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Pancreatic Status Is Not a Risk Factor for Cystic Fibrosis-Related Bone Disease

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ABSTRACT

Background: As the life expectancy of people with cystic fibrosis (PwCF) increases, understanding long-term complications, including CF-related bone disease (CFBD), is crucial.

Objective: This study aimed to longitudinally characterize CFBD and to compare the bone status of pancreatic sufficient (PS) and pancreatic insufficient (PI) PwCF.

Methods: This longitudinal analysis included PwCF older than 8 years of age who had at least one dual-energy X-ray absorptiometry test between 2008 and 2021. Data were collected on serum parameters of bone metabolism, nutritional history, habitual activity, and fractures in addition to other demographic and clinical characteristics.

Results: The study included 80 PwCF: 32 (40%) were PS and 48 (60%) PI. Normal dual-energy X-ray absorptiometry results were found in 42 (53%) patients: 16 (50%) in the PS group and 26 (54%) in the PI group ($p = 0.72$). Three (9%) of the PS group and seven (15%) of the PI group had at least one Z-score below −2 ($p = 0.49$). The longitudinal bone density decline over a mean of 4.8 years was similar in the two groups. In a logistic regression analysis, pancreatic insufficiency was not found to be a risk factor for CFBD. Female sex was the only significant risk factor for a pathological Z-score.

Conclusions: The prevalence and severity of CFBD were not found to correlate with pancreatic sufficiency. The similar prevalence of CFBD between patients with PS and PI suggests that screening, and eventually treatment, should be offered to all PwCF, irrespective of pancreatic status.

1 | Introduction

Cystic fibrosis (CF) is the prominent cause of exocrine pancreatic insufficiency in early life and is a major cause of severe chronic lung disease in children. The increasing life expectancy of people with CF (PwCF) prompts the importance of characterizing long-term multisystemic complications such as CF-related bone disease (CFBD) [1]. CFBD is a progressive bone disease mainly characterized by osteoporosis and low-trauma fractures. CFBD starts at an early age and affects 23%–58% of adults with CF [2, 3].

The International Society for Clinical Densitometry defines osteoporosis in children and young adults by the fulfillment

Abbreviations: BMD, bone mineral density; BMI, body mass index; CF, cystic fibrosis; CFBD, cystic fibrosis-related bone disease; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; FEV_1, forced expiratory volume in 1 s; FEV_1pp, FEV_1, percent predicted; OR, odds ratio; PI, pancreatic insufficient; PS, pancreatic sufficient; PwCF, people with cystic fibrosis.

of one of two criteria. The first criterion is a combination of a bone mineral density (BMD) *Z*-score of ≤ −2 and clinically significant fracture history. The latter is defined as the occurrence of two or more long bone fractures before age 10 years or three or more long bone fractures at any age up to 19 years. The second criterion that fulfills the definition of osteoporosis among children and young adults is the occurrence of one or more vertebral compression fractures without high-energy trauma or local disease, regardless of the BMD *Z*-score [4]. Osteopenia, a less severe form of low BMD, is poorly defined in the pediatric and young adult population. Some authors consider a *Z*-score between −1 and −2 as indicative of osteopenia [5, 6]. In adults, osteoporosis is characterized by a bone density that falls 2.5 standard deviations (SD) below the mean BMD of a sex-matched, young, healthy population (*T*-score). Osteopenia is defined by a *T*-score ranging between −1 and −2.5 [2]. Notably, these classifications were originally designed for postmenopausal women. For young PwCF up to age 50 years, the European Cystic Fibrosis Society recommends using the *Z*-score [7].

Malabsorption and maldigestion are considered an important risk factor for osteoporosis [8]. Thus, it has been assumed that CF patients who are PI would be at higher risk for this complication. PwCF who are pancreatic sufficient (PS) compared to those who are pancreatic insufficient (PI) tend to have milder gastrointestinal manifestations, usually without malnutrition or vitamin deficiencies [9]. Thus, it was suggested that the prevalence of CFBD may be lower in this group. While one study found that exocrine pancreatic insufficiency increased the risk of low BMD [10], in a comprehensive evaluation of factors associated with low BMD, patients with PS and PI presented with similar values [6]. Thus, the aim of this study was to longitudinally characterize CFBD among PwCF and to compare the bone status between those who are PS and PI.

2 | Methods

2.1 | Study Population

We included all the PwCF treated at the CF clinic at Schneider Children's Medical Center who were older than 8 years and who performed at least one dual-energy X-ray absorption (DXA) test during 2008–2021. The test was part of the standard annual review protocol. We excluded patients following solid organ transplantation.

2.2 | Study Design and Data Collection

This longitudinal cohort consisted of a complete chart review of patient information from 2008 to 2021. We retrieved demographic characteristics including age, sex, and clinical characteristics. The latter included the sweat chloride test, forced expiratory volume in 1 s (FEV_1), hepatic disease, CF-related diabetes; treatments including pancreatic enzyme replacement therapy, corticosteroids (pulse, oral, or inhaled), intravenous antibiotics, bisphosphonate, and CF transmembrane conductance regulator (CFTR) modulators.

Pancreatic insufficiency was defined by fecal elastase < 200 mcg/gr. Chronic respiratory infection with *Pseudomonas aeruginosa* (*P. aeruginosa*) was defined using modified Leeds criteria [11]. This entails collecting at least four samples annually, and more than 50% of these samples test positive.

Bone status was assessed by DXA, which was performed routinely for evaluating PwCF as part of standard care protocols. All DXA scans were conducted using the GE Lunar Prodigy (GE HealthCare, Chicago, Illinois, USA), ensuring consistency in measurements. Repeat DXAs for follow-up assessments were performed on the same machine to maintain methodological uniformity and minimize variability. When available, two DXA exams were considered, and the difference between them was assessed. If more than two tests were available, the first and last were used to assess the change over time. DXA test results included *Z*-scores in three locations: the lumbar spine, the femur neck, and the whole body less head. Normal DXA results were defined as having a *Z*-score above −1 at all measurement sites. Osteopenia was defined as a *Z*-score between −1 and −2 at least at one site. Since the definition of osteoporosis requires the presence of a fracture, as outlined in the introduction, we only reported individuals with a *Z*-score below −2. In addition, data that were taken at the time of DXA were collected of the following bone metabolic parameters: serum levels of calcium, phosphorous, vitamin D, vitamin K (prothrombin time), parathyroid hormone, and alkaline phosphatase.

The clinical presentation of CF depends on the type of CFTR genetic variants, which is also an important factor influencing bone health in CF. In this study, we used the accepted classification of minimal function and residual function genetic variants [12]. Minimal function variants are associated with little to no CFTR activity, and residual function variants allow for partial CFTR activity. Individuals with minimal function variants typically exhibit severe disease phenotypes, including pancreatic insufficiency, while those with residual function variants often maintain pancreatic sufficiency and have sweat chloride levels that may be normal or mildly elevated, indicating partially preserved CFTR function.

The patients or their parents were requested to fill out a detailed study questionnaire. This questionnaire accessed information on habitual physical activity (Godin–Shephard Leisure-Time Physical Activity Questionnaire [13]), evaluation of nutritional habits (American Academy of Pediatrics [14]), and previous fracture history. The latter was evaluated using a simple ad hoc fractures questionnaire recalling patients' fractures in the last 10 years. The calculated total calcium intake, derived from food sources or calcium supplements, was compared to the recommended daily intake [15].

Longitudinal analysis was performed in the over 18-year-old group, when two DXA results were available per person. The delta between the two tests was calculated by subtracting the later *Z*-score from the earlier *Z*-score, that is, the more positive the delta, the more bone deterioration occurred.

2.3 | Statistical Analysis

All the results were expressed as mean and SD, or as median with minimum and maximum, or as frequency and percentage. Differences in demographic and clinical characteristics between the PI and PS groups were analyzed using the χ^2 test for categorical variables or an independent samples *t*-test for continuous variables. The Mann–Whitney *U* test was used when the normal distribution was not justified. The Pearson's and Spearman's tests were used for continuous and categorical variables, as appropriate, to analyze correlations between baseline disease (such as *P. aeruginosa*, medications taken, FEV_1 percent predicted (FEV_1pp), and laboratory measurements), bone characteristics, and DXA results. Subsequently, we conducted a logistic regression analysis to compute the odds ratios (OR) and 95% confidence intervals (CI) for pathological bone density *Z*-scores. The following possible predictors were considered: patient's sex, pancreatic function, age, BMI, FEV_1, hepatic disease, CF-related diabetes, steroid treatment, intravenous antibiotics treatment, airway *Pseudomonas* colonization, and CFTR modulator treatment. The analyses were performed using IBM SPSS software (Version 29, Armonk, NY, USA). The tests were two-tailed and $p < 0.05$ were considered statistically significant.

2.4 | Ethical Approval and Consent

The study was approved by the local institutional review board (RMC-0364-18), and informed consent was obtained before the questionnaires were completed.

3 | Results

3.1 | Demographic and Clinical Characteristics

Of the 148 PwCF followed at our center, 80 PwCF fulfilled study criteria and were thus included in the study: 32 (40%) with PS and 48 (60%) with PI. At the completion of the questionnaire, the mean ages of the groups were $32.5 + 15.4$ and $24.6 + 10.3$ years, respectively. The attrition figure (Figure 1) shows no difference in inclusion between the PS and PI groups (67% vs. 64%, $p = 0.89$). The major reasons for not meeting study eligibility criteria were age younger than 8 years ($n = 10$) and the absence of a DXA study. The study population was further classified into two groups to account for differences in bone growth between children and adults; there was one postmenopausal pwCF in the PS group. Table 1 presents the demographic and clinical data for both age groups, classified by PS and PI. Adults in the PI compared to the PS group were notably younger, exhibited lower BMI, and attained a higher percentage of the recommended daily amount of calcium intake. The proportion of patients taking vitamin and calcium supplements was also significantly higher in the PI group. One pwCF was on bisphosphonate therapy in the PS group. Overall, the bone metabolic parameters measured, such as serum vitamin D, parathyroid hormone, and alkaline phosphatase, did not differ significantly between the groups.

3.2 | Bone Health Characteristics

Normal DXA results were found in 42 (53%) patients: 16 (50%) of the PS group and 26 (54%) of the PI group ($p = 0.72$). Osteopenia, that is, a *Z*-score between −1 and −2, was observed in 28 (35%): 13 (41%) PS and 15 (31%) PI ($p = 0.39$), 7 (25%) of the pwCF in the osteopenia group reported fractures in the past. One person in the osteopenia group was a postmenopausal woman who received bisphosphonates. Three (9%) of the PS group and seven (15%) of the PI group had at least one *Z*-score below −2 ($p = 0.49$). The median age of those with *Z*-scores below −2 was 19.5 years. The mean pathological *Z*-score in this group was −2.3. None received bisphosphonates, and only three received supplemental calcium. None of them had pathological fractures.

The only parameter that differed between the PS and PI groups was the mean femur neck *Z*-scores in adults, which unexpectedly were lower for the PS than the PI group (Table 2). Among the pediatric patients, DXA results did not differ between those with PI and PS. The mean femur neck *Z*-score was lower among female than male patients (−0.3 vs. −0.7, $p = 0.004$). The sex distribution was similar between the groups.

Only 47 of the 80 PwCF filled out the questionnaires that are described above. Descriptive analysis showed the absence of a correlation between the mean DXA and physical activity among adult patients who had fractures. Among patients under age 18 years, the femur neck *Z*-score was higher among those who were more rather than less physically active (−0.2 vs. −0.4, $p = 0.021$). No correlations were found between a patient's sex and the number of fractures.

3.3 | Changes in Bone Health Over Time

Not all the subjects performed subsequential DXA studies; however, in those who did, the mean interval between the DXA tests was similar for the PS and PI groups, as shown in Table 3. Overall, significant deterioration was not found over a mean period of 4.8 years; the data were similar for the two groups.

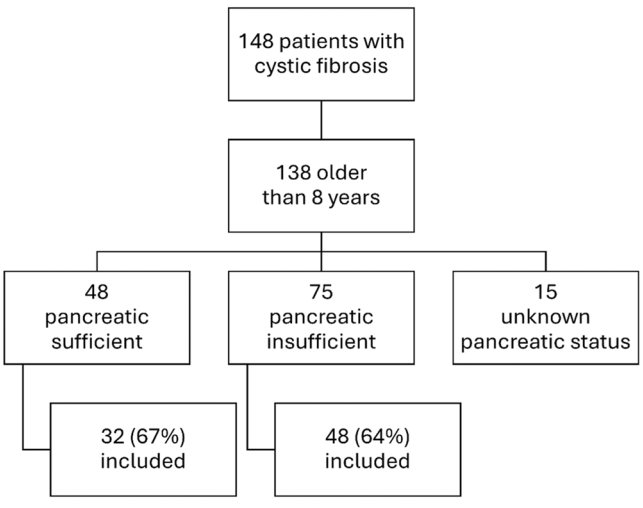

FIGURE 1 | Establishment of the study cohort.

TABLE 1 | Patient characteristics according to two age groups and pancreatic sufficiency.

	Age ≤ 18 years				Age > 18 years			
	PS	**PI**	**Total**	***p* value between PS and PI**	**PS**	**PI**	**Total**	***p* value between PS and PI**
n	5	15	20	—	27	33	60	—
Male	3 (60%)	9 (60%)	12 (60%)	0.693	10 (37%)	17 (52%)	27 (45%)	0.28
Age, mean years	13.8 (1.1)	15.3 (1.9)	14.96 (1.89)	0.056	35.95 (14.3)	28.9 (9.7)	32.1 (12.38)	**0.03**
Minimal function genetic variant	0	15 (100%)	15 (100%)	—	0	33 (100%)	33 (100%)	—
PSA colonization	1 (20%)	6 (40%)	7 (35%)	0.559	9 (33%)	23 (69%)	32 (53%)	**0.018**
Hepatic disease	0	0	0	—	0	4 (12%)	4 (7%)	**0.08**
CFRD	0	0	0	—	1[a] (4%)	13 (39%)	14 (23%)	**0.001**
FEV1pp (%)	93 (11.6)	97.9 (14.4)	96.7 (13.6)	0.468	82.6 (17.8)	85.9 (21.8)	83.9 (20.1)	0.41
BMI kg/m^2	17.3 (4.7)	17.5 (2.8)	17.4 (2.9)	0.834	24.1 (3.5)	21.6 (2.6)	22.7 (3.3)	**0.003**
BMI SDS	−0.7 (1.7)	−0.4 (1)	−0.5 (1.2)	0.713	—	—	—	—
Vitamin D (nmol/L)	52.8 (7.1)	61.5 (28.8)	59.4 (24.8)	0.523	60.3 (27.8)	63.6 (23.9)	62.3 (25.8)	0.620
PTH (ng/L)	33.1 (9.2)	36.5 (16.2)	34.4 (15.9)	0.577	35.1 (12.7)	36.7 (17.7)	36.6 (14.8)	0.696
ALP (U/L)	228.9 (88.3)	229.1 (127.4)	229.1 (115.9)	0.813	130.0 (173.0)	109.4 (36.8)	116. 8 (121.6)	0.548
ADEK multivitamin intake	0	15 (100%)	15 (75%)	**< 0.001**	6 (22%)	30 (90%)	36 (60%)	**< 0.001**
Vitamin D intake	2 (40%)	12 (80%)	14 (70%)	0.131	16 (59%)	22 (66%)	38 (63%)	0.373
Calcium supplement	0	6 (40%)	6 (30%)	0.129	5 (18%)	17 (51%)	22 (36%)	**0.008**
Ca intake % of RDA	0.19 (0.13) [$N = 2$]	1.36 (0.6) [$N = 10$]	1.03 (0.67) [$N = 12$]	**0.001**	0.63 (0.38) [$N = 10$]	1.18 (0.6) [$N = 26$]	1.07 (0.61) [$N = 36$]	**0.003**
Ca supp%	0.07 (0.12) [$N = 2$]	0.10 (0.17) [$N = 10$]	0.09 (0.16) [$N = 12$]	0.945	0.16 (0.26) [$N = 10$]	0.29 (0.34) [$N = 26$]	0.26 (0.33) [$N = 36$]	0.233
CFTR modulators	0	2 (13%)	2 (10%)	0.533	1 (3%)	5 (15%)	6 (10%)	0.636

Note: The data are presented as *n* (%) and mean (SD) unless specifically specified. Bold values indicate statistically significant.

Abbreviations: ADEK, vitamins A, D, E, and K; ALP, alkaline phosphatase; BMI, body mass index; BMI SDS, standardized body mass index; Ca RDA, total calcium intake out of the recommended daily amount; Ca supp%, percent of daily calcium consumption taken in the form of calcium supplements; CFRD, CF-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; FEV1, forced expiratory volume in 1 s; PS, pancreatic sufficient; PSA, *Pseudomonas aeruginosa*; PTH, parathyroid hormone; PI, pancreatic insufficient.

[a]Type 2 diabetes.

TABLE 2 | Mean *Z*-scores (standard deviations) of dual-energy X-ray absorptiometry, by age and pancreatic status.

	Age ≤ 18 years				Age > 18 years			
	PS	PI	Total	*p* value between PS and PI	PS	PI	Total	*p* value between PS and PI
n	5	15	20	—	27	33	60	—
Lumbar spine	−1.12 (0.44)	−0.90 (0.97)	−0.96 (0.86)	0.502	−0.45 (1.22)	−0.4 (1.14)	−0.43 (1.16)	0.872
Femur neck	−0.7 (0.98)	−0.18 (0.92)	−0.29 (0.92)	0.472	−0.67 (0.93)	−0.16 (0.95)	−0.41 (0.97)	**0.043**
Whole body less head	−0.38 (0.47)	−0.41 (1)	−0.40 (0.88)	0.921	−0.64 (1.16) [*N* = 8]	−0.13 (0.78) [*N* = 12]	−0.34 (0.96) [*N* = 20]	0.305

Note: Bold value indicates statistically significant.
Abbreviations: PI, pancreatic insufficient; PS, pancreatic sufficient; SD, standard deviation.

3.4 | Correlations Between Clinical Features and Bone Density

Correlations were examined of clinical characteristics with bone disease status. FEV_1pp was found to correlate with the femur neck *Z*-score in the PI group ($r = 0.33$, $p = 0.03$), but not in the PS group ($r = 0.14$, $p = 0.47$). Analysis by age group showed a strong correlation between FEV_1pp and femur neck *Z*-score among children with PI, adults with PI, and adults with PS ($r = 0.29$, $p = 0.006$; $r = 0.31$, $p = 0.01$; and $r = 0.26$, $p = 0.04$, respectively). The correlation was not significant among children with PS ($r = 0.24$, $p = 0.12$).

Overall, a strong correlation was found between BMI and bone status, though this varied across subgroups. In the PS group, a higher BMI was associated with a better femur neck *Z*-score ($r = 0.35$, $p = 0.02$). A similar, though not statistically significant, trend was observed in the PI group ($r = 0.32$, $p = 0.08$). When considering the PI group based on age, no significant correlation was found between BMI and bone status in patients younger than 18 years ($r = 0.563$, $p = 0.071$). For patients aged 18 years and older, the correlation between BMI and femur neck *Z*-score was also not significant ($r = 0.32$, $p = 0.079$).

In contrast, lung function, as measured by FEV1%, demonstrated a strong positive correlation with femur neck *Z*-score in PI patients younger than 18 years ($r = 0.36$, $p = 0.02$), but no significant correlation was seen in the PS group. Additionally, across all ages, calcium supplementation showed a negative correlation with femur neck *Z*-score in the PI group ($r = -0.33$, $p = 0.07$).

3.5 | Pathological *Z*-Score Prediction

Table 4 presents the results of a logistic regression model for predicting pathological femur neck *Z*-scores, which was defined as below −1. Only female sex was found to be a risk factor (OR 3.16, CI 1.84–8.200). None of the other factors analyzed were found to be statistically significant predictors of pathological femur neck *Z*-score. Namely, an increase of 1% in FEV1pp (OR 0.932, CI 0.880–1.004), pancreatic insufficiency (OR 1.716, CI 0.108–27.202) and other demographic and clinical parameters, including age, BMI, hepatic disease, CF-related diabetes, steroid treatment, intravenous antibiotics treatment, Pseudomonas colonization, and CFTR modulator treatment.

4 | Discussion

We observed a high prevalence of low BMD in PwCF, with no significant difference between those with PS and with PI. Compared to adults with PS, adults with PI were younger, had lower BMI, and received a higher percentage of the calcium recommended daily intake. However, in both children and adults, bone metabolic parameters in the serum did not differ significantly between the PS and PI groups. Unexpectedly, in adults, femur neck *Z*-scores were lower among those with PS than with PI. No other statistically significant differences were found in BMD *Z*-scores between the PS and PI groups. Neither

TABLE 3 | Longitudinal changes in *Z*-scores of dual-energy X-ray absorptiometry for bone mineral density, according to pancreatic sufficiency.

	Pancreatic sufficient		Pancreatic insufficient		
	N	**Mean (SD)**	***N***	**Mean (SD)**	***p* value**
Age (median IQR)	18	37.4 (28.0–42.2)	28	25.3 (17.1–29.6)	0.008
Mean (standard deviation) year difference between the dual-energy X-ray absorptiometry tests	18	4.77 (1.4)	28	4.86 (1.85)	0.371
Delta for the lumbar spine	16	0.43 (0.95)	27	0.09 (0.5)	0.189
Delta for the femur neck	14	0.09 (0.47)	25	0.01 (0.41)	0.594
Delta for the whole body less head	3	0.47 (0.45)	11	−0.22 (0.58)	0.094

Note: The more positive the delta, the more bone deterioration took place.

TABLE 4 | A logistic regression model for predicting pathologic femur neck *Z*-scores in the whole study population.

Factors		**OR**	**95% CI**	***p* value**
Sex	Male	1 (Ref.)		
	Female	3.166	1.184–8.200	0.021
Pancreatic function	PS	1 (Ref.)		
	PI	1.716	0.108–27.202	0.702
Age	Estimate for 1 year	0.909	0.810–1.019	0.101
BMI	Estimate for 1 unit	0.993	0.669–1.302	0.993
FEV1	Estimate for 1%	0.932	0.886–1.004	0.064
Hepatic disease	No	1 (Ref.)		
	Yes	1.837	0.045–17.208	0.747
CFRD	No	1 (Ref.)		
	Yes	1.229	0.129–11.732	0.858
Steroid treatment	No	1 (Ref.)		
	Yes	2.942	0.078–11.635	0.561
IV antibiotics treatment	No	1 (Ref.)		
	Yes	1.189	0.184–7.662	0.856
PSA colonization	No	1 (Ref.)		
	Yes	1.337	0.119–15.878	0.798
CFTRm treatment	No	1 (Ref.)		
	Yes	0.716	0.041–5.255	0.820

Abbreviations: BMI, body mass index; CFRD, CF-related diabetes; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CI, confidence interval; FEV1, forced expiratory volume in 1 s; OR, odds ratio; PSA, *Pseudomonas aeruginosa*.

did the prevalence of normal bone density differ significantly between the groups. Over a mean 4.8-year follow-up, some deterioration in BMD *Z*-scores was observed; however, the changes were modest and not statistically significant for most measures. Specifically, the delta values for the lumbar spine, femur neck and whole body less head did not demonstrate significant differences between the PS and PI groups.

In our cohort, pancreatic insufficiency was not identified as a risk factor for CFBD. Previous studies that investigated this topic yielded conflicting results. Our findings corroborate those of a prospective single-center study of 40 PwCF, which showed comparable BMD in both those with PI and PS [6]. In another study of children with CF, rates of pancreatic insufficiency were similar between those with moderately low BMD and normal BMD [16]. On the other hand, our findings contrast with a study of 68 children with CF, in which a higher incidence of CFBD was demonstrated among those with pancreatic insufficiency [10].

We report a high rate of osteopenia in PwCF, with no significant difference between those with PS and PI. This may be explained by the multifactorial etiology of CFBD, which includes, among others, the nutritional state, vitamin D deficiency, chronic inflammation, steroid use, inactivity, and hypogonadism [3, 17]. Some animal models suggest that CFTR expression on osteoclasts has a direct role in bone turnover [18]. Associations have been reported between poor lung function, decreased physical activity, low nutritional status, and low BMD values [3]. While PwCF with PS may not exhibit identical nutritional deficiencies, other phenomena like significant pulmonary inflammation and the direct impact of CFTR on

osteoclasts could contribute to CFBD. Moreover, for PwCF with PI, attentive nutritional care, strict dietary management, and diligent supplementation are commonplace and may mitigate the impact of the nutritional status compared to those with PS.

Well-established normative databases of femur neck *Z*-scores are available for adults and children and serve as a fundamental component for diagnosing osteoporosis, according to both the World Health Organization and the International Society for Clinical Densitometry [19]. Based on this, in addition to the substantial literature indicating the femur neck site evaluation as a surrogate for eventual fracture risk, we chose this parameter for the correlation and the logistic regression model analysis. Lung function (FEV_1pp) and nutritional status (BMI) demonstrated positive associations with bone density, as seen in previous reports [6, 20]. In a logistic regression model, the female sex emerged as the sole risk factor for pathological femur neck *Z*-scores, emphasizing sex-specific considerations in CFBD.

In our study population, osteopenia, defined as a *Z*-score lower than −1, was observed in 35%, while 12.5% had a *Z*-score below −2, though without fractures, which are necessary for the definition of osteoporosis. Osteopenia and osteoporosis are common conditions, especially among older adults, postmenopausal women, and individuals with chronic health conditions. In postmenopausal women, osteopenia rates can reach up to 48%, while osteoporosis affects 14% of this group. However, these conditions are much less common in younger populations [21, 22]. In pwCF, our study found higher rates of bone density abnormalities compared to the Cystic Fibrosis Foundation 2021 report, which showed 18% osteopenia and 7.5% osteoporosis in adults with CF [23].

International guidelines recommend screening of CFBD in all individuals over the age of 18 and consider screening for select PwCF from age 8 years [17]. Despite that, the CF Foundation Patient Registry reported that only 60% of adult PwCF underwent screening [24]. Notably, screening rates were lower than expected among those who did not require pancreatic enzymes. Similarly, in our cohort, the rate of DXA study uptake was relatively low, even for the PI group.

Our study has several limitations, including its retrospective design, a modest sample size of 80 patients, small subgroup analyses, and reliance on self-reported questionnaires, which may introduce recall bias. The difference in ages between the groups is also a limitation. Moreover, 35% of the PwCF in our center were excluded due to the absence of DXA tests. However, it has the strength of a real-life design, which may be useful for the CF community. The adherence rate was low despite the staff's recommendations that all patients perform it. The study's duration, 2008–2021 may not fully capture recent developments in CF management, specifically the introduction of CFTR modulators. In a preliminary single-center study examining the impact of novel modulator therapy on BMD, a significant increase in BMD parameters was observed after the administration of the modulators [25]. Future research is necessary in order to overcome these limitations and incorporate a more comprehensive analysis of genetic, lifestyle, and treatment factors. This will provide deeper insights into CFBD and help determine whether a true difference in CFBD risk exists between PI and PS groups. In conclusion, this study provides insights into CFBD in PwCF, both with PS and PI. Despite the differences observed in certain characteristics between the two groups, no significant disparities in bone health were detected. Lung function and nutritional status showed positive associations with bone density unrelated to pancreatic status. Until more definitive evidence is available, all CF patients, both PS and PI, should continue to be screened and monitored for bone disease.

Author Contributions

Miri Dotan: methodology, writing – original draft, writing – review and editing. **Maya Trau:** conceptualization, methodology, data curation, writing – review and editing. **Meir Mei-Zahav:** writing – review and editing. **Huda Mussaffi:** writing – review and editing. **Yulia Gendler:** writing – review and editing, formal analysis, conceptualization, methodology. **Hannah Blau:** writing – review and editing. **Dario Prais:** writing – review and editing, conceptualization, methodology, supervision.

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Ethics Statement

The study was approved by the local Institutional Review Board (RMC-0364-18).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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