ORIGINAL ARTICLE

Factors associated with low bone mineral density in patients with cystic fibrosis

Shahid Sheikh · Susan Gemma · Alpa Patel

Abstract Osteoporosis associated with cystic fibrosis is becoming more important as the life expectancy of patients continues to improve. This study was done to determine the prevalence of osteoporosis and osteopenia in CF patients and to identify risk factors. We reviewed the medical charts of 103 adults and adolescents with Cystic Fibrosis who had undergone a dual energy X-ray absorptiometry (DEXA) scan to measure the bone mineral content of the lumbar spine (L1–L4). Disease severity was assessed by lung function and body mass index (BMI) was calculated from weight and height at the time of the DEXA. None of the patients were being treated for low BMD. Random blood samples were analyzed for biochemical markers. The relationship between all these variables and BMD measurements was analyzed. Of 103 patients, ten (9.7 %) patients (9 males, 1 female) were diagnosed with osteoporosis. An additional 36 (35 %) patients (26 males, 10 females) were identified as having osteopenia. BMI, gender, weight, lung functions (FVC, FEV1, and FEF 25–75), and alkaline phosphatase, and 25-OH vitamin D levels were significantly correlated with Z-scores ($p < 0.05$). Stepwise linear regression revealed that a low Z-score was best predicted with low FEV1, male gender, low weight, and low 25-OH vitamin D levels ($p < 0.05$) for each variable. Osteopenia and osteoporosis are common in adults with CF, especially in male patients and in patients with low lung function, body weight, and 25-OH vitamin D levels.

Keywords Cystic fibrosis · FEV1 · 25-OH vitamin D · Osteoporosis · Osteopenia

Abbreviations
BMI   Body mass index
CF   Cystic fibrosis
DEXA   Dual energy X-ray absorptiometry
FEV1   Forced expiratory volume in one second

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Introduction

During the past 15–20 years, the medical management of patients with cystic fibrosis (CF) has shifted from focusing primarily on children to treating an increasing number of adults with this genetic disease. According to the Annual Data Report of the Cystic Fibrosis Foundation 2011 Patient Registry, the median age of survival is 36.8 years [1]. Although the outlook for survival is brighter, medical care teams continue to face challenges in managing secondary complications such as diabetes, liver disease, and osteoporosis in this aging patient population. Numerous studies document the prevalence of low bone mineral density in children, adolescents, and adults with CF [2–9]. Decreased bone mineral density (BMD) contributes to the risk of fractures, spinal kyphosis, and back pain. Moreover, an increasing number of patients with end-stage pulmonary disease are listed for lung transplantation, and many immunosuppressant drugs can accelerate bone loss.

The aim of this study was to assess the prevalence and severity of low bone density in a large heterogeneous population of adolescents and adults with varying severity of cystic fibrosis and to identify possible risk factors associated with low BMD, thus expanding our understanding of low BMD in adolescent and adult patients with cystic fibrosis.

Materials and methods

Out of 375 patients with cystic fibrosis followed at the CF Center at Nationwide Children's Hospital, Columbus, Ohio, 103 adults and adolescents were identified who had fulfilled the inclusion criteria and had undergone a baseline dual energy X-ray absorptiometry (DEXA) scan to measure the bone mineral content of the lumbar spine (L1–L4) and their medical charts were reviewed. This study was approved by the Institutional Review Board of Nationwide Children's Hospital. Patients excluded were younger patients with Tanner stage <5 ($n = 189$), those who had undergone lung transplant ($n = 37$), adolescents and adults with Tanner stage 5 who had not undergone dual energy X-ray absorptiometry to measure the bone mineral content of the lumbar spine (L1–L4) for various reasons including non-compliance ($n = 46$), and patients on chronic oral corticosteroid therapy ($n = 0$). The BMD and Z-scores were done on these patients as a baseline screening, prior to treatment for low BMD. Disease severity was assessed by measuring % predicted forced vital capacity (% FVC), percent predicted forced expiratory volume in one second (%FEV1), and the % predicted forced expiratory flow rate over the middle 50 percent of FVC (%FEF 25–75 %). Pulmonary function tests were conducted at the time of the bone density scan. Body mass index (BMI) was calculated from weight and height at the time of the DEXA. Non-fasting blood levels were analyzed for albumin, calcium, phosphorus, alkaline phosphatase, BUN, creatinine, and 25-OH vitamin D. Co-morbidities including previous diagnosis of cystic fibrosis-related diabetes mellitus and pancreatic insufficiency were documented for each patient. Genotyping was available on 98 of the 103 patients in the study. Our study did not assess physical activity or nutrient intake. Chest radiographs [posterio-anterior (PA) and lateral views] done within 1 year of a DEXA (dual energy X-ray absorptiometry) scan were reviewed for fractures. None of the patients in the study were active smokers and only three patients were past smokers. None of the patients in the study were receiving oral glucocorticoid therapy.

DEXA scans were performed utilizing the Hologic Delphi technique, with the Hologic 4500 Delphi A series, S/N 70724A by Hologic, Inc., 35 Crosby Drive, Bedford, MA 01730. Regions of interest (ROI) were drawn about the lumbar spine (L1–L4), the total left hip, and the total body. Bone mineral density (BMD) was evaluated utilizing the manufacturer's normative reference database. The total estimated effective dose for scans of the total body, lumbar spine, and proximal femur is approximately 5 μSv.

Serum samples for total 25-OH vitamin D were measured by competitive protein binding after column chromatography. Normal 25-OH vitamin D levels were defined as 20–55 ng/ml for children and adults. In patients with cystic fibrosis, total 25-OH vitamin D levels below 30 were considered sub-optimal.

Demographic and clinical data were reported as frequency, percent, mean, and standard deviation. Relationships between these variables and bone density Z-scores and BMD were analyzed with Pearson's or Spearman's correlations, as appropriate. Stepwise linear regression to evaluate the predictive strength of demographic and clinical variables were conducted with Z-score and BMD as dependent variables. A p value of <0.05 was considered statistically significant.

Results

Of 103 patients, 61 were males. Mean age in years was 26.7 ± 7.9 (range 16–53), mean weight in kg was 59.3 ± 11.7, mean height in centimeters was 167.9 ± 8.5, and mean BMI 21 kg/m^2 (± 3.35, range 16–30) (Table 1). Lung functions revealed mean % predicted FEV1 of 62 ± 25.3 (range 14–114), mean % predicted FVC of 76 ± 22, and mean % predicted FEF 25–75 of 45 ± 32 (Table 1).

Twenty-eight patients (13 males, 15 females) had cystic fibrosis-related diabetes mellitus (CFRDM) diabetes. Ninety-eight of 103 patients were pancreatic insufficient and were receiving replacement pancreatic enzymes. Genotyping was available for 98 of the 103 patients in the study. Forty-six (47 %) were homozygous for ΔF508, 44 (45 %) were heterozygous for ΔF508 and eight (8 %) had two non-ΔF508 mutations.

Ten patients (9.7 %, nine males, one female) were diagnosed with osteoporosis based on Z-scores. An additional 36 (35 %) patients (26 males, 10 females) were identified as having osteopenia, using the WHO classification (Table 1).

Compared to females, osteoporosis and osteopenia diagnoses were significantly higher in men, and mean bone density Z-scores were significantly lower (-1.18 ± 1.2 versus to -0.31 ± 1.2, $p = 0.002$) in males (Table 2). Male gender was noted to be a significant independent variable correlating with low Z-scores (Table 1). Weight, BMI, %FEV1, %FEF 25–75, 25-OH vitamin D levels, serum alkaline phosphatase, and gender significantly correlated with Z-scores ($p < 0.05$) (Table 1). Multiple regression

Table 1 Patient (n = 103) demographic and clinical parameters, and correlations with bone density Z-score

Parameter	Mean ± SD	Normal range/ units	Correlation with Bone Density Z-score r	Significance p
Bone density Z-scores	−0.82 ± 1.3			
Age in years	26.7 ± 7.9		−0.11	0.137
Height (cms)	167.9 ± 8.5		−0.09	0.182
Weight (kg)	59.3 ± 11.7		0.19	0.025*
% FVC	76 ± 22		0.35	<0.001*
Body mass index (BMI)	21 ± 3.3	kg/m^2	0.32	<0.001*
% FEV1	62 ± 25		0.37	<0.001*
% FEF 25–75	45 ± 32		0.31	0.002*
Bone mineral density (BMD)	0.96 ± 0.13	g/cm^2		
25-OH vitamin D	21.7 ± 9.5	20–55 ng/ml	0.20	0.022*
Serum albumin	3.8 ± 0.3	3.4–5.2 g/dl	0.08	0.200
Serum calcium (Ca)	9.2 ± 0.4	8.0–10.5 mg/dl	0.11	0.129
Serum phosphorus (PO$_4$)	3.9 ± 0.6	2.5–4.7 mg/dl	0.05	0.325
Serum alkaline phosphatase	118 ± 55	50–240 U/l	−0.30	0.001*
Serum BUN	12.8 ± 3.8	5–18 mg/dl	−0.02	0.434
Serum creatinine	0.84 ± 0.2	0.50–1.20 mg/dl	0.06	0.274
	n (%)		Correlation with bone density Z-score	p
Gender	61 (59.2) male		−0.34**	<0.001*
	42 (40.8) female			
Patients with CFRDM	28 (27 %)		−0.04	0.723
Patients with osteoporosis	10 (9.7 %)		−0.515	<0.001*
Patients with osteopenia	36 (35 %)		−0.577	<0.001*

* Significant at ≤0.05

analyses were conducted to evaluate demographic and clinical variables that best predict bone density Z-scores and BMD. All parameters were entered in the first analysis to identify those that significantly contributed to the model, which were %FEV1, gender, weight, and 25-OH vitamin D levels. These variables explained $r^2 = 0.264$ of the variance in BMD, compared to $r^2 = 0.344$ in bone density Z-scores. In a separate 4-step regression analysis to predict Z-scores, mean %FEV1 explained the most variance ($r^2 = 0.132$), gender added $r^2 = 0.104$, weight added $r^2 = 0.104$, and 25-OH vitamin D levels added $r^2 = 0.032$, for a total amount of variance explained of 0.344 (Table 3). A low bone density Z-score was best predicted by low FEV1, male gender, low weight, and low 25-OH vitamin D levels.

In a review of 25-OH vitamin D levels (normal range 20–55 ng/ml), 23 patients (22 %) had levels of 30 ng/ml or above, 54 (53 %) subjects had levels between 15 and 29 ng/ml, and 26 (25 %) patients had levels below 14 ng/ml. The mean 25-OH vitamin D in ng/dl was 21.7 ± 9.5 (Table 1). Thirty-one patients in our cohort of 103 were supplemented 400–800 IU of vitamin D per day and among them only eight patients had 25-OH vitamin D levels of 30 ng/ml or above. We reviewed chest radiographs (PA and lateral views) of 103 patients done within one year of

DEXA scan, and three out of 103 had evidence of rib fractures and one had vertebral body height loss. Two among the four were males. Two out of four had normal DEXA studies, one had osteopenia, and one with vertebral body height loss had osteoporosis.

Discussion

Our study in adolescents and adults with cystic fibrosis revealed about 45 % incidence of low BMD on DEXA scan, suggesting osteopenia in 10 % and osteoporosis in an additional 35 %, with significant correlation with male gender, low lung function (advancing disease), low weight and BMI (poor nutritional status), and low 25-OH vitamin D (poor absorption) as significant independent variables. Only three patients out of 103 had evidence of rib fracture and one had vertebral body height loss, but none had thoracic vertebral fractures.

The prevalence of decreased bone mineralization in adolescents and adults with CF is well-documented [3, 6–8, 10]. Previous studies have indicated the incidence of osteopenia and osteoporosis ranges from 34 to 79 percent [6–8, 10, 11]. Our cohort revealed 46 (45 %) of the 103

Table 2 Differences in demographic and clinical parameters between males and females

Parameter	Males n (%)	Females n (%)	Significance p
Gender	61 (59.2)	42 (40.8)	
Diabetes mellitus	13 (21 %)	15 (36 %)	0.100
Osteoporosis	9 (15 %)	1 (2 %)	0.040*
Osteopenia	26 (43 %)	10 (24 %)	0.049*
Age in years	27.3 ± 8.7	25.8 ± 6.6	0.600
Height (cm)	173 ± 6	160.6 ± 6	<0.001*
Weight (kg)	64 ± 12	52.5 ± 8	<0.001*
	Mean ± SD	Mean ± SD	p
FVC	76 ± 21	76 ± 24	0.860
FEV1	61 ± 26	64 ± 25	0.650
FEF 25–75	43 ± 32	47 ± 32	0.520
Body mass index (BMI)	21.3 ± 4	20.5 ± 3.0	0.250
Bone density Z-scores	−1.18 ± 1.2	−0.31 ± 1.2	<0.001*
Bone mineral density (BMD)	0.94 ± 0.1	1 ± 0.1	0.029
Vitamin D (25 hydroxy)	20.6 ± 9	23.2 ± 10	0.16
Serum albumin	3.9 ± 0.3	3.7 ± 0.2	0.003
Serum calcium (Ca)	9.2 ± 0.5	9.1 ± 0.3	0.200
Serum phosphorus (PO₄)	3.9 ± 0.6	4 ± 0.6	0.450
Serum alkaline phosphatase	123 ± 60	110 ± 50	0.500
Serum BUN	13.7 ± 4	11.6 ± 2.7	0.010
Serum creatinine	0.9 ± 0.2	0.7 ± 0.1	<0.001*

* Significant at alpha ≤0.05

patients had a Z-score of −1.0 or less. The most common previously published predictors of low bone density appear to be increasing age, reduced BMI, and weight [2–5, 10–12]. Some of the previous studies have suggested a positive correlation between reduced BMD and declining lung function [4, 6–8]. On the other hand, in two previous studies by Bachrach and Donavon [3, 11], there was no significant correlation between BMD and lung function. The conflicting results of the studies may be explained by the diversity in the CF population. The studies conducted over the past 10 years on CF and bone disease have included a wide range of ages and lung function. Two investigators assessed patients with end-stage lung disease who were referred for lung transplantation [11, 13] and neither of them found a positive correlation between BMD and pulmonary function. The authors concluded that the

absence of such a relationship may have been related to patient selection [11], since all of their subjects had severely impaired lung function. In contrast, other studies, including our cohort, assessed patients with a wider range of lung function [4, 6–8], and thus were able to detect a correlation between BMD and pulmonary disease severity. Moreover, the inclusion of children and adolescents in studies makes it difficult to compare to the studies evaluating only adults. However, Buntain and coworkers [12] found a positive association between BMD and FEV1, and BMI and weight for children, adolescents and adults. Our observations also revealed a significant relationship between reduced Z-score and low PFT. A relationship between osteoporosis and %FEV1 is noted in other lung diseases such as COPD, and patients with COPD have an increased risk for osteoporosis compared to those without COPD [14], with an increased vulnerability to fractures—particularly vertebral fractures [15]. The severity of pulmonary disease in patients with COPD is inversely related to reduced BMD [14, 16, 17] and the risk might be much higher when compared to patients with asthma [18].

Vitamin D plays a crucial role in the development and maintenance of bone. The major function of vitamin D is to maintain serum calcium and phosphorus homeostasis by increasing the efficiency of intestinal absorption of these minerals. Previous studies on CF-related osteoporosis have identified suboptimal levels of 25-OH vitamin D in patients with CF [2, 6–8, 11, 19]. However, only a few studies actually found low levels of 25-OH vitamin D to be predictive of reduced BMD [4, 11]. In our cohort, the mean 25-OH vitamin D was 21.7 ng/ml (normal range 10–55 ng/ml) and 78 % of our patients had a 25-OH vitamin D level below the desired minimum level of 30 ng/ml. In our cohort, low 25-OH vitamin D level was a significant independent predictor of reduced BMD (Table 1).

Several studies have analyzed the role of gender in evaluation for reduced BMD in patients with cystic fibrosis, but the results are mixed. Several investigators have found no significant difference in BMD standard deviation or T scores between male and female patients with cystic fibrosis [4, 10, 13]. However, Conway et al. [7], in their cohort of 114 patients (53 males), measured gender specific T scores at three areas (lumber spine L2–L4, right femoral neck, and total body) and reported that 79 % of 53 men and 56 % of 61 women had osteopenia or osteoporosis at one or more sites, with men having a slightly higher prevalence

Table 3 Stepwise regression analysis of demographic and clinical variables that best predict bone density Z-scores

	Model	r	Adjusted r^2	r^2 change	Beta	F	p
1	%FEV1	0.734	0.132	0.132	0.271	16.470	<0.001
2	Gender	0.494	0.229	0.104	−0.477	16.158	<0.001
3	Weight	0.581	0.318	0.094	0.364	116.846	<0.001
4	25-OH vitamin D	0.608	0.344	0.032	−0.180	15.157	<0.001

of osteoporosis at all sites. Gibbens et al. [20] compared 57 patients with cystic fibrosis (29 male, 28 female, aged 3–21 years) with an age, race, and gender-matched control group of 57 healthy subjects and found that patients with cystic fibrosis had significantly lower bone density (10 % lower, $p < 0.001$) than controls. He also noted that in patients with cystic fibrosis, male patients had substantially lower bone density than did female patients ($p < 0.02$), but bone density differences related to gender were not significant after controlling for disease severity. In our group, gender was a significant factor, even after controlling for disease severity (%FEV1). Haworth et al. [6] had a cohort of 143 adult patients with a mean age of 25 years, and expressed BMD results as age and gender matched Z-scores. In his large, unselected population of adults with CF, BMD was significantly lower in men despite the fact that men and women have comparable lung disease and nutritional indices and despite there being no evidence of male hypogonadism. In our study, we had an unselected population of adults with CF with similar disease severity and 25-OH vitamin D levels, and in whom we expressed BMD results as age- and gender-matched Z-scores. In our cohort, Z-scores were significantly lower in men than in women, and male gender was noted to be a significant independent variable correlating with low Z-scores. The gender difference in BMD is not understood, but may be partly explained by the higher early mortality rate in women, which removes the most severely affected female patients from the study population [21].

Comparing our study with a recently published study by Legroux-Gérot and colleagues [8] revealed many similarities and some differences. Our study group had more patients (103 vs. 55) who were younger in age (26 vs. 32 years) with less disease severity (34 % of patients with %FEV1 < 50 %, compared to 52 % in their group). Our group had 45 % of patients with low BMD compared to 78 % in their group. They noted that PFT and BMI were significantly associated with low BMD, while in our study not only PFT and BMI, but also male gender, weight, and 25-OH vitamin D levels had significant independent associations with low BMD. More patients having less disease severity might be responsible for these differences. It is possible that with advancing age, as more patients develop low BMD, these associations are lost.

On the other hand, sub-optimal 25-OH vitamin D levels in our group were noted in 78 % of patients, compared to only 58 % in their group, and one reason might be a higher incidence of malabsorption in our group, as 95 % of patients in our group had pancreatic insufficiency and were on replacement enzyme therapy compared to 71 % in their group. Thus, pancreatic insufficiency may be an important factor in vitamin D absorption. As we had more patients with low 25-OH vitamin D, this factor correlated with low

BMD, but a such correlation was not noted by Legroux-Gérot and colleagues [8].

Some of the limitations of our study include that it was a retrospective review study, thus, there is a limit to the amount of data available. In addition, it was a single-center study with a limited number of patients and a lack of data on previous fractures. In spite of these limitations, our study provides useful information on osteoporosis and osteopenia in patients with cystic fibrosis.

Osteoporosis is a risk factor for the aging CF population. Risk is increased in male patients and in patients with advanced lung disease (low %FEV1) and poor nutrition (low weight and BMI), and in patients with low 25-OH vitamin D levels (either poor nutrition or poor absorption). Monitoring BMD, in all patients with CF should be part of the standard care to prevent ongoing bone loss and associated morbidity. The etiology of decreased BMD in patients with CF is multifactorial, most likely a combination of inadequate peak bone mass during puberty and increased bone losses in adults. As patients with cystic fibrosis are living longer, and quality of life with aging is an important issue, we need to closely monitor co-morbidities including osteopenia and osteoporosis. We should implement preventive therapies, including those that improve mineral deposition at a younger age, which may have a significant impact on quality of life with aging and on their candidacy for lung transplantation.

Appendix

Definition of terms and criteria

Osteoporosis: A disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone loss and to an increased risk of bone fractures.

Osteopenia: Low bone mass for age; a clinically significant decrease in bone mass compared to expected values adjusted for age and gender.

WHO classification for osteoporosis:

Normal—Z-score greater than −1.0,

Osteopenia—Z-score between −1.0 and −2.49,

Osteoporosis—Z-score of −2.5 or less.

Body mass index (BMI): A ratio that indicates appropriate weight for height. Weight in kg divided by height in meters squared.

Dual energy X-ray absorptiometry (DEXA): Measures bone mineral content of regional bones and whole body

(Bone mineral density gm/cm^2). Results are influenced by and referenced to patient's age, height, weight, and Tanner stage.

25-hydroxy vitamin D (25-OH vitamin D): CFF Bone Health Consensus Report (2002) recommends targeting 25-hydroxy vitamin D levels above 30 ng/ml in the CF population [9].

Z-scores: The number of standard deviations (SD) that a BMD measurement is from the mean of an age- and gender-matched control population.

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