for adjusting for body size differences between the CF and control groups. They reported significant deficits in spine and whole body measures despite size adjustments in children, adolescents, and young adults. In the Bianchi study, FEV₁ was lower (12% had FEV₁ <40%) and subjects with diabetes and portal hypertension were included (52). In contrast, Buntain's study of 85 Australian children and adolescents with CF (age 5–18 y) compared to 100 healthy controls found no differences in WB or Sp-BMD following adjustment for age, sex, HT, and LBM (10).

Unexpectedly, the estimated pattern of oral and inhaled glucocorticoid use was not found to significantly impact bone health. These results are in contrast to Bianchi *et al* who reported cumulative glucocorticoid dose. In the present study, subjects were recruited from three centers, and data on glucocorticoid use were available over variable periods of time ranging from a single visit to three years. These data may not accurately depict life-long patterns of glucocorticoid use and are a limitation of this study.

Additional study limitations should be noted. Bone density and bone geometry are key determinants of bone strength. While DXA-derived BMC measures can be adjusted for height, this technique does not account for other differences in bone geometry. Since bone geometry is responsive to muscle forces, states of compromised muscle mass and physical activity, such as occur with CF, may have significant differences in bone geometry that are not captured by DXA. Moreover DXA does not distinguish between cortical and trabecular bone, which may be differentially affected in disease processes. Neither the effects of physical activity on bone health, nor the differences in physical activity between our relatively healthy CF sample and our comparison group were assessed. Finally, while these results may apply to relatively healthy CF populations, generalization to the more severely affected child cannot be assumed.

In children and adolescents with mild to moderate CF and pancreatic insufficiency, 1) stature, 2) LBM, and 3) pulmonary function were independently associated with bone mineral status. While size-adjusted BMC was preserved, worsening disease severity was likely to be accompanied by BMC deficits and the risk of osteoporosis later in life. These findings underscore the importance of optimizing growth, including the accrual of BMC and LBM during childhood and adolescence.

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ABBREVIATIONS

CF, cystic fibrosis
 DXA, dual energy X-ray absorptiometry
 BMC, bone mineral content
 BMD, bone mineral density
 Sp-BMC, spine bone mineral content
 WB-BMC, whole body bone mineral content
 pQCT, peripheral quantitative computed tomography

HT-Z, height standard deviation score
 Wt-Z, weight standard deviation score
 LBM-Z, lean body mass standard deviation score
 BMI-Z, body mass index standard deviation score
 FM-Z, fat mass standard deviation score
 FEV₁, forced expiratory volume in one second
B. cepacia, *Burkholderia cepacia*
 MRSA, methicillin-resistant *Staphylococcus aureus*
 TS, Tanner stage
 BA, bone age
 CDC, Centers for Disease Control and Prevention
 y, years
 BA, bone age

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Figure 1.
Distribution of Whole Body (A) and Spine (B) BMC Relative to Age in Individuals with CF (black diamonds) and Healthy Comparison Group (gray circles).

Table 1Clinical Characteristics of the CF Sample and Healthy Comparison Group [mean $\pm$ SD (range)]

	CFGroup (n=82)	Healthy Comparison Group (n=322)
Sex (Females/Males)	40F/42M	176F/146M
Age, y (range)	13.2 $\pm$ 2.9 (8.2–18.7)	12.9 $\pm$ 2.9 (8.0–18.8)
Pubertal Status (n; years)		
Tanner Stage 1	F (n=4) 10.0 $\pm$ 0.7 M (n=10) 9.9 $\pm$ 1.3	F (n=27) 9.0 $\pm$ 0.9 M (n=32) 9.3 $\pm$ 1.0
Tanner Stage 2	F (n=11) 11.4 $\pm$ 1.3 M (n=11) 11.4 $\pm$ 1.6	F (n=28) 10.0 $\pm$ 1.3 M (n=30) 11.3 $\pm$ 1.6
Tanner Stage 3	F (n=6) 12.3 $\pm$ 1.2 M (n=7) 14.0 $\pm$ 1.5	F (n=40) 12.4 $\pm$ 1.6 M (n=24) 12.8 $\pm$ 1.5
Tanner Stage 4	F (n=14) 15.0 $\pm$ 1.9 M (n=9) 15.8 $\pm$ 2.0	F (n=56) 14.6 $\pm$ 2.0 M (n=34) 15.1 $\pm$ 1.5
Tanner Stage 5	F (n=5) 17.2 $\pm$ 1.3 M (n=5) 17.2 $\pm$ 1.0	F (n=25) 16.0 $\pm$ 1.8 M (n=26) 17.0 $\pm$ 1.3
Anthropometry		
Weight-Z [#]	−0.7 $\pm$ 0.9 (−3.7–1.7) **	0.3 $\pm$ 0.9 (−2.3–2.4)
Height-Z [#]	−0.7 $\pm$ 0.9 (−2.6–1.6) **	0.2 $\pm$ 0.9 (−1.9–2.2)
Body Mass Index-Z [#]	−0.3 $\pm$ 0.9 (−2.7–1.8) **	0.2 $\pm$ 0.9 (−3.1–2.1)
Lean Body Mass-Z [#]	−1.0 $\pm$ 1.0 (−3.7–1.6) **	0.0 $\pm$ 1.0 (−3.2–2.5)
Fat Mass-Z [#]	−0.7 $\pm$ 0.9 (−2.4–1.8) **	0.0 $\pm$ 1.0 (−2.7–3.3)
Glucocorticoid Use, yrs		
Interval assessed	2.4 $\pm$ 0.8 (0–3.0)	
Oral	1.2 $\pm$ 1.0 (0–3.0)	
Inhaled	1.1 $\pm$ 1.0 (0–3.0)	
Serum Values		
IPTH, pg/mL (n=81)	35 $\pm$ 20 (7.4–120)	
25-(OH)-D, ng/mL (n=56)	21 $\pm$ 6 (5–35)	

[#] adjusted for age and sex**
p<0.0001

Table 2
Body Composition as Measured by DXA , Mean $\pm$ SD (95% CI)

	CF	Healthy comparison group
Whole body	(n=79)	(n=318)
Bone area (cm ²)	1537 $\pm$ 280 (1474–1600) **	1660 $\pm$ 329 (1624–1697)
BMC (g)	1388 $\pm$ 421 (1294–1483) *	1542 $\pm$ 520 (1485–1600)
BMD (g/cm ²)	0.885 $\pm$ 0.117 (0.859–0.912)	0.904 $\pm$ 0.135 (0.89–0.92)
Spine	(n=81)	(n=319)
Spine area (cm ²)	46.2 $\pm$ 8.6 (44.3–48.1) **	49.9 $\pm$ 10.3 (48.7–42.2)
BMC (g)	35.6 $\pm$ 14.0 (32.5–38.7) #	40.4 $\pm$ 16.5 (38.6–87.2)
BMD (g/cm ²)	0.75 $\pm$ 0.18 (0.71–0.79)	0.78 $\pm$ 0.18 (0.76–0.80)
Total	(n=79)	(n=318)
Fat mass (kg)	8.9 $\pm$ 4.6 (7.9–9.9) ***	11.2 $\pm$ 5.3 (10.6–11.8)
Lean body mass (kg)	32.5 $\pm$ 9.9 (30.3–34.7) ***	36.1 $\pm$ 11.1 (34.9–37.3)

**
p<0.01

*
p=0.01

p = 0.02

p<0.0001

Table 3
BMC-Z Deficits in Subjects with CF Relative to Healthy Comparison Group after Adjusting for Covariates

Covariates	WB-BMC-Z (95%CI)	p-value	R ²	Sp-BMC-Z (95% CI)	p-value	R ²
Females						
HT-Z	-0.9 (-1.2- -0.5)	<0.001	0.08	-0.8 (-1.1- -0.4)	<0.001	0.07
HT-Z, LBM-Z	-0.2 (-0.5- 0.05)	0.11	0.45	-0.2 (-0.5- 0.1)	0.139	0.36
	-0.1 (-0.4- 0.15)	0.40	0.56	-0.2 (-0.5- 0.1)	0.22	0.42
Males						
HT-Z	-1.1 (-1.2- -0.7)	<0.001	0.14	-0.9 (-1.3 - -0.6)	<0.001	0.11
HT-Z, LBM-Z	-0.4 (-0.7- -0.1)	0.009	0.43	-0.3 (-0.6-0.04)	0.09	0.41
	-0.2 (-0.5- 0.07)	0.154	0.56	-0.01 (-0.3-0.3)	0.922	0.50

Table 4

Results of Multiple Regression Analysis of Clinical Parameters Affecting BMC-Z Scores in Children with CF

	β	p-value	95% CI
Spine			
HT-Z	0.3	0.02	0.07–0.55
LBM-Z	0.52	<0.001	0.26–0.84
FEV ₁ %	0.01	0.04	0.001–0.03
Whole Body			
HT-Z	0.46	<0.001	0.24–0.69
LBM-Z	0.31	0.004	0.09–0.51
FEV ₁ %	0.01	0.02	0.001–0.02