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Body composition, lung function, and prevalent and progressive bone deficits among adults with cystic fibrosis

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ABSTRACT

Introduction: Cystic fibrosis (CF) is associated with osteoporosis and incident fracture. This study assessed independent predictors of baseline and 2-year changes in bone mineral density (BMD) in adults with CF.
Methods: Sixty-four adult patients with CF, ages 18–57, were recruited from the Massachusetts General Hospital Cystic Fibrosis Care Center. Dual-energy X-ray absorptiometry (DXA) was performed at the spine and radius at baseline and 2 years (in 39 subjects). Estimates of fat-free mass index (FFMI) and fat mass index (FMI) were determined using height, weight, and tetrapolar bioelectric impedance analysis. All subjects completed lung spirometry within 1 month of the study visit. Linear regression models evaluated predictors of baseline BMD Z-scores and change in PA spine BMD Z-score over 2 years. Two definitions of low BMD were studied based on Z-score ($\leq$–1.0 and $\leq$–2.0).
Results: Low BMD was present in 52% of subjects. Subjects with low BMD were more likely to be male (67% vs. 32%, $P = 0.009$), were more likely to be currently using glucocorticoids (21% vs. 0%, $P < 0.001$), had lower percent body fat ($P = 0.04$), and were more likely to have had a previous fracture (60% vs. 46%, $P = 0.007$). In multivariable models, greater FFMI and height, but not greater FMI, were associated with greater BMD. In multivariable models, low forced vital capacity (FVC) and greater FMI were associated with greater loss of BMD at the PA spine over two years.
Conclusions: Male sex, short stature, and low lean mass are associated with low BMD in CF. Greater adiposity and lower lung function are predictors of negative change in BMD Z-score over 2 years.

1. Introduction

Long-term survivors of cystic fibrosis (CF) have a dramatic increase in the risk of osteoporosis and incident fracture [1]. A number of risk factors for bone loss and low bone mineral density (BMD) are seen in patients with CF including nutritional deficiency, low physical activity, hormonal alterations, chronic inflammation, and chronic use of glucocorticoids [2]. Alterations in lean mass and fat mass composition are also highly associated with bone outcomes in the general population [3–5]. Previous studies in children and adults with CF have suggested that low lean mass and low fat mass in CF are associated with low BMD [6–8]. Given the normal positive association between lean and fat mass [3], the previously-observed positive associations between fat mass and BMD may be affected by confounding. Therefore, it is important to determine the independent effects of body composition components (lean and fat) on bone outcomes in CF. In a recent cross-sectional study in 55 adults with CF, higher body mass index (BMI) and better lung function were associated with greater BMD [8]. Better lung function and greater lean mass have both been associated with greater bone accrual in longitudinal studies among children with CF [9]. A history of frequent pulmonary infections has been associated with low bone mass and low fat-free mass in young adults with CF. While one study described modest loss of bone mass over time in adults with

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CF [10], no longitudinal studies published to date have evaluated predictors of bone loss in adults with CF.

Utilizing data available from a longitudinal observational cohort study of bone health among adults with CF, this analysis addressed several important aspects of bone health in adults with CF, including the independent associations between lean/fat mass and baseline and 2-year changes in BMD, other potential predictors of bone loss over 2-years (e.g. lung function, adiposity, vitamin D status, and glucocorticoid use), baseline risk factors for prevalent and progressive deficits in BMD and active bone turnover.

2. Methods

Sixty-four adult patients with CF, ages 18–57, were recruited from the Massachusetts General Hospital Cystic Fibrosis Care Center. Eligibility criteria included documentation of an elevated sweat chloride level or mutational analysis diagnostic for cystic fibrosis. From an original sample of 67 patients, three patients were excluded: two had undergone a lung transplant and one had a liver transplant. Sixty-three subjects underwent DXA scanning at the PA spine to measure BMD and were included in this analysis. A physical examination and medical interview were done, including questions about medical history, physical activity, menstrual and/or pubertal development. Fracture histories were obtained by asking "Have you ever broken any bones?" Subjects had fasting blood samples collected before 10:00 am in the Clinical Research Center at the Massachusetts General Hospital. The Subcommittee on Human Studies of the Massachusetts General Hospital approved this study, and each subject gave informed consent.

2.1. Clinical assessments

Laboratory assessments were performed through the Massachusetts General Hospital (MGH) General Clinical Research Center. Serum 25-hydroxyvitamin D (25OHD) and intact parathyroid hormone (PTH) concentrations were measured by radioimmunoassay (Diasorin, Stillwater, MN). Bone-specific alkaline phosphatase (BSAP) was measured using competitive enzyme immunoassays (Metra Biosystems, Mountain View, CA). N-telopeptide (NTX) was measured by a competitive-inhibition enzyme-linked immunosorbent assay (Osteomark). Osteocalcin was measured by an immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). All subjects completed lung spirometry testing within 1 month of the study visit that included measurements of forced vital capacity (FVC) and forced expiratory volume (FEV1). Activity level was assessed using an interview-administered, self-report of activities during the previous 7 days (31). Moderate activity was calculated in hours per week. This variable was highly skewed towards 0 and was dichotomized at the median value (11 hours) for analyses.

2.2. Body size and composition

Height was measured by stadiometer (Holtain Limited, Crymych, UK). Subjects wore a hospital gown for weight, measured by digital scale (SR Instruments, Tonawanda, NY). BMI was calculated as kg/m^2. Estimation of percentage body fat composition was determined by tetrapolar bioelectric impedance analysis (BIA) (BIA 101A, RJL Systems, Inc, Clinton Township, MI) in the supine position [11,12].

2.3. Dual-energy X-ray absorptiometry (DXA) measures

Sixty-three subjects underwent standard DXA of the posterior-anterior (PA) spine and 20 subjects underwent additional measurement of BMD at the radius in the Massachusetts General Hospital Bone Density Center on a QDR4500A model (Hologic Inc, Bedford, MA). A standard quality control program was employed that included daily measurement of a Hologic DXA anthropomorphic spine phantom and visual review of every image by a certified bone densitometrist. The published coefficient of variation at the spine is 1.8% [13]. In our lab, the standard deviations for our short-term in vivo measurements were 0.005 g/cm^2 for the posteroanterior spine. Repeat DXA of the PA spine was performed in 39 subjects at 2-years of follow-up. Based on previous studies of BMD in young adults, a modestly low BMD was defined as a BMD Z-score $\leq$–1 (16th percentile) and an abnormally low BMD was defined as a BMD Z-score $\leq$–2 [14].

2.4. Statistical analysis

Statistical analyses were performed using Stata 11 software (StataCorp, College Station, TX). Fat-free mass and fat mass (kg) were estimated using weight and percent fat. Fat-free mass index (FFMI) and Fat mass index (FMI) were estimated by dividing estimated Fat-free and fat mass by height-squared. Baseline characteristics were summarized using descriptive statistics. Group comparisons were made using Chi^2 tests and *t*-tests or non-parametric equivalents for non-normally distributed data.

Body composition variables were adjusted for gender in all analyses to account for expected gender differences in body composition measures. Pre-specified multivariable models evaluating associations between body composition and BMD were further adjusted for height [9]. Other hypothesized factors associated with BMD Z-score at baseline were evaluated using correlations and univariate linear regression. Hypothesis driven linear regression models were used to identify predictors of change in PA spine BMD Z-score over the 2-year follow-up period and were informed by univariate analyses. Change in BMD and BMD Z-score were skewed and log transformed to fit a normal distribution in regression models (lnskew command). Robust generalized estimating equations (GEE) marginal models using unstructured correlation structures were also utilized to evaluate longitudinal change in PA spine BMD Z-score over the 2-year period. Associations with change over time were assessed using multiplicative interaction terms.

3. Results

3.1. Baseline associations with BMD Z-scores at PA spine and forearm

Baseline characteristics of the subjects with CF are presented in Table 1. Overall, low BMD (Z-score $\leq$ –1) at the PA spine was present in 33 (52%) of subjects. Subjects with low BMD were more likely to be male, were more likely to be currently using glucocorticoids, had lower percent body fat and lower estimated FMI, had greater levels of BSAP and NTX, and were more likely to have had a previous fracture. Fourteen (22%) subjects had a PA spine BMD Z-score considered to be outside of the normal range (Z-score $\leq$ –2). Males were also more likely than females to have a Z-score $\leq$ –2 [11/33 (33%) vs. 3/30 (10%) $P = 0.03$]. However, there were no other statistically significant differences in the factors listed in Table 1 in the 14 subjects with BMD Z-scores $\leq$ –2 (data not shown). Z-scores at the PA spine were significantly lower for men, compared to women [–1.42 (1.18) vs. –0.44 (1.32) $P = 0.004$]. Thus, the average male had a Z-score at the 7th percentile compared to age- and sex-matched reference ranges, while the average female was at the 33rd percentile. Men had increased odds of having a BMD Z-score $\leq$ –1 at the spine [OR 4.22 (1.41, 12.66) $P = 0.01$] and $\leq$–2 at the spine [OR 4.5 (1.12, 18.2) $P = 0.04$]. Men also tended to have lower BMD Z-scores at the radius [–0.49 (1.05) vs. 0.29 (0.69) $P = 0.053$].