Bone accrual and structural changes over one year in youth with cystic fibrosis

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ARTICLE INFO

Keywords:
Cystic fibrosis
Bone accrual
Peripheral quantitative computed tomography
Bone health
DXA velocity
Z score

ABSTRACT

Background: Pediatric bone accrual governs peak bone mass and strength. Longitudinal studies of bone health in youth with cystic fibrosis (CF) may provide insight into CF-related bone disease (CFBD), a prevalent co-morbidity in adults with CF.

Methods: This one-year longitudinal study of youth with pancreatic insufficient CF, enrolled in a nutrition intervention study [n = 62 (36 M/26 F)] 1) examined dual-energy x-ray absorptiometry (DXA)-defined lumbar spine (LS) and total body less head (TBLH) bone accrual and 2) compared their changes in peripheral quantitative computed tomography (pQCT) cortical and trabecular tibial bone density and geometry to those of a healthy reference group [n = 143 (68 M/75 F)].

Main outcome measures were 1) DXA: lumbar spine areal bone mineral density (LSaBMD) and total body less head bone mineral content (TBLH-BMC), sex- and pubertal status-specific, height velocity (HV)-adjusted or HV and lean body mass velocity (LV-HMV)-adjusted annualized velocity-Z scores and 2) pQCT: age, sex, puberty status and, when appropriate, tibial length adjusted Z-scores for bone architecture measures.

DXA velocity-Z were compared to expected mean of 0 and correlations with clinical parameters (age, BMI-Z and FEV1%-predicted) tested. Within-subject comparisons of HV-adjusted and LBHMV-HV-adjusted DXA velocity-Z were conducted in CF.

pQCT Z-scores were compared between the two groups over one year using longitudinal models. Longitudinal relationships between measures of bone health and clinical parameters (age, BMI-Z and FEV1%-predicted) were examined in individuals with CF.

Results: DXA velocity-Z were higher than normal in females (p < 0.05) but not males with CF. HV-adjusted and LBHMV-HV-adjusted velocity-Z did not differ for LsBMD or TBLH-BMC. In males with CF, both HV-adjusted and LBHMV-HV-adjusted LsBMD velocity-Z scores correlated positively with age (HV rho: 0.39; p = 0.045 and LBHMV-HV rho: 0.47; p = 0.0046). In males with CF, BMI-Z correlated positively with HV-adjusted LsBMD velocity-Z (rho: 0.32; p = 0.034), but this relationship did not persist for LBHMV-HV (rho: 0.14; p = 0.42). In females with CF, no correlations between LBHMV-Z scores and age or BMI-Z were found (all p > 0.05). No correlations between LsBMD velocity-Z scores and FEV1%-predicted were seen in either sex (all p > 0.12). LBHMV-BMC velocity-Z scores were not correlated with clinical parameters in either sex (all p > 0.1). At baseline, multiple pQCT parameters were lower in CF (p < 0.05). pQCT Z-scores did not differ between baseline and one-year in either CF or reference group. In a longitudinal model comparing pQCT-Z changes in CF and reference, multiple pQCT-Z outcomes remained lower in CF, but the changes in parameters did not differ in CF vs reference (all p > 0.26). Lower pQCT outcomes in CF were largely restricted to males (CF group female sex

Abbreviations: CF, Cystic Fibrosis; DXA, Dual energy x-ray densitometry; BMC, Bone mineral content; aBMD, areal bone mineral density; HV, height velocity; LBM, lean body mass; pQCT, peripheral quantitative tomography; LS, lumbar spine; TBLH, total body less head; HAZ, height-for-age-Z-score adjusted; Vel-Z, velocity-Z; FEV1; Forced expiratory volume in one second.

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https://doi.org/10.1016/j.jcte.2022.100297
Received 28 December 2021; Received in revised form 21 March 2022; Accepted 24 March 2022
Available online 25 March 2022
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Introduction

With improved survival in individuals with cystic fibrosis (CF), CF-related bone disease (CFBD) has emerged as a prevalent adult morbidity affecting between 13 and 34% of people with CF [1,2]. CFBD is associated with increased rates of rib and vertebral fractures that can impair pulmonary clearance and function [3]. Bone accrual during childhood and adolescence govern accrual of peak bone mass and strength, which are determinants of fragility in later life. In CF, systemic inflammation and alterations in nutritional status, body composition, and endocrine function may underlie failure to accrue bone during this critical phase [1]. Longitudinal studies of bone health in youth and emerging adults are needed to understand the contribution of impaired bone accrual to CFBD and can be leveraged to examine the impact of advances in CF care and bone-specific interventions upon changes in bone.

Dual energy x-ray densitometry (DXA) is the standard for assessing and monitoring bone health. For children and adolescents, robust reference data are available and permit calculations of sex-specific, age-, and height-for-age-adjusted standard deviation scores (Z-score) for bone mineral content (BMC) and areal bone mineral density (aBMD). Sex- and pubertal-status specific reference data for annual bone accrual velocity help parse contributions of growth, pubertal status, and even lean body mass (LBM) accrual upon annualized bone accretion [7]. DXA has a number of limitations in its use in the bone health assessment in youth with chronic illness [4]. First, two-dimensional DXA images do not provide a true volumetric density and systematically inflate deficits in shorter stature and delayed puberty, common issues with pediatric chronic diseases [5]. Additionally, DXA neither differentiates cortical and trabecular bone nor characterizes trabecular density or cortical structure which are relevant for assessing bone fragility [6].

In research settings, peripheral quantitative computed tomography (pQCT) can be employed to differentiate cortical and trabecular bone compartments, measure cortical dimensions, and estimate bone strength in the tibia and radius. Pediatric reference data are now available for pQCT parameters and can be used to generate Z-scores [8]. Cross-sectional studies using pQCT have identified lower cortical and trabecular bone among adult males and females with CF and in female youth with CF but have not leveraged available pediatric reference data [6,9]. Importantly, no longitudinal studies have been performed in children with CF.

Accordingly, we examined annualized DXA bone accrual velocity Z-scores in youth and young adults with CF enrolled in a nutrition intervention study and their associations with clinical parameters [7]. We also compared one year changes in pQCT volumetric bone density and geometry Z-scores in this same cohort and relative to longitudinal reference group [10,11]. We hypothesized that bone accrual and changes in bone density and geometry would 1) be preserved in a generally healthy cohort of youth with CF but 2) less favorable with older age, poorer nutritional status, and worse pulmonary function.

Material and methods

Participants

Individuals with CF and pancreatic insufficiency (PI), ages 5–18 years, were recruited from ten CF centers for a nutrition intervention study between 2007 and 2011 (prior to FDA approval of CFTR modulators). The subset with pQCT at baseline and one year was included in this secondary analysis. Exclusion criteria included FEV1 < 40% predicted, residual pancreatic activity (faecal elastase > 15μg/g stool), liver disease (GGT > 3 × range) or chronic conditions affecting growth, diet, or nutritional status. CF subjects were randomized to receive either a choline-rich structured lipid nutritional supplement, or macronutrient-matched in addition to the standard CF diet with appropriate pancreatic enzyme replacement therapy [12–14]. Healthy Caucasian youth age < 19 years (to match the CF cohort) from the greater Philadelphia area who participated in a study of normal skeletal development served as a reference group [10]. Protocols for both studies were approved by the Institutional Review Board at the Children’s Hospital of Philadelphia, and informed consent was obtained from parents or participants >18 years of age. Assent was obtained from children ages 7–<18.

Anthropometry, pubertal staging, spirometry, DXA and pQCT measurements

Anthropometric measurements and pubertal staging were determined using previously described methods [10–13]. In subjects with CF, forced expiratory volume in one second percent predicted (FEV1%-predicted) was determined [15,16].

Lumbar spine (LS) and total body less head (TBLH) DXA were obtained at baseline for both CF and reference participants. LS DXA was obtained at one year for both groups, and TBLH DXA was obtained at one year in CF only. LBM was measured by DXA. Measurements for the CF group were obtained using a Hologic Discovery bone densitometer in array mode with version 12.4 software. Measurements for the healthy reference group were obtained using a Hologic Delphi/Discovery bone densitometer in array mode with version 12.3 software (Hologic Inc, Marlborough, MA) [10,12]. A spine phantom was scanned daily to monitor equipment performance [10]. pQCT scans of the left distal tibia were acquired using a Stratec XCT 2000 (Orthometrix, White Plains, NY, USA, software version 550) at baseline and one year. Tibia length was measured anthropometrically from the medial malleolus to the proximal medial tibia plateau. The reference line was placed at the proximal edge of the distal growth plate, and scans were acquired at 3%, 38% and 66% of tibia length with a voxel size of 0.4 mm and slice thickness of 2.3 mm. Outcomes included trabecular density at the 3% site and polar unweighted section modulus, cortical area, density, and thickness, and endosteal and periosteal circumferences at the 38% site. Measurement methods have been described [10].
Z-scores

Weight-, height- and BMI-Z-scores were calculated [17]. Sex- and age-specific, height-for-age-Z-score-adjusted LS aBMD Z-scores (HAZ-LSaBMD-Z) and TBLH bone mineral content (BMC) Z-scores (HAZ-TBLH-BMC-Z) were calculated using the Bone Mineral Density in Child- hood Study (BMDCS) reference dataset [6]. For the CF group, annualized LS and TBLH bone accrual were quantified as abMD and BMC velocity Z-scores using published sex- and pubertal status-specific equations that adjusted for height velocity only (HV-LSaBMD-Vel-Z and HV-TBLH-BMC-Vel-Z) as well as for both height velocity and LBM accrual (LBMV-HV-LSaBMD-Vel-Z and LBMV-HV-TBLH-BMC-Vel-Z). The LSaBMD-Vel-Z and TBLH-BMC-Vel-Z scores included here for youth with CF were previously reported in the reference development manuscript as an example of a childhood disease model of bone health [7].

pQCT bone density Z-scores were calculated relative to sex, age, and ancestry using reference values from a large local healthy sample [11]. Additional adjustment for tibial length was used to compute geometry Z-scores (section modulus, cortical area, periosteal circumference, and endosteal circumference) [11].

Calculations

Continuous variables were summarized using median, minimum and maximum (median [min; max]). Between group (CF vs healthy reference and female vs male) differences were tested using unpaired t-test or Wilcoxon rank-sum test, depending upon data normality. Annualized aBMD and BMC velocity-Z-scores were compared to expected average Z-score = 0 (+/−1 standard deviation) using unpaired t-test. Within group differences for continuous variables (baseline vs one year) were analyzed using paired t-test or Wilcoxon matched pairs signed rank test. The potential additional contributions of LBm accrual on bone accrual were studied in CF by comparing 1) HV-LSaBMD-Vel-Z and 2) HV-TBLH-BMC-Vel-Z on bone accrual. The LSaBMD-Vel-Z and TBLH-BMC-Vel-Z scores expected median of 0 (Supplemental Table 2). On average, within subjects, 1) HV-TBLH-BMC-Vel-Z did not differ from LBMV-HV-TBLH-BMC-Vel-Z and 2) HV-LSaBMD-Vel-Z did not differ from LBMV-HV-LSaBMD-Vel-Z (Fig. 1, Supplemental Table 2).

DXA velocity-Z in youth with CF

Overall, sex- and pubertal status-specific, HV- and LBMV-HV-adjusted BMC velocity-Z scores were normal in both males and females with CF. Females had higher than normal HV-LSaBMD-Vel-Z (p = 0.04) and LBMV-HV-LSaBMD-Vel-Z (p = 0.01) compared to an expected median of 0 (Supplemental Table 2). On average, within subjects, 1) HV-TBLH-BMC-Vel-Z did not differ from LBMV-HV-TBLH-BMC-Vel-Z and 2) HV-LSaBMD-Vel-Z did not differ from LBMV-HV-LSaBMD-Vel-Z (Fig. 1, Supplemental Table 2).

Lumbar spine aBMD-velocity and clinical parameters

In males with CF, both HV-LSaBMD-Vel-Z (rho = −0.35; p = 0.045) and LBMV-HV-LSaBMD-Vel-Z (rho = −0.47; p = 0.0046) correlated negatively with age. The positive correlation between BMI-Z and HV-LSaBMD-Vel-Z (rho = 0.37; p = 0.034) was not present for LBMV-HV-LSaBMD-Vel-Z (rho: 0.14; p = 0.42). In females with CF, no correlations between HV-LSaBMD-Vel-Z (rho: −0.15; p = 0.51) or LBMV-HV-LSaBMD-Vel-Z (rho: −0.30; p = 0.16) and age were found. Not unexpectedly, the tendency toward higher HV-LSaBMD-Vel-Z with increasing BMI-Z (rho: 0.38; p = 0.075) did not persist with LBMV-HV-LSaBMD-Vel-Z (rho: 0.15; p = 0.49) (Fig. 2). Neither HV-LSaBMD-Vel-Z nor LBMV-HV-LSaBMD-Vel-Z were correlated with baseline or one-year FEV1 in either males or females (all p > 0.12; data not shown).

In a combined model, HV-LSaBMD-Vel-Z remained positively associated with both BMI-Z and female sex, but its negative relationship with age was tempered (Supplemental Table 3). In a similar model with LBMV-HV-LSaBMD-Vel-Z as the outcome, the relationship of BMI-Z with lumbar spine bone accrual was lost (p = 0.42); however, the negative relationship with age re-emerged (0 = 0.016). No interactions between sex and either BMI-Z or age were found for either adjusted LSaBMD-Vel-Z.

Table 1

| Baseline data for reference and CF groups by sex. |
| Reference (N = 68) | CF (N = 36) |
|---|---|
| **Males** |  |
| Age (y) | 11.2 [5.1; 17.9] 10.8 [5.9; 17.8] 0.54 |
| Height-Z | 0.20 [−1.86; 2.13] −0.35 [−2.01; 0.95] 0.002 |
| Weight-Z | 0.34 [−1.52; 2.39] −0.34 [−1.32; 1.11] 0.004 |
| BMI-Z | 0.14 [−1.62; 2.10] −0.05 [−1.39; 1.18] 0.23 |
| Pubertal Stage | 30 (44%), 9 (13%), 7 17 (47%), 11 (30%), 5 0.06 |
| 1, 2, 3, 4, 5 | 10%, 12 (17%), 9 (14%), 2 (6%), 1 (3%) |
| FEV1% predicted | 100 [48; 136] (n = 34)  |
| **Females** |  |
| Reference (N = 75) | CF (N = 26) |
| Age (y) | 12.1 [5.3; 17.1] 9.3 [5.5; 16.4] 0.07 |
| Height-Z | 0.37 [−1.24; 1.95] −0.77 [−2.63; 1.72] <0.0001 |
| Weight-Z | 0.34 [−1.27; 1.91] −0.42 [−1.94; 1.36] <0.0001 |
| Pubertal Stage | 24 (32%), 8 (10%), 12 12 (46%), 6 (23%), 3 (12%), 5 (19%), 0 0.14 |
| 1, 2, 3, 4, 5 | (16%), 27 (30%), 5 (6%) |
| FEV1% predicted | 93.5 [36; 161]  |
In females with CF, baseline age was negatively correlated with section modulus, cortical area, cortical thickness, and cortical density Z-scores while BMI-Z was positively correlated with section modulus and periosteal circumference Z-scores and FEV1 positively correlated with section modulus, cortical area and periosteal circumference Z-scores (Example of these relationships shown in Fig. 3 and data shown in Supplemental Table 4).

To compare one-year pQCT-Z changes in CF and reference, age-, sex- and BMI-Z adjusted longitudinal models were constructed. As expected, BMI-Z remained positively associated with pQCT-Z parameters. Multiple pQCT-Z outcomes remained lower in CF vs. reference, but the change in these parameters did not differ in CF vs reference (all \( p > 0.26 \) for CF group*visit interaction). The positive beta-coefficients for the CF group*female sex interaction suggest that the lower outcomes in CF were largely restricted to males (Table 2).

Clinical parameters and pQCT outcomes in males and females with CF

To examine the longitudinal relationships of bone geometry and strength with clinical parameters in CF, models that included age, BMI-Z, FEV1, and visit were constructed for males and females separately. In males, pQCT-Z outcomes did not change over the year and were positively associated with both BMI-Z and FEV1. Age was negatively associated with section modulus and periosteal circumference (Table 3A). The relationships between periosteal circumference and BMI-Z (\( p < 0.001 \)) and FEV1 (\( p = 0.03 \)) but not age (\( p = 0.16 \)) persisted with adjustment for endosteal circumference-Z with which periosteal circumference is robustly associated (\( \beta = 0.59, P < 0.001 \)).

As occurred with males, pQCT-Z outcomes did not change over the year and multiple pQCT measures were positively associated with FEV1 in females with CF. In contrast, pQCT-Z were not associated with BMI-Z (Table 3B). The relationship between periosteal circumference and FEV1 (\( p = 0.099 \)) was tempered with adjustment for endosteal circumference-Z with which periosteal circumference is robustly associated (\( \beta = 0.32, P < 0.001 \)). Also distinct from males, cortical density-Z was negatively associated with age and FEV1.

Discussion

With improved longevity, bone health in people with CF is of increasing importance. As the foundation for adult bone health is laid during childhood, understanding risk factors for compromised bone accrual and architecture is crucial to determine screening, prevention and intervention for CFBD. The present study leveraged one-year longitudinal data and sex- and pubertal status-specific equations that adjusted for height velocity as well as height velocity and lean body mass accrual. While DXA measures of bone health were generally normal in youth with CF and accrual was normal over one year, accrual tended to be worse at older ages and better with higher BMI-Z, a finding at least partly attributable to lean body mass gains. Despite generally normal measurements and accrual over one year, deficits in bone geometry and strength were found and associated with the same clinical factors and with pulmonary function.

Dxa

Multiple studies have demonstrated lower BMD in adults with CF. However, the onset and progression of compromised bone is unknown [1]. We aimed to examine bone accrual in childhood, as a mechanism for development of CFBD. As bone accrual is a dynamic process, dependent on age, sex, puberty and height velocity, as well as lean body mass accrual we leveraged previously derived DXA velocity-Z scores which accounted for these confounders.

Bone accrual over one year was normal in CF, and we found a
positive association between accrual and BMI-Z. The relationship between BMI-Z and bone health was also examined by Sharma et al, who demonstrated a positive relationship between change in BMI-Z and change in bone-area-for-height-adjusted-Z-score over an average of 4.0 years [19]. As BMI-Z is a surrogate for nutritional status, LBM, and weight-bearing forces, these factors may underlie these relationships. In the functional muscle-bone unit model, additional lean body mass may exert more muscle forces on bone, thereby improving bone mineral deposition [20]. Supporing this conclusion, the relationships of BMI-Z with bone accrual-Z were no longer present with use of velocity-Z that accounted for LBM accrual over the year.

Highly effective modulator therapies are associated with increases in BMI-Z and LBM [21,22] and, thus, have the potential to alter the trajectory of bone health in CF. Use of LBM velocity-adjusted bone accrual-Z scores as used here, may be able to ascertain the extent to which improvements in bone accrual are attributable to LBM; if accrual remains robust after this adjustment, additional roles of reduced inflammation and direct bone effects may be operative. Ongoing studies are designed to address these questions [23].

The present study also found sex differences in bone density and bone accrual. Males with CF had lower baseline HAZ-TBLH-BMC-Z compared to the reference cohort, but one-year bone TBLH BMC accrual was normal. Lumbar spine bone accrual was normal in males with CF but was slower than that of their female counterparts and more slow at older ages. These sex and age differences persisted with adjustment for lean body mass accrual. Rossini et al found adult males with CF had lower lumbar spine and whole body T-scores and slightly higher rates of vertebral fractures than females [18]. Our findings suggest that sex-specific bone differences may begin in childhood and be influenced by differences in bone accrual, but the mechanism remains to be elucidated. Of course, these differences may be more greatly related to the robust lumbar spine accrual in the CF female cohort (0.40 [1.32; 1.61]) than impairments in the CF male cohort (−0.13 [−3.28; 2.17]).

**pQCT**

While most baseline DXA scores were not different between the cohorts, multiple pQCT parameters were lower in CF and highlight the increased sensitivity of pQCT to detect bone alterations. DXA may not accurately predict fracture risk in CF, as Stephenson et al found higher BMD in individuals with CF with fractures, as compared to those without [6].

Our findings of pQCT deficits are consistent O’Brien et al. and Kelly et al. However, in contrast to the present study, O’Brien et al examined the radius, which is a skeletal site exposed to limited weight-bearing loads, and the current study of tibia pQCT utilized more robust reference data [24,25]. A cross sectional study using HR-pQCT in adults with CF demonstrated inferior bone microarchitecture that was worse than expected for the lower BMI [9]. Despite the baseline differences between CF and reference, and a trend toward earlier pubertal status in males with CF, the various pQCT parameters of bone geometry and strength examined in this study remained stable over one year in our youth with CF. These findings suggest that, while deficits in cortical and trabecular bone appear early in CF, substantial losses do not occur over just one year in a generally healthy CF population.

Our findings of bone deficits in a healthy cohort of youth with CF suggest that sex-specific bone differences may begin in childhood and be influenced by differences in bone accrual, but the mechanism remains to be elucidated. Of course, these differences may be more greatly related to the robust lumbar spine accrual in the CF female cohort (0.40 [1.32; 1.61]) than impairments in the CF male cohort (−0.13 [−3.28; 2.17]).

**Fig. 2. Relationships between HV-LSaBMD-Vel-Z and clinical parameters in CF.** In males with CF, HV-LSaBMD-Vel-Z and LBMV-HV-LSaBMD-Vel-Z (rho: −0.47; p = 0.0046) were negatively correlated with age. HV-LSaBMD-Vel-Z was positively correlated with BMI-Z; the latter relationship did not persist for LBMV-HV-LSaBMD-Vel-Z (rho: 0.14; p = 0.42). In females with CF, neither HV-LSaBMD-Vel-Z nor LBMV-HV-LSaBMD-Vel-Z were related to age while the tendency for higher HV-LSaBMD-Vel-Z with increasing BMI-Z did not persist for LBMV-HV-LSaBMD-Vel-Z (rho: 0.15; p = 0.49). Lines of fit are shown in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
suggest bone accrual and strength impairments may be present early in life and not completely dependent on health status. Consistent with these findings, cavarial organ cultures from mice with genetic inactivation of CFTR demonstrated less bone formation and lower numbers of osteoblasts than cultures from wild type [26]. While few studies have examined bone differences in infants and young children with CF, linear growth might be utilized as a surrogate measure of bone health. Early nutritional interventions in infants diagnosed at birth led to normal weight status at age one year, but persistent length deficits [27]. These early length deficits are likely responsible for persistent short stature in CF, as height velocity in mid- to late- childhood was found to be normal [28].

While studies in mice, infants and young children suggest some bone deficits in CF exist due to fundamental differences present at birth; clinical factors, likely also contribute to differences throughout life. In our generally healthy population of youth with CF, multiple markers of bone health were associated with higher BMI-Z and improved pulmonary function, and were more prominent in males than in females. Additionally, youth with CF demonstrated worse pQCT-Z scores at older ages. Given that ~ 11% of bone mass is accrued during the period of emerging adulthood, this phase may represent a critical time in development of CFBD [7]. Brookes et al identified multiple compromised
 parameters improved in adults with two years of treatment with the CFTR modulator, ivacaftor. The roles of reduced inflammation, altered the disease landscape for the majority of people with CF, were not available to participants at the time of this study, and thus, may limit the generalizability of these results to the present day, when the majority of patients with CF over age 6 are treated with HEMT. Interestingly, while Putman et al found pQCT changes in adults after two years of ivacaftor, there were no changes seen in children, which highlights the potential contribution of intrinsic bone deficits in CF [30]. Findings from this study may inform future investigations of bone geometry and strength in youth treated with HEMT. Finally, the pQCT measured the tibia, a weight-bearing long bone, not spine or ribs where CF pathologic fractures occur. Future studies of DXA in CF should examine the hip and radius, as people with CF will likely also be at increased risk of traditional osteoporotic fractures associated with aging. The 2011 European and Australian guidelines recommend DXA starting around eight years of age [31–33]. The 2005 US guidelines recommend only screening children with risk factors for low BMD, and if normal bone density (T/Z score ≥ 1.0), at initial evaluation, repeating once every five years [1]. This approach may limit the ability to detect changes occurring during emerging adulthood, which is a vulnerable period of bone accrual. Future studies should look more closely at bone health during this window of development, to inform future guidelines for evaluating bone density in CF. In conclusion, bone accrual was preserved in youth with CF, but was worse with older age and better with higher BMI-Z, the latter attributable to greater lean body mass accrual. Despite the preserved DXA outcomes, deficits in bone geometry and strength were present and became more prominent during emerging adulthood, especially among males. Longer longitudinal studies with a focus on the timing of bone deficits are warranted to determine the appropriate screening interval in this population and to better understand the relationships of DXA-

### Table 2
Longitudinal model of pQCT-Z outcomes over one year in CF vs Reference adjusted for sex and baseline age and BMI-Z.

| pQCT-Z Score          | Baseline Age | BMI-Z | Visit | CF Group | CF Group*Visit | CF Group*Sex |
|-----------------------|--------------|-------|-------|----------|---------------|--------------|
|                       | β            | p-value | β    | p-value | β    | p-value | β    | p-value | β    | p-value |
| Section Modulus       | −0.01        | 0.20   | 0.51  | < 0.001 | −0.08 | 0.41   | −0.56 | < 0.001 | 0.14 | 0.41   |
| Cortical Density      | −0.05        | 0.003  | 0.02  | 0.770   | 0.02  | 0.87   | −0.30 | 0.13    | 0.13 | 0.39   |
| Cortical Area         | 0.00         | 0.73   | 0.55  | < 0.001 | −0.06 | 0.52   | −0.64 | < 0.001 | 0.20 | 0.28   |
| Cortical Thickness    | 0.005        | 0.72   | 0.41  | < 0.001 | −0.03 | 0.81   | −0.62 | 0.0010  | 0.24 | 0.26   |
| Periosteal Circumference | −0.01       | 0.32   | 0.49  | < 0.001 | −0.07 | 0.42   | −0.39 | 0.0003  | 0.11 | 0.50   |
| Endosteal Circumference | −0.01    | 0.35   | 0.20  | < 0.001 | −0.05 | 0.63   | −0.02 | 0.89    | −0.04 | 0.82   |
| Trabecular Density    | 0.00         | 0.96   | 0.23  | < 0.001 | 0.00  | 0.99   | −0.13 | 0.56    | −0.06 | 0.82   |

### Table 3
A and B: Relationships of pQCT-Z scores over one year with clinical parameters in CF.

| pQCT-Z Outcome | Age | BMI-Z | FEV1 % predicted | Visit |
|----------------|-----|-------|------------------|-------|
|                | β   | p-value | β    | p-value | β    | p-value |
| Section Modulus | −0.14 | 0.001  | 0.58  | 0.002  | 0.02 | 0.004  |
| Cortical Density | −0.07 | 0.16   | 0.11  | 0.59   | −0.01 | 0.09   |
| Cortical Area   | −0.08 | 0.11   | 0.85  | < 0.001 | 0.02 | 0.02   |
| Cortical Thickness | 0.09  | 0.07   | 1.03  | < 0.001 | 0.01 | 0.45   |
| Periosteal Circumference | −0.15 | < 0.001 | 0.38 | 0.02   | 0.02 | 0.002  |
| Endosteal Circumference | −0.12 | 0.96   | −0.06 | 0.98   | −0.30 | 0.05   |
| Trabecular Density | −0.10 | 0.09   | 0.59  | 0.02   | 0.01 | 0.25   |

**Males**

| pQCT-Z Outcome | Age | BMI-Z | FEV1 % predicted | Visit |
|----------------|-----|-------|------------------|-------|
|                | β   | p-value | β    | p-value | β    | p-value |
| Section Modulus | −0.04 | 0.20   | 0.22  | 0.049  | 0.03 | 0.001  |
| Cortical Density | −0.23 | < 0.001 | −0.01 | 0.94   | −0.02 | 0.006  |
| Cortical Area   | −0.07 | 0.07   | 0.22  | 0.10   | 0.01 | 0.01   |
| Cortical Thickness | −0.08 | 0.10   | 0.18  | 0.32   | 0.01 | 0.26   |
| Periosteal Circumference | −0.03 | 0.36   | 0.17  | 0.10   | 0.01 | 0.001  |
| Endosteal Circumference | −1.77 | 0.47   | 1.78  | 0.47   | 0.02 | 0.92   |
| Trabecular Density | −0.02 | 0.69   | 0.34  | 0.13   | −0.01 | 0.04   |

**Females**

| pQCT-Z Outcome | Age | BMI-Z | FEV1% predicted | Visit |
|----------------|-----|-------|------------------|-------|
|                | β   | p-value | β    | p-value | β    | p-value |
| Section Modulus | −0.04 | 0.20   | 0.22  | 0.049  | 0.03 | 0.001  |
| Cortical Density | −0.23 | < 0.001 | −0.01 | 0.94   | −0.02 | 0.006  |
| Cortical Area   | −0.07 | 0.07   | 0.22  | 0.10   | 0.01 | 0.01   |
| Cortical Thickness | −0.08 | 0.10   | 0.18  | 0.32   | 0.01 | 0.26   |
| Periosteal Circumference | −0.03 | 0.36   | 0.17  | 0.10   | 0.01 | 0.001  |
| Endosteal Circumference | −1.77 | 0.47   | 1.78  | 0.47   | 0.02 | 0.92   |
| Trabecular Density | −0.02 | 0.69   | 0.34  | 0.13   | −0.01 | 0.04   |

* The relationship between periosteal circumference and FEV1 % predicted (p = 0.099) was tempered with adjustment for endosteal circumference-Z with which periosteal circumference is robustly associated (β = 0.32, P < 0.001).

* The positive relationships between periosteal circumference and BMI-Z (p < 0.001) and FEV1 % predicted (p = 0.03) but not age (p = 0.16) persisted with adjustment for endosteal circumference-Z with which periosteal circumference is robustly associated (β = 0.59, P < 0.001).
defined bone density with more refined measures of bone fragility and ultimately with fracture risk.

**Funding acquisition**

This work was supported by NIDDK (R44DK060302), and the Nutrition Center at the Children’s Hospital of Philadelphia (VS) and the Cystic Fibrosis Foundation (BASS2000) (RB).

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at [https://doi.org/10.1016/j.jcte.2022.100297](https://doi.org/10.1016/j.jcte.2022.100297).

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