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Trabecular and cortical bone deficits are present in children and adolescents with cystic fibrosis☆

Andrea Kelly [a,c], Joan Schall [b], Virginia A. Stallings [b,c], Babette S. Zemel [b,c,*]

[a] Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, 3535 Market St., Philadelphia, PA 19104, USA
[b] Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, 3535 Market St., Philadelphia, PA 19104, USA
[c] Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

Osteopenia and increased fracture rates are well-recognized in adults with CF, but neither the specific contributions of cortical and trabecular bone deficits to bone fragility nor their presence in youth with CF are well-characterized. This study sought to characterize cortical and trabecular volumetric bone mineral density (vBMD), geometry, and biomechanical competence in children with CF and determine their relationship to growth, body composition, and disease severity. Peripheral quantitative computerized tomography (pQCT) measures of total, cortical, and trabecular vBMD, cortical, muscle, and fat cross-sectional areas (CSA), periosteal and endosteal circumferences, and the polar unweighted section modulus (Zp) of the tibia were converted to age- and tibial length-adjusted Z-scores in 97 CF and 199 healthy children (aged 8–21 y). Effects of body composition and pulmonary function (forced expiratory volume in 1 s, FEV1) upon pQCT outcomes were determined using linear regression. Children with CF (FEV_1%-predicted: 84.4 + 19.7) had lower weight-, height-, BMI-, and whole body lean mass (LBM)-Z and tibial length. Females with CF had lower ($p < 0.01$) total and trabecular vBMD; cortical, muscle, and fat CSA; Zp and periosteal circumference than females in the healthy reference group. These bone differences persisted after adjustment for BMI-Z and to a great extent following adjustment for muscle CSA. Males with CF had lower ($p < 0.01$) cortical, muscle, and fat CSA and their trabecular vBMD deficit approached significance ($p = 0.069$). Deficits were attenuated by adjustment for BMI-Z and to a greater extent adjustment for muscle CSA-Z. The relationship between FEV1%-predicted and pQCT outcomes persisted only in males following adjustment for age and BMI-Z. The CF cohort had lower tibial muscle CSA than expected for their LBM. In this relatively healthy, young CF cohort, deficits in trabecular and multiple cortical bone parameters were present. In females, deficits were greater at older ages and were not fully explained by alterations in body composition. In males worsening pulmonary function was associated with greater deficits that was not explained by increasing age or compromised nutritional status. The occurrence of these differences in CF youth highlights the importance of instituting measures to optimize peak bone mass early in the course of CF.

1. Introduction

Decreased bone mineral density (BMD) [1] and increased fracture rates, particularly of the ribs and vertebrae, are well-documented in adults with cystic fibrosis (CF) and can lead to significant morbidity including further compromised lung function [2]. Despite significant advancements in CF therapy, bone outcomes have not significantly improved over the past 15 to 20 y [3]. A number of factors likely contribute to compromised bone health in CF: chronic inflammation, poor nutrition, vitamin and mineral malabsorption, physical inactivity, systemic glucocorticoid use, as well as hypogonadism [4]. Additionally, lower than average lean body mass (LBM) is recognized in CF [5–10]. According to the functional muscle-bone unit hypothesis, bone structure and strength are responsive to muscle forces [11,12]. LBM is an indirect measure of the biomechanical loading of muscle on bone, and LBM deficits in CF may contribute to bone deficits [6,13]. The direct role of CF

Abbreviations: CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; CSA, cross-sectional area; DXA, dual energy x-ray densitometry; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LBM, lean body mass; LBMI, lean body mass index; QCT, quantitative computed tomography; pQCT, peripheral quantitative computed tomography; hr-pQCT, high resolution peripheral quantitative computed tomography; vBMD, volumetric bone mineral density; Zp, polar unweighted section modulus.

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* Corresponding author at: Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia, 3535 Market St., Philadelphia, PA 19104, USA.
E-mail addresses: kellya@email.chop.edu (A. Kelly), schall@email.chop.edu (J. Schall), stallings@email.chop.edu (V.A. Stallings), zemel@email.chop.edu (B.S. Zemel).

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transmembrane conductance regulator (CFTR) in bone accrual is also undergoing evaluation [14,15].

Dual energy x-ray densitometry (DXA) is the recommended technique for diagnosing osteoporosis and low bone mass—it is accessible and reference data are available. This modality has a number of potential limitations for children with chronic disease [4]. DXA acquires a two-dimensional image of bone and does not provide a true volumetric measure of density [16]. In children who are short for their age and/or who have delayed puberty, BMD may be underestimated by DXA because of smaller bone size rather than truly decreased density [17]. In relatively healthy CF children and adolescents, we found that shorter stature largely explained decreased DXA-measured BMD, particularly in females [18]. Further, DXA neither provides distinct measures of trabecular and cortical bone density nor characterizes bone geometry and strength, and, thus, is limited in its ability to identify specific bone deficits.

Quantitative computed tomography (QCT) measures volumetric bone mineral density (vBMD), and provides separate measures of cortical and trabecular bone for axial and appendicular areas [19]. Peripheral QCT (pQCT) assessment of radius and tibia has been used to assess cortical and trabecular vBMD as well as cortical dimensions. Because this latter modality requires less radiation, it has also been used in children. Total and trabecular vBMD can be measured at the metaphyses while indicators of cortical bone strength (vBMD, endosteal and periosteal circumferences, cross-sectional area [CSA], section modulus) can be determined at the mid-shaft [19]. A further refinement of this technology, available in just a few research settings, is high resolution pQCT (hr-pQCT). This technique provides information on microarchitecture [19]. Use of this modality has recently been reported in young adults with CF in whom reduced CSA and reduced total and trabecular vBMD were found [20].

The extent to which children and adolescents with CF have specific bone deficits in cortical and trabecular density, bone geometry, and bone strength has received limited attention. Also, because of linear growth and body composition alterations in children with CF, it is important to determine whether potential bone deficits are greater than expected for these known determinants of bone strength. To address these knowledge gaps, we assessed bone health in CF using pQCT scans of the distal tibia to measure trabecular and cortical vBMD, bone geometry (CSA as well as endosteal and periosteal circumferences), and bone strength (section modulus) in a relatively healthy population of youth and young adults with CF. We hypothesized that bone deficits in CF would increase with age and would be worse in females compared to males. Additionally, these deficits would not be entirely explained by deficits in growth and lean mass but would be related to lung function as an overall indicator of health status in CF.

2. Materials and methods

2.1. Participants

Individuals with pancreatic insufficient CF, ages 8 to 21 y were recruited from the Cystic Fibrosis Centers at The Children's Hospital of Philadelphia, the Hospital of The University of Pennsylvania, Philadelphia, PA and Hershey Medical Center, Hershey, PA for a bone health study conducted at The Children's Hospital of Philadelphia [18]. Data were collected during the period from November 2000 to February 2002. The diagnosis of CF was confirmed by documentation of a positive sweat test and/or diagnostic CF genotyping. The diagnosis of pancreatic insufficiency was based upon 72-hour fecal fat analyses (<93% absorption) and/or stool trypsin concentration (<80 μg/g).

Inclusion criteria included an FEV1%-predicted >40%, ages 8 to 25 y. Participants were excluded for known, cirrhosis or portal hypertension, history of lung or liver transplant, or presence of other major medical conditions not associated with CF that could potentially affect growth and nutrition. By virtue of the FEV1%-predicted and liver disease criteria, no participant was awaiting transplant at the time of study.

For CF participants, medical records were reviewed and data were collected for genotype as well as systemic glucocorticoid use. CF genotype was categorized as homozygous for ΔF508 mutation, compound heterozygous with one ΔF508 allele, or other variants. To capture oral glucocorticoid use, CF clinic charts were retrospectively reviewed. The interval captured by the chart review included up to two years prior to the study visit. The interval duration (months), total number of visits, and the number and percent of visits during which oral glucocorticoids were prescribed were recorded.

A subset (n = 199) of healthy children and young adults from the Philadelphia area, ages 8 to 21 y, enrolled in a larger study (n = 863) of normal skeletal development were used as reference group [21,22] [18]. The subset was selected based on the pQCT measurement protocol such that it matched that used with the CF group. A subset of 462 healthy participants of European ancestry provided values used to generate reference ranges for body composition as described below.

The Institutional Review Boards at each of the participating institutions approved the study protocols under which these data were collected. 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. The Institutional Review Board of the Children's Hospital of Philadelphia approved the study protocol for the analyses presented here.

2.2. Anthropometry & puberty staging

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, Crymych, UK). BMI (weight / height^2) was calculated. Age- and sex-adjusted Z scores for height, weight, and BMI were calculated using current reference data (Centers for Disease Control and Prevention 2000 growth charts for the United States) [23]. Puberty status was ascertained using a validated self-assessment questionnaire to categorize Tanner stages (TS) of pubic hair distribution (both sexes), and either genital development (males) or breast development (females) [24]. For analysis, pubertal status was defined by genital status in males and breast development in females.

2.3. Dual energy x-ray absorptiometry

As previously published, whole body scans were acquired using a fan beam array DXA (Hologic Delphi, Bedford, MA, USA) at The Children's Hospital of Philadelphia, and analyzed using the Discovery software (version 12.3) [18]. Measurements were obtained using standard positioning techniques, and whole body scans were analyzed to generate estimates of lean body mass (LBM, kg) excluding the head region. The instrument was calibrated daily with a hydroxyapatite phantom. The in vitro coefficient of variation (CV) was <0.6%; the in vivo CV was <1%. As previously published [5], lean body mass index (LBMI = LBM / height^2) was calculated for participants with CF and the healthy reference group. Age-based reference curves were generated for males and females from 462 healthy participants in the reference group using the lambda-mu-sigma (LMS) method [25]. This method summarizes data skewness (L), median (M), and variability (S) relative to age. LBMI was then converted to sex- and age-specific standard deviation scores (LBMI-Z) for the CF and controls age ≤ 20 y using the LMS values as described by Cole and Green [26].

2.4. Peripheral quantitative computed tomography (pQCT)

All pQCT scans were performed at The Children's Hospital of Philadelphia and were acquired in the left tibia using a Stratec XCT2000 device (Orthometrix, White Plains, NY) with a 12-detector unit, voxel