Bone involvement in young adults with cystic fibrosis – a Portuguese cohort

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Dear editor,

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease among Caucasian populations and its diagnosis is based upon the finding of genetic and/or functional abnormalities of the cystic fibrosis transmembrane regulator (*CFTR*) gene, involved in multiple organic functions[1,2]. With regard to CF-related bone disease (CFBD), it is expected that it becomes even more prevalent in this group of patients as the median age of survival continues to increase[3].

The aim of this work is to characterize CFBD in a Portuguese young adult CF cohort. We performed a cross-sectional, observational study of all adult CF patients in a CF Portuguese reference centre between January 2017 and January 2019. Bone densitometry scan (DXA) scans were performed using the Lunar IDXA ME and BMD Z-scores for lumbar spine (LS), femoral neck (FN) and total femur (TF) were calculated. CFBD was diagnosed in the presence of a BMD Z-score of – 2.0 or lower and/or a fragility fracture history and low BMD was diagnosed when BMD Z-scores were between -1 and -2[4]. All data were analysed using IBM SPSS Statistics version 23.

Of 30 patients, 53.3% were males (n=16). Median age was 32.5 (27.0; 42.3) and median body mass index (BMI) was 22,04 (19,85; 24,55), with 4 patients (13.3%) being underweight (BMI<18.5 kg/m²). Median 25-OH-vitD was 24 ng/mL (16.00; 31,25), with 12 patients (40.0%) presenting hypovitaminosis D and 2 patients (6.7%) with severe vitamin D deficit (<10 ng/mL), despite all patients were supplemented with cholecalciferol (minimum dose of 667 UI to a maximum dose of 20 010 UI per day) to achieve 25OHVitD levels above the reference range. Median ionized calcium was 2.56 mEq/L (2.48; 3.80), (reference interval=

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TABLE I. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF CYSTIC FIBROSIS PATIENTS

	Males (n=16)	Females (n=14)	Difference between groups (p-value)
Age	32.5 (28.0; 42.0)	32.5 (26.8; 42.3)	0.967
DF508 homozygous n (%)	9 (56.3%)	4 (28.6%)	0.465
Pancreatic insufficiency n (%)	14 (87.5%)	7 (50.0%)	0.028
CF diabetes	5 (31.3%)	4 (28.6%)	0.715
BMI	21.6 (19.6; 24.6)	22.6 (20.6;24.1)	0.480
%FEV1	79.2 (41.8; 92.1)	75.0 (45.9; 82.3)	0.371
%FVC	85.4 (75.0; 107.0)	89.0 (55.0; 100.8)	0.739
Bone density FN Z-score	-1.10 (-1.78; -0.03)	-0.90 (-1.55; -0.30)	0.930
Bone density FT Z-score	-0.85 (-1.38; 0.45)	-0.30 (-1.10; 0.35)	0.598
Bone density LT Z-score	-1.05 (-1.85; -0.43)	-0.95 (-1.83; -0.27)	0.677
25-OH-vitD ng/mL	26.5 (19.0; 31.0)	17.5 (13.8; 33.8)	0.371
Serum creatinine mg/dL	0.75 (0.71; 0.95)	0.65 (0.52; 0.78)	0.053

Data are expressed as median with percentiles 25 and 75, respectively, in parentheses. Differences between groups were calculated using Mann–Whitney U test.

BMD, bone mineral density; BMI, body mass index; %FEV1, forced expiratory volume in 1 s % predicted; FN, femural neck ; FT, femural total; %FVC, forced vital capacity % predicted; LS, lumbar spine; 25-OH-vitD, 25-hydroxyvitamin D.

TABLE II. CORRELATIONS BETWEEN BMD AND CLINICAL AND BIOCHEMICAL VARIABLES IN CYSTIC FIBROSIS PATIENTS

Variable	Median (P25; P75)	FN BMD (p-value)	LS BMD (p-value)
Age	32.5 (27.0; 32,5)	-0.212 p=0.269	-0.055 p=0.605
BMI	22,04 (19,85; 24,55)	0.287 p=0.131	0.614* p<0.01
%FEV1	76.4 (49.5; 87.3)	0.109 p=0.573	0.126 p=0.506
%FVC	85.6 (71.6; 103.2)	0.167 p=0.388	0.202 p=0.283
Bone density FN Z-score	-0.90 (-1.70; -0.10)	0.916* p<0.001	0.569* p=0.001
Bone density FT Z-score	-0.60 (-1.30; 0.40)	0.788* p<0.001	0.547* p=0.002
Bone density LT Z-score	-1.00 (-1.83; -0.48)	0.625* p<0.001	0.924* p<0.001
25-OH-vitD ng/mL	24 (16.00; 31.25)	0.250 p=0.128	0.222 p=0.120
Serum creatinine mg/dL	0.72 (0.61; 0.93)	0.056 p=0.789	0.110 p=0.609
GFR mL/min/1.73m^2	115.5 (95.8; 128.3)	0.075 p=0.700	-0.076 p=0.690

Correlations were calculated using Spearman's rank order (r).* indicates r values with statistical significance at the level of 0.05.
BMD, bone mineral density; BMI, body mass index; %FEV1, forced expiratory volume in 1 s % predicted; FN, femural neck ; FT, femural total; %FVC, forced vital capacity % predicted; GFR, Glomerular filtration rate; LS, lumbar spine, 25-OH-vitD, 25-hydroxyvitamin D.

2.26- 2.64); and median phosphorus was 3.30 mg/dL (2.7 to 4.5), (reference interval= 2.7 - 4.5 mg/dL). Seven patients had undergone lung transplantation, maintaining systemic corticosteroid therapy, mostly at a high dosage (4 patients taking prednisolone >7.5 mg per day).

Nine patients (30.0%) had cystic fibrosis-related diabetes mellitus (CFRDM) and 21 (70.0%) had pancreatic insufficiency under replacement pancreatic enzymes. Thirteen (43.3%) were homozygous for del508 and 10 (33.3 %) were heterozygous for del508. Four patients (13.3%) were diagnosed with osteoporosis based on Z-scores (lumbar spine, total femur and/or femoral neck) and 15 patients (50%) had low BMD. Seven patients (23.3%) were under anti-osteoporotic treatment: 4 under alendronate, 2 under zoledronate and 1 patient under denosumab, treatment duration between 2 and 7 years. Among them, 2 (6.7%) had fragility fractures: both vertebral and non-vertebral.

A moderate correlation was found between the LS BMD and BMI and, as expected, FN BMD and LS BMD have moderate to strong correlations with BMD Z scores (Table II).

Despite the young age of our cohort, we found a high prevalence of osteoporosis and low BMD, of 13.3% and 50%, respectively. This is consistent with previous published data, as a systematic literature review presented a 23.5% prevalence of osteoporosis and a 38% prevalence of osteopenia in young adults with CF[5]. Regarding the prevalence of fractures, our study reported a value below what has been reported previously (6.7% in our cohort against values between 14% and 53%)[5-7].

Nevertheless, the small sample size does not allow to assess the real impact of CF related risk factors in BMD and a cross-sectional analysis can lead to an information bias from incomplete medical records. Finally, we highlight the fact that this is the first study in Portugal describing bone disease in a CF cohort in a tertiary hospital, where CF patients have a multidisciplinary approach and are given the state-of-the art treatment.

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