BONE HEALTH OUTCOMES IN POST-LUNG TRANSPLANT PATIENTS WITH CYSTIC FIBROSIS

by

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ABSTRACT

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Background: Osteoporosis is a common comorbidity in patients with cystic fibrosis (CF). Although lung transplantation (LTx) improves quality of life of CF patients, there is little research examining long-term bone health outcomes following LTx in these patients.

Objective: We sought to compare long-term bone health outcomes in LTx patients with and without CF, as well as determine factors associated with adverse bone health in CF patients.

Methods: Data were collected on 59 patients who underwent LTx between 2006-2019, including 30 with CF and 29 without CF. We compared baseline characteristics, long-term bone mineral density (BMD) trends, and fracture incidence between the two patient populations, and examined factors associated with post-LTx fractures in CF patients.

Results: Compared with non-CF patients, patients with CF were younger, had lower body mass index, and lower baseline BMD Z-scores at the lumbar spine, femoral neck, and total hip (all $p<0.001$). BMD at all sites declined in both groups in the first year post-LTx. In subsequent years, CF patients exhibited better BMD recovery relative to pre-transplantation, but continued to have lower BMD post-LTx. Post-transplant fractures occurred in 30% and 34% of CF and non-CF patients, respectively. CF patients who developed fractures after LTx had significantly lower BMD and lower pre-transplantation percent predicted forced expiratory volume in one second (FEV1%).

Conclusion: Although CF patients exhibit better BMD recovery following LTx compared to their non-CF counterparts, CF patients start with significantly lower pre-LTx BMD and experience a similarly high rate of post-LTx fractures. These findings highlight the unique contribution of the CF disease process to bone health, as well as a clear need for better prevention and treatment of osteoporosis in CF patients before and after LTx.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

Cystic fibrosis (CF) is a common genetic disease that affects over 30,000 individuals in the United States [1]. The disease is characterized by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes an ATP-gated chloride channel that regulates ion and water transport across apical membranes of epithelial cells [2]. CFTR dysfunction leads to the disruption of multiple organ functions, resulting in lung disease, gastrointestinal abnormalities, impaired growth, diabetes, infertility, and other clinical complications. Of these, obstructive lung disease, caused by recurrent pulmonary infections and chronic inflammation, is the main cause of mortality in these patients [3]. Ultimately, many CF patients that develop end-stage pulmonary disease eventually require lung transplantation (LTx); in 2019 alone, 241 CF patients received lung transplants [1].

Medical care for patients with CF has greatly improved over the past few decades, resulting in increased life expectancy [1]. As a result, however, CF-related comorbidities present an increasing burden [4]. Importantly, previous studies have reported a high prevalence of low bone mineral density (BMD) and fractures in CF patients [5]. The causes of bone disease in CF patients are likely multifold. First, intestinal malabsorption and associated hypovitaminosis D may lead to increased bone resorption due to secondary hyperparathyroidism [6]. Second, pancreatic endocrine insufficiency often results in CF-related diabetes and has been shown to negatively impact bone health [7]. Hypogonadism, a known contributor to bone loss [8], was found to be associated with lower BMD and increased fracture risk in CF patients [9]. Due to recurrent pulmonary infections, chronic inflammation and subsequent treatment with long term glucocorticoids also contribute to

CF-related bone disease [10, 11]. In addition, the CFTR gene is expressed in human bone and thus may also contribute to CF-related bone disease via impaired osteoblast maturation [12, 13]. Despite the benefits of LTx in CF patients with end-stage pulmonary disease, preexisting low bone density may be exacerbated by high dose immunosuppressive medications and reduced physical activity early following transplantation [14]. Among LTx candidates, those with CF have abnormally low bone densities, despite the group's much younger average age [15].

Cross-sectional studies have examined prevalence and risk factors for osteoporosis in LTx candidates [15, 16], and, there is evidence to suggest bisphosphonates may minimize long-term bone loss following LTx in CF patients [17, 18]. However, there is limited research investigating long-term bone health specifically in CF patients following LTx.

Given the multifactorial effects of both the CF disease process and LTx on bone, we sought to examine the long-term outcomes of bone health in CF patients receiving LTx. We examined the variables that influence BMD and fracture incidence and compared CF patients to a non-CF LTx patient population. To accomplish this, we collected data from the charts of LTx patients with and without CF and performed analyses to observe trends and identify associations.

CHAPTER 2: METHODS

Subjects

Patients with CF who underwent LTx at UT Southwestern between January 1, 2006 and January 1, 2019 were selected for potential inclusion in this study. We excluded patients if they had history of multiple organ transplants, no pre-transplant dual-energy x-ray absorptiometry (DXA) scan within 2 years of the transplant date, or died or had no follow-up DXA scan within 2 years post-transplant. After these exclusions, a total of 30 patients with CF were included in this analysis (Figure 1). An additional 29 LTx patients without CF were included in the study as a control group. Criteria for inclusion of non-CF patients were the same as those of CF patients, including requirement of BMD measurements on the same DXA instrument. The transplant-associated diagnoses of non-CF patients included 7 with chronic obstructive pulmonary disease, 18 with idiopathic pulmonary fibrosis/interstitial lung disease, two with pulmonary arterial hypertension, one with acute respiratory distress syndrome, and one with bronchiolitis obliterans organizing pneumonia. This study was approved by the IRB of UT Southwestern.

Measurements and calculations

LTx patients underwent clinical measurements prior to and each year following LTx, which included bone density scans, pulmonary functions tests (PFTs), and serum labs. Bone densities were measured at the lumbar spine, femoral neck, and total hip using DXA on the same Hologic Discovery DXA system machine. BMD T- and Z-scores were calculated according to reference data, which included NHANES and Hologic for hip and spine

measurements, respectively. Abstracted PFT data included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and 6-minute walk distance (6MWD). Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the CKD-EPI equation. Medication use, including glucocorticoids, calcium supplements, vitamin D supplements, bisphosphonates and other anti-osteoporosis medications, and CFTR modulators, was collected from patients' charts. Other relevant aspects of patient histories, such as demographic data, smoking history, genotype studies, fracture history, and history of comorbidities, were also extracted from patients' charts.

Statistical analyses

Baseline characteristics and descriptive statistics were summarized by study group between CF vs. non-CF patients, and fracture vs. non-fracture within post-LTx CF patients. Categorical variables were presented as frequency and percentages, while continuous variables were expressed as mean with standard deviation or median with interquartile range. The distribution of continuous variables was assessed by the Shapiro-Wilk normality test and normal probability plots. Fisher exact test was used to compare categorical variables between study groups as appropriate. One-way analysis of variance, unpaired *t*-test, and non-parametric Wilcoxon Rank Sum test were used to compare continuous variables between all study groups. BMD, T-scores, and Z-scores were compared between study groups using unpaired *t*-test, whereas paired *t*-test was applied to compare BMD changes in the first, second, and third post-LTx years vs. baseline. A repeated analysis of variance with group x time interaction was used to analyze the change in BMD over time (from baseline to year 3 post-LTx) within CF and

non-CF patients, as well as between CF and non-CF patients. Data were analyzed using SAS Version 9.4 (SAS Institute, Cary, NC), and GraphPad Prism 9. All statistical tests were two-sided, and $p < 0.05$ was considered significant.

CHAPTER 3: RESULTS

Baseline characteristics and bone densities

30 LTx patients with CF and 29 LTx patients without CF were included in this study. There was a similar distribution of genders between the two groups, although those with CF were significantly younger and had a lower BMI (both $p < 0.001$) (Table 1). Both groups of patients were predominantly Caucasian. Twenty (69%) of the non-CF patients were previously smokers, while none of the CF patients had a history of smoking. Creatinine levels did not significantly differ between the two groups ($p = 0.099$), although eGFR was greater in CF patients ($p < 0.001$).

Among CF patients, 14 (47%) were homozygous for the delta F508 mutation, 13 (43%) were heterozygous, 2 (7%) carried other CFTR mutations, and one did not have a CFTR genotype study available (Table 2). 26 patients had a history of CF-related diabetes (CFRD), while all 30 had a history of pancreatic insufficiency. Surprisingly, 18 (60%) CF patients undergoing LTx had a history of nephrolithiasis.

At baseline, patients with CF had significantly lower absolute BMD values at the lumbar spine ($p = 0.0042$) and total hip ($p = 0.044$) compared to non-CF patients, but femoral neck BMDs were similar ($p = 0.36$) (Table 1). CF patients exhibited lower baseline Z-scores at all three sites ($p < 0.001$), although the magnitude of the difference was greatest at the lumbar spine.

We compared CF patients with BMD below or within the expected range for their age, based on Z-scores of ≤ -2 and > -2, respectively [19] (Table 2). Those with lower Z-scores had significantly lower baseline BMI ($p = 0.031$) and FEV1 ($p = 0.028$). Baseline FEV1 percent predicted and 6MWD were also lower in the low Z-score group, although they did not reach statistical significance ($p = 0.068$ and $p = 0.056$, respectively). Lastly, pre-transplant inhaled glucocorticoid use was greater in CF patients with a Z-score ≤ -2 ($p = 0.047$). There were no significant differences in the prevalence of CF-related comorbidities, LTx-associated metrics, and baseline serum lab values between the two groups (Table 2).

Changes in bone mineral density following transplant

In the CF group, lumbar spine, femoral neck, and total hip BMDs all significantly declined in the first year following LTx, with the greatest relative decline occurring at the femoral neck (Fig. 2A- C). However, lumbar spine BMD returned to baseline by the second year, whereas the femoral neck and total hip BMDs do not return to baseline until the third post-transplant year. Non-CF patients also exhibited significant declines in BMD in the first post- transplant year (Fig. 2D-F). In non-CF patients, lumbar spine BMD did not return to baseline until the third post-transplant year, while the femoral neck and total hip BMD did not seem to recover after the first-year decline. By the third post-transplant year, lumbar spine, femoral neck, and total hip Z-scores in CF patients remained significantly below non-CF patients ($p < 0.001$) (Table 3). Significant time x group interaction was seen for BMD at the femoral neck ($p = 0.019$), and possibly the spine ($p = 0.12$), but not at the total hip ($p = 0.55$).

Post-transplant fractures

During the study period, 9 (30%) CF patients experienced 14 fractures and 10 (34%) non-CF patients experienced 15 fractures (Table 4). There was a greater number of rib fractures but less vertebral fractures in those with CF. Most post- transplant fractures in non-CF patients occurred in the first post- transplant year, whereas most fractures in the CF patients were spread out across the second, third, and fourth post-transplant years.

Following LTx, all CF patients received both calcium and vitamin D supplementation, while nearly all (97%) continued to take oral glucocorticoids (Table 5). CFTR modulators were discontinued following LTx in the 6 CF patients previously receiving them. Bisphosphonates were used by nine (30%) CF patients pre-LTx and ten (33%) CF patients pos-LTx. Bisphosphonate users pre-LTx (Table 6) and post-LTx (Table 7) had similar age, BMI, and gender distribution as non-users, but exhibited lower BMD.

Among CF patients, those who experienced post-LTx fractures were also more likely to exhibit lower BMD compared to those without fractures (Table 8). T-scores were lower at the femoral neck ($p = 0.017$) and total hip ($p = 0.050$) at baseline, and lower at the lumbar spine ($p = 0.0050$) and femoral neck ($p = 0.0034$) 2 years post-LTx. Z-scores were lower at the femoral neck ($p = 0.040$) at baseline, as well as the lumbar spine ($p = 0.0070$) and femoral neck ($p = 0.014$) 2 years post-LTx. Pre-LTx FEV1 percent predicted values were lower in CF patients with post-LTx fractures compared to those without ($p = 0.042$), although absolute FEV1 did not reach significance ($p = 0.064$). Overall, CF patients without and with post-transplant fractures had similar demographic characteristics and laboratory measurements, including

medication use. We also did not observe any significant differences in post-LTx cumulative steroid doses and percent change in BMD between CF patients with vs. without post-LTx fracture. In contrast, we did not observe any differences in BMD, T-scores, or Z-scores between non-CF patients with and without post-LTx fractures (Table 9).

CHAPTER 4: DISCUSSION

There is limited published information on longitudinal changes in BMD and fracture incidence post-lung transplantation in CF patients. In this study of LTx patients, we observed significant differences in bone density between CF and non-CF patients pre- and post-LTx: Our results show abnormally low pre-LTX BMD in CF patients compared to their age-, race-, and gender-matched healthy peers, as well as to other non-CF LTx recipients (Table 3). Importantly, this study illustrates the differences in the long-term post-LTx trends of bone density in CF patients compared to those with other causes of end-stage lung disease. In particular, hip and femoral neck BMD declined significantly in the first year post-LTx but returned to pre-transplant level in CF patients but declined and remained below baseline in non-CF patients. In addition to low BMD, more severe lung disease (lower FEV1%) pre-LTX was associated with lower baseline BMD and higher incidence of post-transplant fractures in CF patients.

In our study, CF patients exhibited better recovery in BMD following LTx at some skeletal sites compared to non-CF patients: A repeated measures analysis of variance found that overall BMD change over time was significantly different at the femoral neck ($p = 0.019$), and possibly at the lumbar spine ($p = 0.12$), but not at the total hip ($p = 0.55$). The more rapid recovery seen in CF patients may be due to younger age, despite the persistence of their CF-related comorbidities outside the lungs. We speculate that CF patients may have had greater physical activity following LTx com- pared to the older non-CF patients. In addition, the greater proportion of post-menopausal patients in the non-CF group may contribute to their

worse bone recovery. Even with recovery of lung function and inflammation, however, abnormally low BMD persists years after LTx in CF patients, and does not recover beyond their baseline values, consistent with a previous study by Durette et al. [20]. The causes of this are likely multifold. First, CF-related co-morbidities, such as pancreatic insufficiency (by impacting calcium and vitamin D absorption) and diabetes, and high rates of glucocorticoid use remain after transplant, continuing to adversely im- pact bone metabolism. Second, recent studies show that mutated CFTR may directly contribute to bone disease at the cellular level. CFTR was found to be expressed in human osteoblasts and osteoclasts [12], and CF mouse models exhibit low bone density, even in the absence of lung disease [21, 22]. Lastly, because CF patients experience slower bone mineral accretion during adolescence, and thus lower peak bone density [23], their BMD may be unable to recover beyond peak BMD attained during young adulthood. Thus, effects of CFTR dysfunction may both directly and indirectly alter bone metabolism and contribute to persistently low BMD post-LTx.

We observed a high rate of post-transplant fractures in our CF population, with 30% experiencing at least one fracture. Compared to the non-CF population, CF patients presented with a similar number of fractures, despite their much younger age. CF patients were also less likely to receive post-LTx bisphosphonates, although the reasons for this are likely multifold, including the lower use of bisphosphonates in younger patients with osteoporosis in general. Although a prior study by Aris et al. indicates that bisphosphonate may improve BMD in CF patients following transplantation, it is unclear whether it significantly reduces fracture rates [17]. On average, CF patients who developed post-LTx fractures were more likely to exhibit lower post-LTx T-scores; however, changes in BMD from baseline to 2 years post-LTx did not

appear to predict fracture incidence in our cohort. These results are in contrast with those of Durette et al., who found no significant differences in BMD up to 2 years post-LTx between CF patients who did and did not develop fractures [20]. Unlike the CF population, these densitometric parameters were not associated with post-LTx fracture incidence in the non-CF population (Table 9), although our small sample size precludes definitive conclusions. The relationship between FEV1% and BMD in CF patients is consistent with previous studies examining the general CF population [24]. However, the association we observed between FEV1% and post-LTx fractures contrasts that of Giorgia et al., who found no difference in pre-LTx FEV1% between those with and without post-LTx fractures [25]. In our study, CF patients with lower pre-LTx Z-scores had lower pre-LTx BMI, although we did not observe any difference in other traditional risk factors for osteoporosis (such as age, female gender, and glucocorticoid use) between those with and without post-LTx fractures. Thus, BMD and baseline lung function appear to be better predictors of post-LTx fracture in our study.

Although nephrolithiasis is more prevalent in those with CF compared to the general population [26], we observed an unusually high prevalence of nephrolithiasis (60%) in these patients compared with previous reports of 4.1% [26] or 19% [16]. The higher prevalence in our population may be due to higher antibiotic use, chronic calcium supplementation, and/or increased incidental findings of asymptomatic stones from frequent abdominal imaging in LTx candidates compared to the general CF population. This may also be due to the higher rate of more severe CFTR mutations present in our population, which was recently identified as a risk factor for nephrolithiasis [27]. Further studies are necessary to elucidate the underlying mechanisms behind these associations.

The results of this study have important implications in the clinical management of LTx candidates with CF. Despite the high prevalence of pre- and post-LTx calcium and vitamin D supplementation, along with moderate bisphosphonate use (Table 5), pre- and post-LTx BMD values remained below reference ranges for a healthy population. Additionally, CF patients exhibited a more favorable recovery in their BMD after transplant compared to non-CF LTx recipients but were at a similarly high risk of developing fractures relative to their significantly older non-CF peers. Thus, the current management of bone health in LTx patients with CF may be insufficient, although existing pharmacologic treatments for osteoporosis and CF are being investigated specifically for their use in managing CF-related bone disease [28, 29].

This study is subject to several limitations. Most importantly, we ran analyses on relatively small sample sizes, thus limiting our statistical power. We specifically limited our sample of patients to only those with available baseline and long-term BMD data because there is limited research on BMD changes post-LTx. The small numbers of patients were due to exclusion of some LTx patients with either missing baseline DXA scan or limited post-transplant DXA data, resulting in a potential bias for healthier patients who were more readily able to have routine imaging per- formed. Similarly, the exclusion of those who died within two years post-transplant may have also selected for healthier patients and, presumably, better bone health. Still, the baseline characteristics of CF patients in our study, including BMD at the lumbar spine, femoral neck, and total hip, were similar to those of other CF populations of LTx candidates described in recent studies [16, 30]. Thus, it is likely our population is representative of the patients with CF who are candidates for LTx. Conversely, one strength of this study was that all BMD measurements were performed on the same DXA machine, and

thus variations in instrument-dependent calibration did not affect BMD readings. Due to the retrospective nature of our study, patients' pre-LTx BMD ("baseline") was performed at different time intervals before the transplantation date. By design, we required this pre-LTx BMD to be less two years before transplantation, and the median duration between baseline DXA scan and LTx was 291 days. We acknowledge that some patients may have experienced declines in BMD between their baseline DXA scan and the time of LTx. In this study, we did not analyze associations with certain bone metabolism-related parameters, such as serum parathyroid hormone, gonadal status, or bone turnover markers, due to incomplete data. Thus, conclusions regarding altered bone mineralization versus resorption could not be made. Finally, our control (non-CF) lung transplant group consisted of patients with different underlying lung diseases, that may have impacted BMD and fracture risk differently. Our choice of control patients was primarily dictated by the same inclusion/exclusion requirements as the CF group (including the need for pre- and post-LTx BMD measurements on the same DXA instrument). These requirements may have limited the generalizability of our findings.

Overall, the high prevalence of fracture and persistently low BMD post-LTx highlight the unique contribution of the CF disease process to long-term bone health compared to other causes of end-stage lung disease, as well as the significant burden of CF-related bone disease in these LTx patients. Additional studies in larger populations of LTx patients are necessary to confirm these trends and associations. Still, there exists a clear need for continued aggressive prevention and treatment of osteoporosis in LTx patients with CF.

LIST OF TABLES

Table 1. Comparison of baseline characteristics in cystic fibrosis and non-cystic fibrosis lung transplant patients.

	Cystic fibrosis	Non-cystic fibrosis	P value
Patient characteristics			
Population size	30	29	
Age, years	32.8 ± 10.0	56.7 ± 10.7	<0.001
Gender, female	15 (50%)	12 (41%)	0.60
Postmenopausal	1/15 (7%)	7/12 (58%)	0.0085
Height (cm)	164.3 ± 7.2	168.8 ± 7.7	0.025
Weight (kg)	53.2 ± 9.6	78.4 ± 16.7	<0.001
BMI, kg/m^2	19.7 ± 3.0	26.7 ± 4.4	<0.001
Race (W/B/H/A)	25/2/3/0	24/4/0/1	
Ex-smoker	0 (0%)	20 (69%)	<0.001
Serum lab values			
Alkaline phosphatase, U/L	129 ± 65	63 ± 19	<0.001
Creatinine, mg/dL	0.70 ± 0.24	0.81 ± 0.26	0.099
eGFR, mL/min	122 ± 30	94 ± 19	<0.001
25-OH vitamin D, ng/mL	32.9 ± 11.1	N/A	N/A
Bone densities			
Lumbar spine			
BMD, g/cm^2	0.833 ± 0.138	0.964 ± 0.169	0.0042
T-score	-2.0 ± 1.2	-1.0 ± 1.6	0.0045
Z-score	-2.0 ± 1.1	-0.3 ± 1.6	<0.001
Left femoral neck			
BMD, g/cm^2	0.676 ± 0.122	0.708 ± 0.142	0.36
T-score	-1.7 ± 0.9	-1.5 ± 1.0	0.45
Z-score	-1.6 ± 0.8	-0.7 ± 1.0	<0.001
Left total hip			
BMD, g/cm^2	0.767 ± 0.124	0.841 ± 0.145	0.044
T-score	-1.6 ± 0.8	-1.1 ± 0.9	0.064
Z-score	-1.6 ± 0.8	-0.7 ± 1.0	<0.001
Bisphosphonate use			
Pre-transplant	9 (30%)	8 (28%)	1.0
Post-transplant	10 (33%)	21 (72%)	0.0040

Data displayed as mean ± SD or N (%). BMI: body mass index; eGFR: estimated glomerular filtration rate; BMD: bone mineral density; N/A: Not available.

Table 2. Comparison of baseline characteristics in CF patients with bone mineral density Z-scores greater than or less than or equal to -2.

	Z-score > -2	Z-score ≤ -2	P value
Patient characteristics			
Population size	11	19	
Gender, % female	6 (55%)	9 (47%)	1.0
Age at transplant, years	32.2 ± 11	33.1 ± 10	0.82
Height (cm)	167.0 ± 8.2	162.7 ± 6.3	0.12
Weight (kg)	59.3 ± 11.6	49.7 ± 6.0	0.0058
BMI, kg/m^2	21.2 ± 3.6	18.8 ± 2.2	0.031
Race			0.48
White	8 (73%)	17 (89%)	
Hispanic	2 (18%)	1 (5%)	
African American	1 (9%)	1 (5%)	
CFTR genotype[1]			1.0
Delta F508 homozygous	5 (45%)	9 (50%)	
Other	6 (55%)	9 (50%)	
Comorbidities			
CF-related diabetes	10 (91%)	16 (84%)	1.0
Pancreatic insufficiency	11 (100%)	19 (100%)	1.0
Nephrolithiasis	8 (73%)	10 (53%)	0.44
Falls	2 (18%)	5 (26%)	1.0
Pre-transplant fractures	5 (45%)	8 (42%)	1.0
Lung transplant			
LAS at transplant	42.8 ± 5.0	50.8 ± 18.8	0.37
Waitlist time, days	44 [13, 299]	125 [18, 324]	0.38
Length of hospital stay, days	16.2 ± 5.9	16.1 ± 10.0	0.98
Pulmonary function tests			
FVC, L	2.10 ± 0.67	1.74 ± 0.62	0.15
FVC, % predicted	48.4 ± 14.6	43.0 ± 12.7	0.31
FEV1, L	1.20 ± 0.40	0.90 ± 0.28	0.028
FEV1, % predicted	33.4 ± 10.9	26.9 ± 7.1	0.068
6-minute walk distance, m	335 ± 54	277 ± 86	0.056
Serum lab values			
Alkaline phosphatase, U/L	143 ± 77	121 ± 58	0.40
Creatinine, mg/dL	0.78 ± 0.20	0.66 ± 0.26	0.26
Hemoglobin A1c, %	6.4 ± 0.7	6.7 ± 1.0	0.36
25-OH vitamin D, ng/mL	32.7 ± 12.0	33.1 ± 10.9	0.93
eGFR, mL/min	113 ± 27	125 ± 32	0.35
Pre-transplant medication use			

Glucocorticoids			
Inhaled	7 (64%)	18 (95%)	0.047
Oral	10 (91%)	18 (95%)	1.0
Nasal	9 (82%)	14 (74%)	1.0
Calcium replacement	9 (82%)	13 (68%)	0.67
Vitamin D replacement	10 (91%)	19 (100%)	0.37
Bisphosphonates	2 (18%)	7 (37%)	0.42
CFTR modulators	3 (27%)	3 (16%)	0.64

[1]Total numbers reduced due to exclusion of one patient with missing genotype studies.
Data displayed as mean ± SD, median [IQR], or N (%). BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; CF: cystic fibrosis; LAS: lung allocation score; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; eGFR: estimated glomerular filtration rate.

Table 3. Comparison of post-transplant bone mineral densities in cystic fibrosis and non-cystic fibrosis lung transplant patients.

	Cystic fibrosis	Non-cystic fibrosis	P value
BMD, g/cm²			
Lumbar spine			
1st year	0.809 ± 0.118	0.901 ± 0.169	0.036
2nd year	0.825 ± 0.107	0.901 ± 0.150	0.041
3rd year	0.816 ± 0.140	0.923 ± 0.144	0.027
Left femoral neck			
1st year	0.632 ± 0.089	0.662 ± 0.128	0.35
2nd year	0.638 ± 0.104	0.649 ± 0.126	0.73
3rd year	0.626 ± 0.083	0.650 ± 0.125	0.49
Left total hip			
1st year	0.739 ± 0.090	0.785 ± 0.152	0.23
2nd year	0.736 ± 0.100	0.778 ± 0.145	0.23
3rd year	0.710 ± 0.089	0.787 ± 0.149	0.061
T-scores			
Lumbar spine			
1st year	-2.3 ± 1.0	-1.5 ± 1.6	0.055
2nd year	-2.2 ± 1.0	-1.5 ± 1.4	0.056
3rd year	-2.3 ± 1.2	-1.3 ± 1.2	0.019
Left femoral neck			
1st year	-2.1 ± 0.7	-1.9 ± 1.0	0.36
2nd year	-2.0 ± 0.8	-2.0 ± 0.9	0.77
3rd year	-2.1 ± 0.7	-2.0 ± 1.0	0.50
Left total hip			
1st year	-1.8 ± 0.6	-1.5 ± 1.0	0.25
2nd year	-1.9 ± 0.7	-1.6 ± 1.0	0.21
3rd year	-2.1 ± 0.7	-1.5 ± 1.0	0.041
Z-scores			
Lumbar spine			
1st year	-2.2 ± 0.9	-0.8 ± 1.7	0.002
2nd year	-2.2 ± 0.9	-0.8 ± 1.6	<0.001
3rd year	-2.2 ± 1.1	-0.5 ± 1.1	<0.001
Left femoral neck			
1st year	-2.0 ± 0.7	-1.1 ± 1.0	<0.001
2nd year	-1.9 ± 0.8	-1.1 ± 0.9	0.002
3rd year	-1.9 ± 0.7	-1.1 ± 0.8	<0.001
Left total hip			
1st year	-1.8 ± 0.6	-1.0 ± 1.0	0.004

2nd year	-1.8 ± 0.7	-1.0 ± 1.0	0.002
3rd year	-1.9 ± 0.7	-1.0 ± 0.8	<0.001

Data displayed as mean ± SD or median [IQR].

Table 4. Post-transplant fractures in cystic fibrosis and non-cystic fibrosis lung transplant patients.

	Cystic fibrosis	Non-cystic fibrosis
Patients with fractures	9	10
Total number of fractures	14	15
Fracture locations		
Vertebrae	3	6
Ribs	5	2
Upper extremity	2	2
Lower extremity	4	5
Fractures per year		
1st year	1	9
2nd year	5	0
3rd year	3	0
4th year	2	1
5th-10th year	3	5

Data displayed as N.

Table 5. Medication use before and after lung transplantation in cystic fibrosis patients.

	Pre-transplant	Post-transplant
Glucocorticoids		
Inhaled	25 (83%)	6 (20%)
Oral	28 (93%)	29 (97%)
Nasal	23 (77%)	10 (33%)
Calcium replacement	22 (73%)	30 (100%)
Vitamin D replacement	29 (97%)	30 (100%)
Bisphosphonates	9 (30%)	12 (40%)
CFTR modulators	6 (20%)	0 (0%)

Data displayed as N (%). CFTR: cystic fibrosis transmembrane conductance regulator.

Table 6. Clinical characteristics of cystic fibrosis patients receiving vs. non-receiving bisphosphonates *pre-transplantation*

	Pre-transplant bisphosphonate use	No pre-transplant bisphosphonate use	P value
Patient characteristics			
Population size	9	21	
Age, years	33.5 ± 10.3	32.5 ± 10.1	0.80
Gender, female	3 (33%)	12 (57%)	0.43
BMI, kg/m^2	20.1 ± 2.2	19.5 ± 3.3	0.67
Bone density			
Lumbar spine			
BMD, g/cm^2	0.792 ± 0.133	0.851 ± 0.139	0.29
T-score	-2.6 ± 1.1	-1.8 ± 1.1	0.099
Z-score	-2.5 ± 1.0	-1.8 ± 1.2	0.16
Left femoral neck			
BMD, g/cm^2	0.615 ± 0.113	0.702 ± 0.118	0.072
T-score	-2.3 ± 0.8	-1.5 ± 0.9	0.028
Z-score	-2.1 ± 0.7	-1.4 ± 0.7	0.035
Left total hip			
BMD, g/cm^2	0.715 ± 0.114	0.787 ± 0.124	0.17
T-score	-2.1 ± 0.7	-1.4 ± 0.8	0.077
Z-score	-2.0 ± 0.7	-1.5 ± 0.8	0.10

Data displayed as N (%) or mean ± SD.

Table 7. Clinical Characteristics of cystic fibrosis patients receiving vs. non-receiving bisphosphonates *post-transplantation*

	Post-transplant bisphosphonate use	No post-transplant bisphosphonate use	P value
Patient characteristics			
Population size	10	20	
Age, years	35.3 ± 11.1	31.6 ± 9.4	0.35
Gender, female	4 (40%)	11 (55%)	0.70
BMI, kg/m^2	20.3 ± 2.2	19.4 ± 3.4	0.44
Bone density			
Lumbar spine			
BMD, g/cm^2	0.787 ± 0.127	0.856 ± 0.140	0.20
T-score	-2.6 ± 1.1	-1.8 ± 1.2	0.078
Z-score	-2.4 ± 1.0	-1.8 ± 1.2	0.19
Left femoral neck			
BMD, g/cm^2	0.615 ± 0.107	0.707 ± 0.120	0.050
T-score	-2.3 ± 0.8	-1.5 ± 0.9	0.021
Z-score	-2.0 ± 0.7	-1.4 ± 0.8	0.060
Left total hip			
BMD, g/cm^2	0.714 ± 0.106	0.791 ± 0.125	0.12
T-score	-2.0 ± 0.7	-1.4 ± 0.8	0.056
Z-score	-1.9 ± 0.7	-1.4 ± 0.8	0.13

Data displayed as N (%) or mean ± SD.

Table 8. Comparison of cystic fibrosis patients with and without post-transplant fractures.

	Without fractures	With fractures	P value
Patient characteristics			
Population size	21	9	
Gender, female	10 (48%)	5 (56%)	1.0
Age at transplant, years	30.1 ± 8.1	37.3 ± 12.6	0.10
Height (cm)	163.3 ± 6.6	166.8 ± 8.3	0.23
Weight (kg)	52.7 ± 8.7	54.6 ± 11.8	0.61
BMI, kg/m^2	19.7 ± 3.1	19.5 ± 2.9	0.86
Race			0.57
White	17 (81%)	8 (89%)	
Hispanic	3 (14%)	0 (0%)	
African American	1 (5%)	1 (11%)	
CFTR genotype[1]			0.43
Delta F508 homozygous	9 (43%)	5 (63%)	
Other	12 (57%)	3 (38%)	
Comorbidities			
CF-related diabetes	19 (90%)	7 (78%)	0.56
Nephrolithiasis	12 (57%)	6 (67%)	0.70
Falls	3 (14%)	4 (44%)	0.15
Pre-transplant fractures	9 (43%)	4 (44%)	1.0
Lung transplant			
LAS at transplant	46 ± 16	52 ± 18	0.49
Waitlist time, days	80 [18, 299]	44 [16, 210]	0.31
Length of hospital stay, days	16.7 ± 9.6	14.8 ± 6.1	0.58
Pulmonary function tests			
FVC, L	1.96 ± 0.70	1.71 ± 0.55	0.36
FVC, % predicted	47.2 ± 13.4	40.8 ± 13.3	0.25
FEV1, L	1.10 ± 0.38	0.83 ± 0.23	0.064
FEV1, % predicted	31.8 ± 9.4	24.4 ± 6.7	0.042
6-minute walk distance, m	303 ± 76	288 ± 93	0.64
Serum lab values			
Creatinine, mg/dL	0.67 ± 0.24	0.78 ± 0.23	0.30
Alkaline phosphatase, U/L	140 ± 69	99 ± 40	0.15
Hemoglobin A1c, %	6.40 ± 0.75	7.04 ± 0.99	0.088
25-OH vitamin D, ng/mL	32.4 ± 11.8	34.2 ± 9.8	0.74
eGFR, mL/min	123 ± 31	112 ± 29	0.39
Pre-transplant medication use			
Glucocorticoid use			

Inhaled	18 (5%)	7 (78%)	0.62
Oral	20 (95%)	8 (89%)	0.52
Nasal	16 76%)	7 (78%)	1.0
Calcium replacement	17 (81%)	5 (56%)	0.20
Vitamin D replacement	21 (100%)	8 (89%)	0.30
Bisphosphonate	4 (19%)	5 (56%)	0.082
CFTR modulators	5 (24%)	1 (11%)	0.64
Post-transplant cumulative prednisone exposure[2]			
Total steroids, mg	9200 ± 2070	8286 ± 1261	0.23
Total steroids by weight, mg/kg	175 ± 46	164 ± 33	0.50
Change in BMD, %			
Lumbar spine			
1st year	-6.4 [-8.5, 0.3]	-15.5 [-18.1, -9.5]	0.051
2nd year	-0.8 [-6.7, 6.8]	-2.2 [-8.1, 3.1]	0.35
Left femoral neck			
1st year	-10.1 [-14.8, -4.7]	-11.6 [-12.9, -4.7]	0.94
2nd year	-2.8 [-11.0, 1.7]	-7.8 [-12.6, -3.7]	0.27
Left total hip			
1st year	-8.7 [-11.1, -1.8]	-6.2 [-11.0, -4.0]	0.92
2nd year	-5.2 [-10.9, 4.5]	-2.6 [-9.5, -0.9]	0.74
T-score			
Lumbar spine			
Baseline	-1.78 ± 1.12	-2.63 ± 1.12	0.067
1st year	-2.19 ± 1.00	-2.80 ± 1.08	0.29
2nd year	-1.83 ± 0.91	-2.96 ± 0.67	0.0050
Left femoral neck			
Baseline	-1.47 ± 0.94	-2.33 ± 0.57	0.017
1st year	-2.09 ± 0.72	-2.30 ± 0.56	0.64
2nd year	-1.74 ± 0.77	-2.73 ± 0.57	0.0034
Left total hip			
Baseline	-1.39 ± 0.84	-2.06 ± 0.69	0.050
1st year	-1.86 ± 0.64	-1.63 ± 0.51	0.56
2nd year	-1.68 ± 0.71	-2.28 ± 0.59	0.051
Z-score			
Lumbar spine			
Baseline	-1.81 ± 1.09	-2.51 ± 1.16	0.13
1st year	-2.22 ± 0.98	-2.1 ± 0.10	0.84
2nd year	-1.91 ± 0.82	-2.91 ± 0.68	0.0070
Left femoral neck			

Baseline	-1.41 ± 0.78	-2.06 ± 0.65	0.040
1st year	-1.99 ± 0.69	-1.90 ± 0.95	0.83
2nd year	-1.64 ± 0.68	-2.41 ± 0.72	0.014
Left total hip			
Baseline	-1.44 ± 0.75	-1.93 ± 0.75	0.11
1st year	-1.87 ± 0.61	-1.47 ± 0.65	0.31
2nd year	-1.66 ± 0.64	-2.13 ± 0.72	0.11

[1]Total numbers reduced due to exclusion of one patient with missing genotype studies.

[2]Dosing displayed as prednisone equivalents over the first year post-lung transplantation. Two patients from the "without fractures" group were excluded due to incomplete steroid use data.

Data displayed as mean ± SD, median [IQR], or N (%). BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; CF: cystic fibrosis; LAS: lung allocation score; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; eGFR: estimated glomerular filtration rate.

Table 9. Comparison of bone densities in non-cystic fibrosis patients with and without post-transplant fractures.

	Without fractures	With fracture	P value
Change in BMD, %			
Lumbar spine			
1st year	-7.3 [-10.0, 0.1]	-7.5 [-11.8, -2.1]	0.35
2nd year	-4.9 [-8.4, 0.0]	-4.0 [-6.6, -2.9]	0.35
Left femoral neck			
1st year	-5.8 [-8.4, -1.3]	-8.6 [-10.3, -3.3]	0.41
2nd year	-6.0 [-9.4, -2.4]	-11.5 [-13.5, -5.1]	0.17
Left total hip			
1st year	-4.6 [-7.1, -2.0]	-9.2 [-9.4, -6.3]	0.066
2nd year	-4.8 [-6.6, -2.4]	-8.2 [-10.4, -4.8]	0.15
T-score			
Lumbar spine			
Baseline	-0.9 ± 1.6	-1.2 ± 1.5	0.65
1st year	-1.3 ± 1.7	-1.9 ± 1.3	0.38
2nd year	-1.5 ± 1.4	-1.6 ± 1.5	0.78
Left femoral neck			
Baseline	-1.4 ± 1.2	-1.8 ± 0.7	0.39
1st year	-1.7 ± 1.1	-2.2 ± 0.5	0.17
2nd year	-1.8 ± 1.1	-2.3 ± 0.3	0.13
Left total hip			
Baseline	-1.0 ± 1.0	-1.4 ± 0.7	0.30
1st year	-1.3 ± 1.1	-1.9 ± 0.6	0.16
2nd year	-1.4 ± 1.1	-1.9 ± 0.7	0.26
Z-score			
Lumbar spine			
Baseline	-0.2 ± 1.5	-0.5 ± 1.8	0.66
1st year	-0.7 ± 1.7	-1.1 ± 1.7	0.50
2nd year	-0.7 ± 1.4	-0.9 ± 1.9	0.85
Left femoral neck			
Baseline	-0.6 ± 1.1	-1.0 ± 0.8	0.38
1st year	-0.9 ± 1.0	-1.4 ± 0.8	0.18
2nd year	-0.9 ± 1.0	-1.5 ± 0.7	0.12
Left total hip			
Baseline	-0.6 ± 1.0	-0.9 ± 1.0	0.54
1st year	-0.9 ± 1.1	-1.4 ± 0.8	0.24
2nd year	-0.9 ± 1.0	-1.3 ± 1.0	0.38

Data displayed as mean ± SD or median [IQR].

LIST OF FIGURES

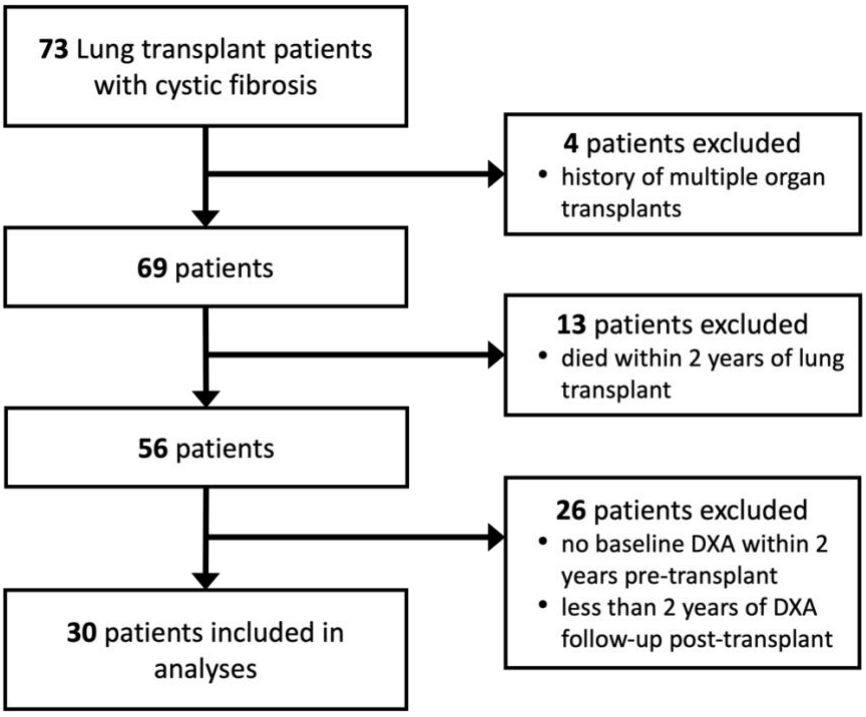

Figure 1. Flowchart of patient inclusion. A total of 73 lung transplant recipients with cystic fibrosis were identified. After exclusion based on multiple transplants, death within 2 years of transplant, and missing DXA data, 30 patients were included in the study. DXA: Dual-energy X-ray absorptiometry.

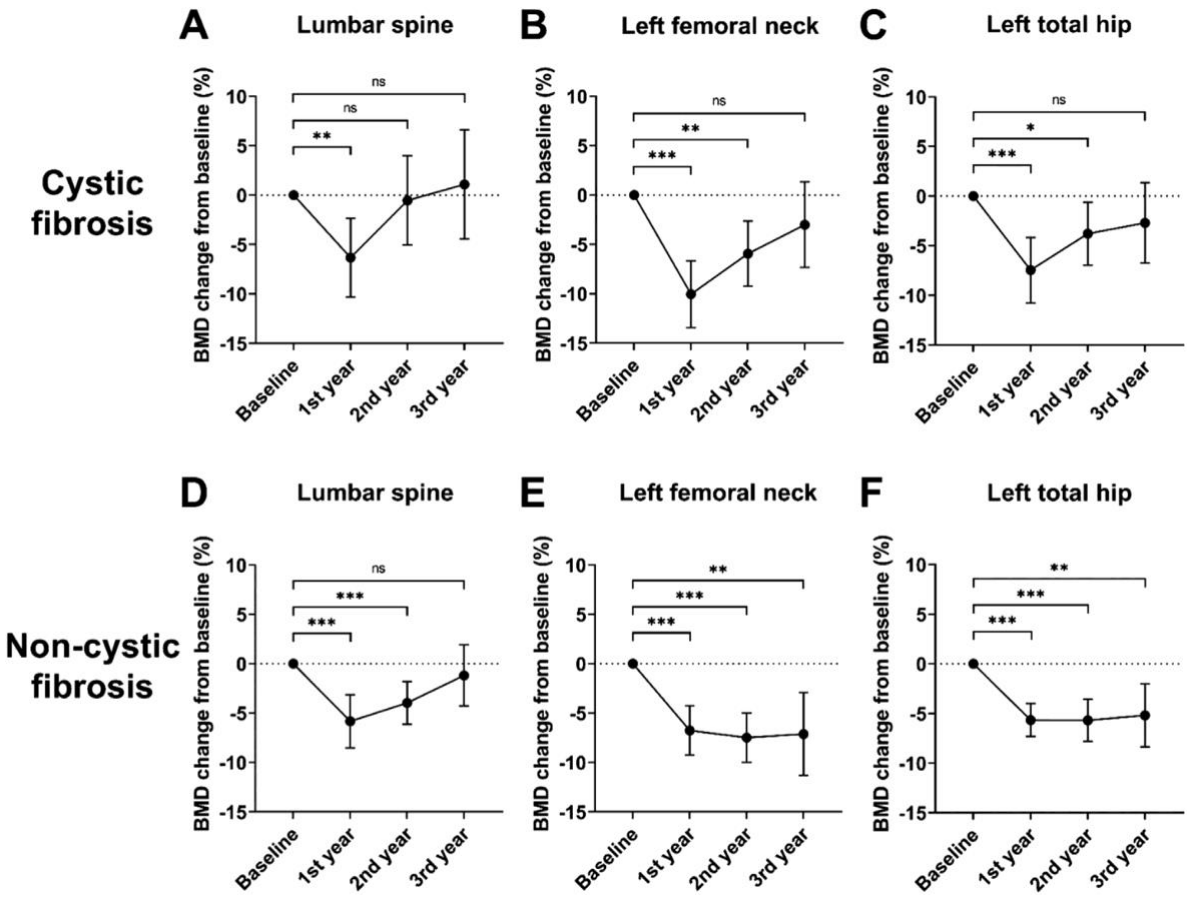

Figure 2. Change in bone mineral density post-lung transplantation in recipients with and without cystic fibrosis. In cystic fibrosis patients, A) lumbar spine BMD significantly declined in the first year after lung transplant but returned to baseline by the second year; B) Left femoral neck BMD significantly declined in the first year and returned to baseline by the third year; C) Left total hip also significantly declined in the first year and returned to baseline by the third year. Although non-cystic fibrosis patients exhibited a significant decline in BMD at all sites, D) the lumbar spine BMD returned to baseline by the third post-transplant year; whereas E) the left femoral neck and F) left total hip bone densities did not recover. Data displayed as mean ± 95% CI. BMD: bone mineral density.
$*p < 0.05$, $**p < 0.01$, $***p < 0.001$, ns = not significant (paired *t*-test).

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VITAE

Vincent (January 9th, 1996-present) is a Vietnamese American student born and raised in Plano, TX. He became interested in natural sciences from an early age, collecting fossils and minerals and exploring the outdoors throughout his childhood. He discovered his passion for medicine after an internship at the National Institutes of Health while completing his undergraduate degree in biology at the University of Texas at Dallas. He graduated in 2018 *summa cum laude* with Major Honors and attended the University of Texas Southwestern Medical School in 2019. Following graduation with his M.D. with Distinction in Research, he will be pursuing residency training in psychiatry, where he hopes to treat mental health disorders and better understand the intersection of biology and behavior.

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