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Young adults with cystic fibrosis have altered trabecular microstructure by ITS-based morphological analysis

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Abstract

Summary—Young adults with cystic fibrosis have compromised plate-like trabecular microstructure, altered axial alignment of trabeculae, and reduced connectivity between trabeculae that may contribute to the reduced bone strength and increased fracture risk observed in this patient population.

Introduction—The risk of fracture is increased in patients with cystic fibrosis (CF). Individual trabecular segmentation (ITS)-based morphological analysis of high-resolution peripheral quantitative computed tomography (HR-pQCT) images segments trabecular bone into individual plates and rods of different alignment and connectivity, which are important determinants of trabecular bone strength. We sought to determine whether alterations in ITS variables are present in patients with CF and may help explain their increased fracture risk.

Methods—Thirty patients with CF ages 18–40 years underwent DXA scans of the hip and spine and HR-pQCT scans of the radius and tibia with further assessment of trabecular

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Compliance with ethical standards

Conflicts of interest None.

microstructure by ITS. These CF patients were compared with 60 healthy controls matched for age (± 2 years), race, and gender.

Results—Plate volume fraction, thickness, and density as well as plate-plate and plate-rod connectivity were reduced, and axial alignment of trabeculae was lower in subjects with CF at both the radius and the tibia ($p < 0.05$ for all). At the radius, adjustment for BMI eliminated most of these differences. At the tibia, however, reductions in plate volume fraction and number, axially aligned trabeculae, and plate-plate connectivity remained significant after adjustment for BMI alone and for BMI and aBMD ($p < 0.05$ for all).

Conclusions—Young adults with CF have compromised plate-like and axially aligned trabecular morphology and reduced connectivity between trabeculae. ITS analysis provides unique information about bone integrity, and these trabecular deficits may help explain the increased fracture risk in adults with CF not accounted for by BMD and/or traditional bone microarchitecture measurements.

Keywords

Bone microarchitecture; Cystic fibrosis; Dual-energy X-ray absorptiometry; High-resolution peripheral quantitative computed tomography; Individual trabecula segmentation

Introduction

Patients with cystic fibrosis (CF) have an increased risk of low bone density and fracture. Over the past several decades, patients with CF have been living longer, and skeletal complications have become increasingly prevalent [1, 2]. Patients with CF have multiple risk factors for low bone density, including pancreatic insufficiency, poor nutrition, chronic inflammation, delayed puberty, vitamin D deficiency, glucocorticoid use, and possibly cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction itself [3]. Despite clinical guidelines published in 2005 [1] and 2011 [4] focused on addressing some of these modifiable risk factors for poor bone health, CF-related bone disease continues to remain a significant clinical problem [5]. Fractures in patients with CF can have particularly adverse consequences. For example, rib fractures may lead to splinting, reduced lung volumes, and compromised airway clearance, and vertebral fractures may result in significant pain, kyphosis, and extrinsic lung restriction. Ultimately, severe bone disease may constitute a contraindication to lung transplantation.

Multiple studies have confirmed that areal bone mineral density (aBMD) measured by DXA is reduced in patients with CF [6–10]. However, DXA images are two-dimensional and may be artifactually low in individuals with smaller bones, leading to an underestimation of three-dimensional bone density [11]. Moreover, DXA may not accurately predict fractures in patients with CF [12]. To understand the alterations in three-dimensional bone structure and density in patients with CF, we previously performed a cross sectional study evaluating bone microarchitecture of the radius and tibia using high-resolution peripheral quantitative computed tomography (HR-pQCT) in young adults with CF compared to age-, gender-, and race-matched healthy volunteers [13]. We found that at the radius and tibia, young adults with CF had smaller bone cross-sectional area, lower volumetric BMD, and compromised

cortical and trabecular microarchitecture. These differences were associated with lower estimates of bone strength. These deficits, particularly in trabecular bone at the tibia, were greater than expected based on BMI and DXA-derived areal BMD differences.

Individual trabecula segmentation (ITS) is a recently developed approach to characterizing the morphology of trabecular bone, including the orientation, connectivity, and plate and rod-like structure of individual trabeculae. Previous studies have shown that variations in plate and rod characteristics may help explain skeletal differences between Chinese and Caucasian women [14, 15], premenopausal women with idiopathic osteoporosis [16], and amenorrheic female athletes [17]. In particular, alterations in plate and rod structure were found to discriminate postmenopausal women with prevalent fragility fracture despite no differences in DXA-derived BMD T-scores [18, 19]. At present, this tool has not been studied in the CF population, and the underlying differences in trabecular plate and rod morphology, connectivity, and orientation in young adults with CF are not currently known.

The goal of this study was to characterize the trabecular rod- and plate-like structure of the radius and tibia of young adults with CF using ITS and to determine whether alterations in these variables may explain the increased fracture risk observed in this patient population.

Materials and methods

Subjects and eligibility criteria

Subject recruitment and eligibility have been previously described [13]. Briefly, young adults with CF ages 18–40 were recruited from the Massachusetts General Hospital (MGH) and Boston Children's Hospital (BCH) Cystic Fibrosis Centers. Exclusion criteria for subjects with CF included history of solid organ transplantation, current pregnancy, and *Burkholderia dolosa* infection. Potential subjects who met inclusion/exclusion criteria were approached at their routine clinic visits and invited to participate in the study. Data from healthy volunteers were obtained from the MGH HR-pQCT normal reference database. Two healthy volunteers were matched to each subject with CF by age (within 2 years), race, and gender. Exclusion criteria for healthy volunteers included current pregnancy or history of disorders known to affect bone metabolism. The protocol was approved by the Partners Healthcare Human Research Committee with ceded review by the Boston Children's Hospital Committee on Clinical Investigation. Written informed consent was obtained from all participants.

Clinical assessments

In subjects with CF, information regarding medical history, hospitalizations, medication use, fracture history, pubertal and reproductive history, lifetime glucocorticoid exposure, most recent pulmonary function test results, and CF genotype was obtained from surveys and review of medical records. Race was self-reported. When available, reported fractures were confirmed with x-ray reports. In all subjects, height was measured on a wall-mounted stadiometer and weight on an electronic scale.

Laboratory assessment

Morning fasting serum and urine samples were obtained in subjects with CF and were processed through the Massachusetts General Hospital Clinical Laboratory Research Core. Serum 25-hydroxyvitamin D (25[OH]D) levels were measured by chemiluminescent microparticle immunoassay (Abbott Diagnostics, Abbott Park, IL). Bone specific alkaline phosphatase (BSAP) levels were obtained by enzyme immunoassay (Quidel Corporation, San Diego, CA). Parathyroid hormone (PTH) and C-telopeptide (CTX) levels were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN). Urine N-telopeptide (NTX) levels were measured by competitive-inhibition enzyme-linked immunosorbent assay (Alere Scarborough Inc, Scarborough ME) and amino-terminal propeptide of type I collagen (P1NP) by quantitative radioimmunoassay (Orion Diagnostica, Espoo, Finland).

DXA scans

Areal BMD of the lumbar spine in the posterior-anterior (PA) projection, total hip, femoral neck, and total body less head were measured using DXA (Discovery A, Hologic Inc, Bedford, MA). Total body scans were analyzed for body composition, including lean and fat mass. A standard quality control program was employed that included daily measurement of a Hologic DXA anthropomorphic spine phantom and visual review of all images by an experienced investigator.

HR-pQCT scans

HR-pQCT (Xtreme CT, Scanco Medical AG, Basserdorf, Switzerland) scans of the distal radius and tibia were obtained using previously described methods [20–22]. The non-dominant limb was scanned at a fixed distance of 9.5 mm (radius) and 22.5 mm (tibia) from the endplate, consisting of 110 CT slices with an isotropic voxel size of 82 μm . The contralateral limb was imaged if the subject reported a prior fracture of the non-dominant limb. Quality control was maintained with daily scanning of the manufacturer's phantom. HR-pQCT scans were repeated if significant motion artifact was noted. Standard HR-pQCT outcomes, extended cortical analyses, and microfinite element analyses have been previously reported.

Individual trabecula segmentation

The trabecular bone compartment of each HR-pQCT image was manually extracted from the cortex and underwent ITS-based analyses as previously described [16, 23, 24]. The following trabecular morphological parameters were obtained: plate and rod bone volume fraction (pBV/TV and rBV/TV); axially aligned bone volume fraction along the longitudinal axis (aBV/TV); trabecular plate and rod number density (pTbN and rTbN, 1/mm); mean trabecular plate and rod thickness (pTbTh and rTbTh, mm); mean trabecular plate surface area (pTbS, mm²); mean trabecular rod length (rTbL, mm); and plate-plate, plate rod, and rod-rod junction density (P-P JuncD, R-P JuncD, and R-R JuncD, 1/mm³). Plate-to-rod ratio (PR ratio) was calculated as the plate bone volume divided by the rod bone volume.

Statistical analysis

Statistical analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). Clinical characteristics of subjects with CF and healthy volunteers were compared using independent samples two-sided *t* tests for normally distributed data or Wilcoxon rank sum for non-normally distributed data. Primary outcomes were ITS-derived trabecular parameters at the radius and tibia. The study was designed to match two healthy volunteers to each subject with CF to minimize effects of age, race, and gender on bone outcomes. To account for this matching, generalized linear models adjusting for each matched group were used to compare differences in means of areal BMD and HR-pQCT parameters between CF subjects and healthy volunteers. Multivariable linear regression was then performed adjusting for BMI, followed by an additional analysis adjusting for total hip areal BMD in addition to BMI. BMI was chosen as a covariate of interest based on correlation with total BV/TV at the radius and tibia (Pearson $r=0.53-0.57$, $p < 0.001$) and based on the fact that BMI tends to be lower in CF patients and has been shown to correlate with important clinical outcomes in this patient population. Total hip areal BMD was chosen because this site represents a balance of both cortical and trabecular bone.

To evaluate associations between ITS parameters and clinical characteristics, laboratory results, and bone strength estimates among subjects with CF, correlations were performed using Pearson correlation coefficient, or Spearman correlation coefficient in the case of non-normally distributed data. Linear regression was used to determine if the presence of F508del mutation was a significant predictor of ITS parameters in subjects with CF.

Data are reported as mean $\pm$ standard deviation (SD) unless otherwise noted, and *p* values <0.05 are considered statistically significant.

Results

Cohort characteristics and aBMD

Clinical characteristics of the healthy volunteers and the subjects with CF are presented in Table 1. The mean age of all subjects was 25 years, and 60 % were female. All subjects enrolled in this study were of Caucasian race, which reflects the Caucasian predominance observed in the CF population. Young adults with CF were shorter, weighed less, and had a lower BMI than healthy volunteers.

The clinical characteristics of the CF cohort have been previously described in detail [13]. This represents an ambulatory population with mild-to-moderate pulmonary impairment indicated by a mean fractional expired volume in 1 s (FEV1) of 75 ± 24 % of the predicted value. Most subjects had at least one copy of the most common mutation, delF508, and 90 % had pancreatic insufficiency requiring pancreatic enzyme replacement. CF-related diabetes was present in 17 % of patients. Median 25(OH)D level was 28 (range 12–90) ng/mL, and 25(OH)D levels did not vary by season of study visit ($p = 0.41$). Subjects reported dietary and supplement vitamin D intake of 2380 ± 2490 IU/day and calcium intake of 2240 ± 1750 mg/day. Mean age of menarche in females was 12.7 ± 1.3 years, and two subjects reported a history of amenorrhea greater than 3 months. All women were premenopausal. Two men reported a history of delayed puberty, and none of the male subjects reported a history of

hypogonadism or were treated with testosterone replacement at the time of the study visit. Twenty-three percent of subjects had experienced at least one fracture involving a rib (3 patients), wrist (2 patients), ankle (1 patient), or vertebra (1 patient).

Subjects with CF had lower areal BMD at the lumbar spine, total hip, femoral neck, and total body less head. BMD Z-scores were below -1.0 in 73 % of CF subjects and below -2.0 in 23%.

ITS results

Radius—ITS results of the radius are presented in Table 2 and Fig. 1. On unadjusted analyses, subjects with CF had significantly compromised plate-like characteristics of trabecular bone of the radius, with lower pBV/TV, pTbN, pTbTh, and pTbS. P-P JuncD and R-P JuncD were reduced in CF patients, indicating lower plate connectivity. CF subjects had a lower total proportion of plate-like bone volume (PR ratio) and had fewer axially aligned trabeculae (aBV/TV) compared with healthy volunteers. Rod-like characteristics were similar between groups except for a slightly reduced rTbTh observed in CF patients.

After adjustment for BMI, all differences were attenuated with the exception of rTbTh, and adjustment for BMI and aBMD eliminated all differences between subjects with CF and healthy volunteers.

Tibia—Similar to the radius, plate-like differences predominated at the tibia (Table 2, Figs. 1 and 2), with lower pBV/TV, pTbTh, pTbN, P-P JuncD, and R-P Junc D in subjects with CF compared to healthy volunteers. Axial alignment (aBV/ TV) was also reduced. Rod-like trabecular bone characteristics were similar with the exception of a lower rBV/TV in CF patients, and the P:R ratio was similar between the two groups.

These differences remained significant after adjustment for BMI with the exception of rBV/TV and pTbTh. Accounting for both BMI and aBMD, subjects with CF continued to have reduced pBV/TV, aBV/TV, pTbN, and P-P JuncD compared to healthy volunteers.

ITS predictors of estimated bone strength

As previously published, estimated bone strength by microfinite analyses was lower in young adults with CF compared to healthy volunteers [13]. ITS parameters strongly correlated with compressive stiffness at both the radius and the tibia in patients with CF. The strongest ITS predictors of stiffness and failure load at both the radius and the tibia, respectively, were pBV/TV ($r = 0.89$ and 0.78 , $p < 0.0001$), aBV/TV ($r = 0.87$ and 0.76 , $p < 0.0001$), pTbN ($r = 0.87$ and 0.73 , $p < 0.0001$), and P-P JuncD ($r = 0.89$ and 0.73 , $p < 0.0001$). At the radius, pTbTh ($r = 0.87$) and R-P JuncD ($r = 0.88$) were also strongly correlated with stiffness ($p < 0.0001$).

Associations of plate bone volume fraction with clinical characteristics

As illustrated in Table 3, multiple clinical variables were associated with the volume of plate-like trabeculae at the radius and tibia. Pulmonary status, reflected by FEV1, showed the strongest correlation with pBV/TV at both the radius and the tibia. BMI and lean mass,

although not fat mass, were also strongly correlated with plate-like trabecular bone. Bone resorption markers (serum CTX and urine NTX) showed no significant correlations (data not shown), but markers of bone formation (P1NP and BSAP) were positively associated with pBV/TV at the radius, with a similar though nonsignificant trend at the tibia. Serum 25(OH)D concentration was positively correlated with pBV/TV at the tibia, although not at the radius. PTH was negatively associated with pBV/TV at the radius with a similar trend at the tibia ($p = 0.05$). The presence or absence of the F508del mutation and reported lifetime oral glucocorticoid exposure did not affect plate-like bone qualities (data not shown). ITS variables did not distinguish between patients who had experienced prior fracture, although the small number of fractures ($n = 7$) limited the power to detect this association.

Discussion

In this study, ITS-based morphological analysis of HR-pQCT images revealed significant differences in trabecular bone characteristics between young adults with CF and age-, race-, and gender-matched healthy volunteers. Patients with CF had fewer, thinner, and less connected trabecular plates and altered alignment of trabeculae, whereas rod-like morphology remained relatively preserved. Because these plate-like qualities had the strongest correlation with bone strength estimates, alterations in trabecular plates may help explain the tendency for CF patients to fracture trabecular-rich bones, such as ribs and vertebrae. Clinical factors including nutritional status, vitamin D and PTH levels, and lung function were directly associated with the fraction of plate-like trabeculae, suggesting that addressing these potentially modifiable issues may represent important interventions for improving bone structure.

To our knowledge, this is the first study to use ITS-based morphological analysis to characterize trabecular bone morphology and structure in the CF population. We previously found that young adults with CF patients have compromised bone microarchitecture using HR-pQCT-based standard analysis and extended cortical analysis [13]. At the radius, reductions in cortical and trabecular thickness along with trabecular density were noted, and at the tibia, patients with CF had lower trabecular vBMD that was associated with fewer and thinner trabeculae along with wider separation and greater heterogeneity. However, the specific trabecular morphological differences could not be appreciated without using ITS. Adding to these prior data, we have now determined that reductions in trabecular vBMD are primarily due to altered plate-like trabecular morphology, alignment, and connectivity with relative preservation of the rod-like structure of bone.

Previous studies utilizing ITS have confirmed that trabecular microstructure, especially the plate-like morphology and the axial alignment of trabeculae, is of particular clinical importance. Postmenopausal women with osteopenia and fractures had fewer trabecular plates, less axially aligned trabeculae, and less trabecular connectivity than those without fractures, despite similar DXAT-scores [18]. Similar to our findings in patients with CF, premenopausal women with idiopathic osteoporosis had decreased plate volume fraction along with a less connected and less axially aligned trabecular network, although trabecular plate and rod thickness were unchanged in these patients, compared to the reduced plate thickness noted in young adults with CF [16]. Similarly, plate-like trabeculae were found to

be depleted in postmenopausal women with primary hyperparathyroidism [25]. Greater plate bone volume fraction and high plate number density were also noted in premenopausal Chinese women compared to Caucasian women [26], and Chinese women have a greater loss of plate-like trabeculae with aging [14]. In addition, amenorrheic athletes had decreased plate volume fraction, plate number density, and plate-plate connectivity, and those athletes with recurrent stress fractures had alterations in plate volume fraction, axially aligned trabeculae, plate number and thickness, and connectivity at the radius [17]. These differences are similar to the findings in young adults with CF in this study, which may help to explain their increased fracture risk.

We previously reported that young adults with CF have compromised estimated bone strength at the radius and tibia by microfinite element analysis [13]. In the present study, we found that bone strength estimates in patients with CF were strongly associated with plate-like characteristics of trabeculae. These findings are similar to other studies showing that plate-like trabeculae were the primary determinants of bone strength, and a higher plate-to-rod ratio was associated with greater estimated bone strength [23, 27]. Deficits in trabecular plate structure and connectivity leading to lower bone strength may explain as to why patients with CF often fracture trabecular-rich bones, such as ribs and vertebrae.

Optimizing nutritional status is an important goal for all patients with CF, and nutritional deficits likely contribute to the pathogenesis of CF-related bone disease. Maintaining a normal BMI has been associated with improved pulmonary status and survival [28], and low BMI is a known risk factor for low BMD and fracture in CF patients [7, 9, 29–32]. In our study, lower BMI was associated with lower pBV/TV at the radius, and a reduction in lean mass appears to be the most important contributor to this relationship. In addition, when we adjusted our analyses for BMI, most of the differences between subjects with CF and healthy volunteers at the radius became attenuated, suggesting the important contribution of BMI and nutritional status to the differences noted between healthy volunteers and CF patients in non-weight-bearing trabecular bone. However, trabecular alterations remained significant at the tibia even after accounting for BMI, which could suggest that other factors, including the effects of lower weight applied to weight-bearing bones and/or reduced physical activity, may potentially lead to suboptimal trabecular structure over time.

Other clinical characteristics may also affect trabecular morphology in patients with CF. Lung function was strongly associated with pBV/TV, suggesting that declining pulmonary status may coincide with loss of plate-like trabeculae, possibly due to related factors such as inflammation, chronic respiratory acidosis, or other factors. Vitamin D deficiency is common among children and adults with CF, and 25(OH)D levels were found to be directly associated with pBV/TV at the tibia, suggesting that this variable may also affect weight-bearing trabecular bone. Although 25(OH)D was not associated with total vBMD or failure load [13], we speculate that vitamin D deficiency may be contributing specifically to trabecular deficits not captured by HR-pQCT measures that reflect both the trabecular and cortical compartments. PTH values were inversely associated with pBV/TV, which may reflect secondary hyperparathyroidism related to inadequate calcium intake or calcium malabsorption affecting plate volume. Although bone resorption markers were not associated with trabecular bone deficits, markers of bone formation were correlated with

pBV/TV, which is consistent with our prior finding that lower BSAP was directly associated with lower failure load [13]. Previous studies suggest that CF-related bone disease represents an altered bone turnover state, with low bone formation and elevated bone resorption [8, 33, 34], and these results suggest that reduced bone formation rather than increased resorption may be the primary influence on trabecular plate alterations. Although a specific bone phenotype corresponding to CFTR genotype has not yet been established, we did not observe a correlation with trabecular bone outcomes and the presence of one or more copies of F508del, the most common CFTR mutation. Patients with CF are also at risk for delayed puberty and hypogonadism, which may be playing a role in the trabecular deficits noted in this study. We also did not detect trabecular differences between patients who had a history of fracture compared to those who did not, although the power to detect such differences was limited.

Recent studies in animal models and cultured human bone cells have suggested that CFTR itself may be playing a role in the CF related bone disease. CFTR knockout mice have deficits in cortical and trabecular bone structure in the absence of respiratory and gastrointestinal disease that appears to be due to an underlying uncoupling of bone turnover, with increased bone resorption and reduced bone formation [35, 36]. Not only is CFTR expressed in human osteoblasts and osteoclasts [37], but it appears to affect osteoprotegerin (OPG) production, which is a key regulator in the Wnt signaling pathway [38–40]. Moreover, treatment with a CFTR corrector (miglustat) improved bone formation, microarchitecture, and mass in *delF508* mice [41]. This growing body of literature supports the hypothesis that the trabecular deficits observed in young adults with CF may in part be related to CFTR dysfunction itself.

Areal BMD as measured by DXA was significantly lower in young adults with CF compared with healthy volunteers in this study; however, this technique does not capture the three-dimensional microstructural alterations that contribute to bone integrity. After multivariable adjustment for aBMD in addition to BMI, subjects with CF continued to have compromised plate-like trabecular structure and connectivity and altered axial alignment at the tibia, suggesting that ITS analysis identifies alterations in trabecular networks beyond what is appreciated in standard clinical bone imaging studies. Future studies will be important to determine if this may represent useful clinical tool in the evaluation of CF-related bone disease.

This study has several limitations. The relatively small sample size limited the ability to detect small differences in trabecular bone; however, the fact that many significant differences were noted suggests that the study was sufficiently powered and findings were striking. In addition, subjects were scanned using the manufacturer's recommended region of interest at a fixed distance from the radial and tibial endplate. Given the height differential between CF patients and healthy volunteers, this may lead to a different ROI than had a percent site relative to the length of the limb been used [42]. As previously discussed [43], we do not believe that utilizing a relative site vs. a fixed site would alter the conclusions of this study. Also, we studied bone microstructure only in the appendicular skeleton, and it is not clear whether the same patterns would be seen at axial skeletal sites. In addition, BSAP may be a less specific marker of bone turnover in patients with CF given the possible cross-

reactivity with alkaline phosphatase, which may be elevated in CF patients due to biliary obstruction. Finally, this cross-sectional study was not able to identify the many variables affecting bone health in the years prior to this evaluation, and other clinical factors may have contributed to the noted alterations in trabecular bone that were not captured by this study.

In conclusion, young adults with CF had fewer, thinner, and less connected trabecular plates and altered axially aligned trabeculae compared to healthy volunteers, and these differences may contribute to compromised bone strength and increased fracture risk observed in this population. ITS-based morphological analysis provides unique information about trabecular microstructure that is not captured in DXA or standard HR-pQCT analyses, particularly at the tibia. Further studies are needed to delineate the underlying pathogenesis of these alterations and to determine the role of ITS analyses in the clinical bone health evaluation for patients with CF.

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Fig. 1.
Percent difference $\pm$ SEM in ITS parameters between young adults with CF and healthy volunteers at the radius (a) and tibia (b). *Different from controls at $p < 0.05$

Fig. 2.
HR-pQCT scans of the tibia after trabecular segmentation in a representative 28-year-old woman with CF (**a**) and 28-yearold healthy female volunteer (**b**)

Table 1

Clinical and demographic characteristics and DXA aBMD results

	Mean (SD or SE) or n (%)		
	Subjects with CF (n = 30)	Healthy volunteers (n = 60)	p value
Age (years)	25.0 (5.0)	25.3 (4.3)	0.80
Female	18 (60 %)	36 (60 %)	
Height (cm)	165 (8)	170 (9)	0.01
Weight (kg)	57.0 (10.6)	71.6 (14.8)	<0.01
BMI (kg/m ²)	20.8 (3.2)	24.5 (3.7)	<0.01
DXA aBMD (g/cm ²)			
Total hip	0.879 (0.024)	1.052 (0.017)	<0.01
Femoral neck	0.770 (0.025)	0.947 (0.018)	<0.01
Lumbar spine	0.973 (0.021)	1.079 (0.015)	<0.01
Total body	0.970 (0.018)	1.081 (0.013)	<0.01

BMI body mass index, *CF* cystic fibrosis, *DXA* dual-energy X-ray absorptiometry, *aBMD* areal bone mineral density

Table 2Individual trabecula segmentation (ITS) results (mean $\pm$ SE)

ITS parameter	Radius		Tibia	
	CF subjects	Healthy volunteers	CF subjects	Healthy volunteers
Plate bone volume fraction (pBV/TV)	0.104 $\pm$ 0.008 ^a	0.127 $\pm$ 0.006	0.136 $\pm$ 0.008 ^{a,b,c}	0.173 $\pm$ 0.006
Rod bone volume fraction (rBV/TV)	0.170 $\pm$ 0.004	0.174 $\pm$ 0.003	0.131 $\pm$ 0.006 ^a	0.150 $\pm$ 0.004
Axial bone volume fraction (aBV/TV)	0.111 $\pm$ 0.006 ^a	0.128 $\pm$ 0.004	0.133 $\pm$ 0.006 ^{a,b,c}	0.154 $\pm$ 0.004
Trab plate number density (pTbN, 1/mm)	1.45 $\pm$ 0.02 ^a	1.54 $\pm$ 0.02	1.50 $\pm$ 0.023 ^{a,b,c}	1.62 $\pm$ 0.016
Trab rod number density (rTbN, 1/mm)	1.91 $\pm$ 0.02	1.90 $\pm$ 0.02	1.71 $\pm$ 0.03	1.78 $\pm$ 0.02
Mean trab plate thickness (pTbTh, mm)	0.203 $\pm$ 0.002 ^a	0.210 $\pm$ 0.001	0.217 $\pm$ 0.003 ^{a,b,c}	0.229 $\pm$ 0.002
Mean trab rod thickness (rTbTh, mm)	0.211 $\pm$ 0.001 ^{a,b}	0.214 $\pm$ 0.002	0.217 $\pm$ 0.001	0.216 $\pm$ 0.001
Mean trab plate surface area (pTbS, mm ²)	0.153 $\pm$ 0.002 ^a	0.159 $\pm$ 0.002	0.174 $\pm$ 0.004	0.177 $\pm$ 0.003
Mean trab rod length (rTbL, mm)	0.651 $\pm$ 0.002	0.644 $\pm$ 0.003	0.655 $\pm$ 0.004	0.649 $\pm$ 0.003
Rod-rod junction density (R-R JuncD, 1/mm ³)	2.10 $\pm$ 0.11	2.41 $\pm$ 0.08	2.13 $\pm$ 0.16	2.39 $\pm$ 0.11
Plate-rod junction density (P-R JuncD, 1/mm ³)	4.21 $\pm$ 0.17 ^a	4.64 $\pm$ 0.12	3.66 $\pm$ 0.18 ^{a,b}	4.69 $\pm$ 0.13
Plate-plate junction density (P-P JuncD, 1/mm ³)	2.10 $\pm$ 0.11 ^a	2.42 $\pm$ 0.08	2.17 $\pm$ 0.08 ^{a,b,c}	2.74 $\pm$ 0.06
Plate:rod ratio (PR ratio)	0.61 $\pm$ 0.06 ^a	0.76 $\pm$ 0.04	1.13 $\pm$ 0.13	1.29 $\pm$ 0.09

^a $p < 0.05$ on unadjusted analysis comparing CF subjects with age-, gender-, and race-matched healthy volunteers;^b $p < 0.05$ after adjustment for BMI;^c $p < 0.05$ after adjustment for BMI and total hip aBMD

Table 3Correlation coefficients (*r*) between pBV/TV and clinical characteristics of young adults with CF

	Radius		Tibia	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
FEV1	<i>0.52</i>	<i><0.01</i>	<i>0.64</i>	<i><0.01</i>
BMI	<i>0.39</i>	<i>0.03</i>	0.23	0.22
Lean mass	<i>0.47</i>	<i><0.01</i>	<i>0.50</i>	<i><0.01</i>
25(OH)D	0.25	0.18	<i>0.39</i>	<i>0.03</i>
PTH	<i>-0.37</i>	<i>0.04</i>	-0.35	0.05
BSAP	<i>0.43</i>	<i>0.02</i>	0.31	0.09
P1NP	<i>0.40</i>	<i>0.03</i>	0.35	0.05

Italicized values indicate statistical significance ($p < 0.05$)

FEV1 fractional expired volume in 1 s, *BMI* body mass index, *25(OH)D*, 25-hydroxyvitamin D, *PTH* parathyroid hormone, *BSAP* bone specific alkaline phosphatase, *P1NP* amino-terminal propeptide of type I collagen, *pBV/TV* plate bone volume fraction, *pTbN* trabecular plate number density, *PP JuncD* plate-plate junction density