Prevalence of low bone mineral density in adolescents and adults with cystic fibrosis

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Summary

Objective: The aim of this cross-sectional study was to evaluate the prevalence of low bone mass density in cystic fibrosis patients as well as to evaluate the factors associated with bone mass in such patients.

Methods: Bone mass density was measured by dual-photon X-ray absorptiometry of lumbar spine (L1-L4), in patients ≤19 years old, or lumbar spine and femur (total and neck) in patients ≥20 years old. Evaluations of nutritional status, biochemical parameters, and lung function were performed. Medication data were obtained from medical records.

Results: Fifty-eight patients were included in the study (25 males/ 33 females), mean age 23.9 years (16-53years). The prevalence of bone mass below the expected range for age at any site was 20.7%. None of the subjects had history of fracture. Lumbar spine Z-score in cystic fibrosis patients correlated positively with body mass index (r= 0.3, p=0.001), and forced expiratory volume in the first second (% predicted) (r=0.415, p=0.022). Mean lumbar spine Z-score was higher in women (p=0.001), in patients with no pancreatic insufficiency (p=0.032), and in patients with no hospitalization in the last 3 months (p=0.02). After multivariate analysis, body mass index (p= 0.001) and sex (p=0.001) were independently associated with Z-score in lumbar spine.

Conclusion: Low bone mass is a frequent problem in patients with CF, being independently associated with body mass index, and male sex.

Key words: cystic fibrosis, bone, bone density, bone loss, bone diseases, metabolic, risk factors.

Introduction

Advances in the care of patients with cystic fibrosis (CF) increased survival. Bone health is important for the quality of life in aging patients, and became more relevant in patients affected with CF[1-4].

Several studies described lower bone mass density (BMD) in patients with CF, which increases fracture risk [5-8]. Bone fractures can cause pain, decrease respiratory status, and are a contraindication for lung transplantation in these patients[9,10].

Cross-sectional studies in adults (age range from 16-60 years) with CF demonstrated that 6 to 68% had Z-scores ≤-2.0[8,11-16]. Therefore, understanding the mechanisms of low BMD in CF patients is important to improve its prevention and treatment. Abnormal calcium homeostasis, poor nutritional status, chronic inflammation, or inactivity associated with lung infection exacerbations could be responsible for bone abnormality[5,8,12,17-19]. Low BMD has been independently associated with malnutrition, male sex, ·F508 mutation, and severe lung injury[14]. Other potential risk factors described were use of glucocorticosteroids, hypogonadism, decreased physical activity, malabsorption of calcium and vitamins, chronic infections, and inflammatory cytokines[5,8,11,17,18,20-23].

In Brazil, just one study evaluated the prevalence of low BMD in patients with CF[24]. As bone mass is dependent on ethnic factors[25] and the prevalence of CFTR gene mutations is not the same in different populations[26, 27], it is important to study how bone mass is affected in patients with cystic fibrosis in different regions of the world. Therefore, the aim of this study was to evaluate the prevalence of low BMD in CF patients in a tertiary care facility in Porto Alegre, state of Rio Grande do Sul, Brazil, (30° S) as well as to evaluate the factors associated with low bone mass in these patients.

METHODS

The study was carried out in the outpatient program for adolescents and adults with CF at the Hospital de Clínicas de Porto Alegre (HCPA), from February 25th to September 23th, 2011, after approval by the institution's Ethics Committee. Each patient gave written consent before inclusion in the study.

Inclusion criteria

Patients 16 years old or older with CF confirmed by sweat test (Cl⁻≥60 mEq/L) in two occasions or CFRT gene mutation in both alleles were included.

Exclusion criteria: Organ transplant.

Experimental design: Cross-sectional study. Data were obtained in the medical records and during interviews with the patients.

Evaluation of BMD

BMD was measured by dual-photon X-ray absorptiometry (DXA), with HOLOGIC QDR4500A, equipped with standard density software (version 8.26) (4500 Acclaim densitometer, Hologic, Wattham, MA, USA). Regions evaluated were lumbar spine, L1- L4, in patients ≤19 years old, or lumbar spine and femur (total and neck) in patients ≥20 years old. Bone mass below the expected range for age was defined by Z-score as ≤ – 2.0 in premenopausal women and in men ≤ 50 years old. Osteoporosis was diagnosed when the T-score was ≤-2.5 in perimenopausal or postmenopausal women or men > 50 years old[28,29].

Evaluation of nutritional status and biochemical parameters

The nutritional status was evaluated by weight, height, and body mass index (BMI). In patients <20 years old, BMI ≥ percentile 50 for age and sex was considered appropriate; in patients >20 years BMI was considered appropriate when it was ≥ 22kg/m² for women and ≥23kg/m² for men[30, 31]. Calcium ingestion was estimated by food frequency questionnaire. Serum samples were stored at -80⁰C, until measurements in the same assay run. Serum C-reactive protein (CRP), calcium, phosphate, magnesium, and albumin levels were measured by routine methods. Serum 25(OH) vitamin D [25(OH)D] and parathyroid hormone (PTH) levels were measured, respectively, by chemiluminiscence method (Liaison®, Diasorin, Stillwater, MN, USA; intrassay coefficient of variation of 5.5%), and by sandwich immunoassay to Intact PTH (iPTH, Siemens, Tarrytown, NY, USA; intrassay coefficient of variation 5.2%).

Evaluation of lung function

Lung function was evaluated through spirometry (Jaeger, Version 4.34, Würzburg, BY, Germany). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁) and FEV₁/FVC were measured three times, and the best result was registered. All parameters were reported as absolute values and as percent of predicted for normal values [32]. The number of exacerbations and hospital admissions in the last year was determined. The assessment of the CF clinical severity and chest radiological severity were scored by a trained pulmonologist physician using the Shwachman-Kulczycki score (SK)[33], and the score of Brasfield[34]. Data from lung bacteria were collected.

Pharmacologic treatment

Medications in use were obtained from medical files and adherence to medications was confirmed during medical appointments.

Statistical analysis

The prevalence of bone mass below the expected range for age, and osteoporosis were calculated. Factors associated with the Z-score in the lumbar spine were evaluated by the correlation tests of Pearson or Spearman, Student t or Mann-Whitney tests, when indicated. Backwards multiple linear regression, including factors associated with lumbar Z-score with p<0.2, was performed to identify factors independently associated to it. All calculations were made in SPSS Software 16.0 (Chicago, IL, EUA).

RESULTS

Sixty-nine patients were eligible, and 58 agreed to participate and were included in the study. Their baseline characteristics are shown in Table 1.

All patients had clinical aspects compatible with CF. The diagnosis was confirmed by sweat test in 53 (91%) patients which had at least two positive test results; in five (9%) patients, the diagnosis was established by CFTR gene abnormalities. CFTR gene testing was performed in 33 (57%) patients: 8 (24%) were homozygous for ·F508 mutation, 23 (70%) were compound heterozygotes, and two (6%) had no identified abnormality.

TABLE 1 Baseline characteristics of cystic fibrosis patients (n=58)

Age (years)	23.9±7.6
Male/Female	25/33
Weight (kg)	58.7±10.5
Height (m)	1.7±0.07
BMI (kg/m²)	21.2±3.5
Estimated daily calcium ingestion (mg)	1466 (898/2360)
Serum albumin (g/dL)	4.5±0.27
Serum calcium (mg/dL)	9.4±0.27
Serum phosphate (mg/dL)	4.2 ±0.53
Serum magnesium (mg/dL)	2.1±0.13
Serum PTH (pg/mL)	33.9±18.1
Serum 25(OH)vitamin D (ng/mL)	28.5±11.0
Serum C-reactive protein (mg/L)	9.8 (<4/29.1)
FVC (L)	2.99±1.1
FVC (% predicted)	71.9±25.6
FEV1(% predicted)	60.59±28.84
FEV1/FVC	69.85±15.83
Shwachman-Kulczycki score	77.0±15.2
Brasfield score	16.9±5.1
Number of lung exacerbations in 12 months	2 (0/3)
Hospitalizations in the last month, n (%)	3 (5.2)
Hospitalizations in the last three months, n (%)	10 (17.2)
Hospitalizations in the last year, n (%)	17 (29.3)
Pancreatic exocrine insufficiency, n (%)	42 (72)
Diabetes mellitus, n (%)	8 (13.8)

Data are shown as mean±SD, or median (percentile25/75), or number (n);
BMI: Body mass index; PTH: parathyroid hormone; FVC: Forced vital capacity;
FEV1: Forced expiratory volume in 1s.

All patients with pancreatic insufficiency were treated with pancreatic enzymes and vitamins A, D, E, and K, and seven patients received calcium supplementation. Three (9.1%) women were using oral contraceptive. All women had normal menstrual periods, except one that had already undergone menopause.

Inhaled corticosteroid therapy was used by 17 patients (29.3%), and none used oral glucocorticosteroids. *S. aureus*, *P. aeruginosa* and *B. cepacia* were present in respectively, 45 (77.6%), 33 (56.9%), and 13 (22.4%) of the patients. Sixteen patients (28%) had severe lung disease with FEV1 predicted below 40%. According to the Shwachman-Kulczycki score, 37 (64%) of the patients were in good or excellent clinical condition.

BMD was assessed in the lumbar spine (L1-L4) in 58 patients; it was also measured in the proximal femur (total and neck) in 38 patients aged 20 years or more. The prevalence of bone mass below the expected range for age, Z-score <-2.0, at any site was 20.7% (9 males and 3 females); 9 patients were ≥ 20 years, so BMD was assessed in lumbar spine and proximal femur: 5 had low BMD only in L1-L4, one had low BMD only in proximal femur, and three had low BMD in both. One of the patients, a 53-year old postmenopausal woman, had osteoporosis. None of the subjects had history of fracture, and no vertebral fracture was described in the lateral chest X-ray. The mean Z-score for lumbar spine was -0.93±1.2, ranging from 1.6 to -3.2.

Serum total testosterone, bioavailable testosterone, and estradiol levels were measured in all male patients, and the means were, respectively, 4.7±2.1 ng/mL, 2.1±0.82 ng/mL, and 29±14.2 pg/mL. Serum estradiol was positively correlated with serum testosterone levels (r = 0.550, p=0.004), and bioavailable testosterone levels (r = 0.477, p=0.016).

Lumbar spine Z-score in CF patients correlated positively with BMI, and with FEV1 (% predicted), and mean lumbar spine Z-score was higher in women, in patients
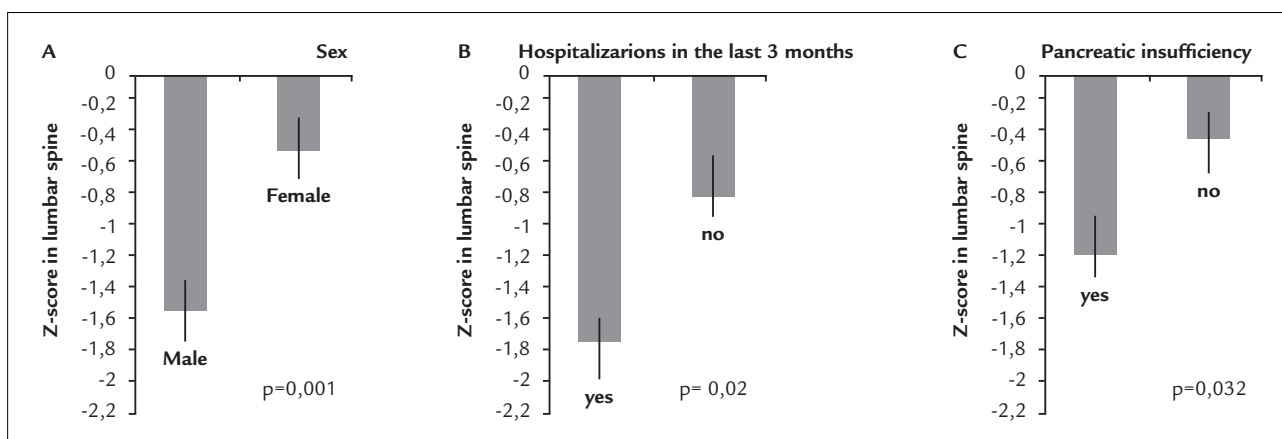

FIGURE 1 Mean lumbar spine Z-score in patients with cystic fibrosis and its association with sex (A), hospitalization in the last 3 months (B), and pancreatic insufficiency (C). Data are shown as mean ± standard error of the mean.

with no pancreatic insufficiency, and in patients with no hospitalization in the last 3 months, as shown in Figure 1.

There was a positive correlation between lumbar Z-score and BMI (r=0.420, p=0.001) and lumbar Z-score and predicted FEV1(%) (r=0.300, p=0.02). There was no correlation of lumbar Z-score and age (r=-0.199, p=0.134), predicted FEV1(%)/FVC ratio (r=0.193, p=0.147), SK score (r=0.202, p=0.129), Brasfield score (r=0.041, p=0.762), serum albumin (r=0.055, p=0.681), CRP (r=-0.165, p=0.732), calcium (r=0.046, p=0.216), phosphate (r=-0.063, p=0.638), magnesium (r=-0.036, p=0.638), PTH (r=0.005, p=0.971), and 25(OH)D (r=-0.181, p=0.173) levels, estimated calcium ingestion (r= -0.049, p=0.716), and lung exacerbations in 12 months (r=0.053, p=0.694).

Mean lumbar spine Z-score were similar in patients taking omeprazole (-1.29±1.25; n=10) or not (-0.82±1.16; n=48), p=0.255; using inhaled glucocorticosteroid (-0.74±1.14; n=17) or not (-1.01±1.21;n=41), p=0.421; with bacterial colonization for *P. aeruginosa* (-0.97±1.1, n=33) or not (-0.89±1.33; n=25), p=0.806; *B. cepacea* (-0.85±1.04, n=13)) or not (-0.96±1.24, n=45), 0.769; *S. aureus* (-0.86±1.08, n=45) or not (-1.20±1.52, n=13) p=0.344; with diabetes mellitus (-1.55±1.16, n=8) or not (-0.83±1.8, n=50), p=0.115; with hospitalization in the last year (-1.30± 1.2,n=17) or not (-0.78±1.17, n=41), p=0.126; and with hospitalization in the last month (-1.47±1.4, n= 3) or not (-0.90±1.19, n=55), p=0.430.

Multivariate stepwise backwards analysis revealed that BMI (p= 0.001), and sex (p=0.001) were independently associated with lumbar spine Z-score (Table 2).

TABLE 2 Factors independently associated with lumbar spine Z-score by multivariate stepwise backwards analysis

	B	Standard Error	Beta	p
Z-score				
Sex	0.970	0.262	0.406	0.001
BMI	0.135	0.37	0.397	0.001

Included in the model: Sex, BMI, FEV1 % predicted, number of hospitalizations in the last three months, pancreatic insufficiency and serum 25-hydroxyvitamin D levels.

DISCUSSION

In the present study, 20.7% of the adolescent and adult CF outpatients had bone mass below the expected range for age (Z-score ≤ 2.0 in lumbar spine and/or femur). In the univariate analysis, Z-score in lumbar spine was associated with sex, BMI, FEV1 (% predicted), FVC%, number of hospitalizations in the last three months, and pancreatic insufficiency. After multivariate regression analysis including all the above, except CFV%, due to its strong association with FEV1(%predicted), and serum 25(OH) levels, only sex and BMI were independently associated with Z-score in lumbar spine.

The prevalence of bone mass Z-score<-2.0 in lumbar spine was 14.6%, in the patients studied by Lucidi et al [37], and 25% in the patients studied by Dodd et al [12]; these small differences could be due to age, and clinical conditions of patients in different series. Lower prevalence of low bone mass in lumbar spine (1/17) was described by Street et al [13], but it cannot be excluded that this result was due the small size of the sample. Despite the high prevalence of low bone mass, no fractures were observed in our study. As fractures were evaluated by history and routine lateral chest radiography in our patients, the prevalence of fractures could have been underestimated.

Other studies described the prevalence of low bone mass in any site, lumbar spine, total body and femoral neck and/or total femur, despite of age below 20 years, and found higher prevalence from 23% to 68% [12, 15, 16, 18, 38-41]. Proximal femur BMD measurement is not considered appropriate for measurement of bone mass before skeletal maturity, because of higher variability and lack of reproducibility in this age group [35, 36].

Some factors have been associated with bone mass, like poor growth, delayed maturation, malnutrition, muscle deficits, decreased physical activity, chronic inflammation, and use of medications such as glucocorticoids [2].

Several studies evaluated Z-score in lumbar spine and factors possibly associated with it [5, 6, 8, 12-14, 17, 21, 23, 24, 37, 39, 41, 42], nevertheless, some did not assess confounding. Positive factors independently associated with bone mass in lumbar spine were BMI, FEV1 (% predicted), fat mass, body weight, age of puberty, body cell mass in children and adolescents, SK score and serum leptin[5, 6, 8, 14, 23, 39, 42]. Negative factors independently associated with bone mass were deltaF508, male sex, log of serum alkaline phosphatase, enteral nutrition, number of days of hospitalization in the last year, number of hospital admissions in the last year, physical activity score, oral/inhaled corticosteroids[14, 17, 23, 39]. Probably all those factors reflected disease intensity, except for male sex. Why male subjects with CF had lower bone mass is unknown.

Haworth et al also found BMD significantly lower in men, despite comparable lung function, nutritional indices, and no evidence of male hypogonadism [40]. In our male subjects, there was no association between Z-score in lumbar spine with serum total testosterone levels, nor serum bioavailable testosterone levels, so hypogonadism probably was not contributing to low bone mass. Acquired aromatase deficiency could have occurred in these male pa-

tients, as described in another infectious disease [43], but all patients had serum estradiol levels in the normal range.

Of the nutritional factors associated with bone mass, the most important are vitamin D, calcium ingestion, and BMI [4]. Although 25(OH)D was below 30ng/mL in 60.3% of the patients (data not shown), there was no independent association between lumbar spine Z-score and serum 25(OH)D levels.

Glucocorticoids can decrease bone mass, when administered by the nasal route, if the amount absorbed is enough for systemic effects [44]. In our study, there was no association of inhaled steroids use with lumbar spine Z-score, as described previously [13,37], probably due to low dose and/or low absorption in these patients. Importantly, none of our patients used oral corticosteroids.

Conclusion

Low bone mass is a frequent problem in patients with CF, being associated with BMI, and male sex.

Resumo

Prevalência de densidade mineral óssea baixa em adolescentes e adultos com fibrose cística.

Objetivo: Determinar a prevalência de massa óssea baixa em pacientes adolescentes e adultos com fibrose cística e estudar os fatores potencialmente associados.
Métodos: Densidade mineral óssea foi determinada por absorciometria por dupla emissão de raios X na coluna lombar em pacientes ≤ 19 anos e na coluna e no fêmur em pacientes ≥ 20 anos. Avaliações nutricionais, bioquímicas e pulmonares foram realizadas. Dados referentes ao tratamento farmacológico foram coletados.
Resultados: 58 pacientes foram incluídos no estudo (25 homens/33 mulheres), média de idade de 23,9 anos (16-53). Massa óssea abaixo da esperada foi verificada em 20,7% dos pacientes. Não houve histórico de fratura. Z-score da coluna lombar associou-se positivamente com índice de massa corporal (r=0,3; p=0,022), volume expiratório forçado (% previsto) (r=0,415; p=0,001). A média do Z-score da coluna foi mais alta nas mulheres que nos homens (p=0,001), em pacientes que não possuíam insuficiência pancreática (p=0,02) e em pacientes que não haviam sido hospitalizados nos últimos três meses (p=0,032). Os fatores encontrados como preditores independentes de Z-score da coluna lombar foram sexo masculino (p=0,001) e índice de massa corporal (p=0,001).
Conclusão: Massa óssea baixa é frequente em pacientes com FC, estando associada independentemente com índice de massa corporal e sexo masculino.

Unitermos: fibrose cística, densidade óssea, massa óssea, perdas ósseas, doenças ósseas.

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