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Avaliação da densidade mineral óssea em doentes com fibrose quística

Evaluation of bone mineral density in cystic fibrosis patients

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Resumo

A esperança de vida dos doentes com fibrose quística (FQ) tem vindo a aumentar, sendo mais frequente a identificação de osteoporose. A patogénese de uma baixa densidade mineral óssea (DMO) na FQ parece ser multifactorial e o objectivo deste trabalho foi avaliar a prevalência de baixa DMO num grupo de doentes com FQ e a sua correlação com outros parâmetros avaliados.

O estudo incluiu 22 doentes com FQ com idades compreendidas entre os 14 e os 45 anos (média 26,3), dois dos quais transplantados pulmonares. A DMO foi avaliada por densitometria óssea ao nível da coluna lombar e do colo do fémur. Estes dados foram correlacionados com os valores séricos de 25-hydroxivitamina D, o IMC e o volume expiratório máximo forçado no primeiro segundo (VEM).

Abstract

Patients with cystic fibrosis (CF) have an increasing life span and osteoporosis has become a more recognised problem in these patients. The pathogenesis of low bone mineral density (BMD) in CF seems to be multifactorial and the aim of this study was to assess the prevalence of low BMD in a group of CF outpatients and to relate the findings with the variables studied.

The study included 22 patients aged between 14 and 45 years (mean age 26.3). Two of the subjects were lung transplant patients. BMD was assessed by dual-energy X-ray absorptiometry (DEXA) at the lumbar spine (LS) and femoral neck (FN). This data was correlated with serum 25-hydroxy vitamin D (25-OHD) levels, BMI and the forced expiratory volume in one second (FEV₁).

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Os valores da DMO (*Z-score* e *T-score*) variaram entre 0,6 e -6 e entre 0,5 e -6,7, respectivamente, a nível da coluna lombar e entre 0,6 e -3,9 e 0,6 e -4,1 a nível do colo do fémur. A média das concentrações séricas de 25-(OH)D (12,57 ng/ml) encontrava-se no limite inferior da normalidade (10-60 ng/ml). Em média os doentes não apresentavam malnutrição mas os valores de IMC variam entre 15,2 e 33,7 kg/m². Relativamente à função pulmonar, 64% dos doentes apresentavam VEM inferior a 80% e, destes, quatro tinham valores inferiores a 40%. Foi encontrada uma correlação positiva entre valores baixos de DMO e VEM, assim como entre valores de DMO e 25-OHD. Não houve correlação linear entre IMC e DMO.

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Palavras-chave: Fibrose quística, densidade mineral óssea, vitamina D.

BMD (*Z-score* and *T-score*) ranged from 0.6 to -6 and from 0.5 to -6.7 at LS; at FN the scores ranged from 0.6 to -3.9 and from 0.6 to -4.1. The mean serum 25-OHD concentration (12,57 ng/ml) was at the low end of the normal range (10-60 ng/ml). On average patients did not present with malnutrition, however BMI ranged from 15.2 to 33.7 kg/m². Lung function status was assessed by FEV₁; 64% of patients had FEV₁ below 80% and within this group four patients had a FEV₁ under 40%.

There was a positive correlation between low BMD and 25-OHD concentrations and also between BMD and FEV₁. There was no linear correlation between BMD and BMI.

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Key-words: Cystic fibrosis, bone mineral density, vitamin D.

Introduction

Low bone mineral density was first recognised to occur in patients with Cystic Fibrosis (CF) in the late 1970s¹ and much research has been performed investigating the prevalence, natural history, prevention and treatment of CF-related low bone mineral density (BMD).

The aetiology of low BMD in CF patients is likely to be multifactorial and includes malabsorption of vitamins and minerals, hormonal deficiencies, systemic glucocorticoid use, inflammatory cytokines in moderate/severe lung disease, nutritional status, decreased physical activity and CF-related diabetes². Prevention and recognition of low BMD is important as the clinical consequence

of fragility fracture can impact adversely on the health of the individuals. Vertebral and rib fractures are particularly detrimental, as sputum clearance can be compromised, resulting in pulmonary exacerbations. Furthermore, it is becoming increasingly common for patients to be refused lung transplantation if they have low BMD.

The purpose of this study was to assess bone mineral density in a cystic fibrosis outpatient clinic population and to investigate the relationship between BMD and forced expiratory volume in one second (FEV₁), body mass index (BMI) and 25-hydroxvitamin D (25-OHD) serum levels.

Material and methods

This was a prospective study carried out over a six month period and 22 CF patients from the outpatient clinic were included. A diagnosis of CF was made by sweat test and genotyping. The two patients who had received a lung transplant were also included. All the subjects underwent Dual-Energy X-ray Absorptiometry (DEXA) studying and BMI, FEV₁ and 25-OHD measurements.

Additional data was obtained from the outpatient clinic files which are regularly updated.

BMD was measured using DEXA testing at the Nuclear Medicine Department of Coimbra University Hospital. All tests were performed with the same unit. Bone density was measured at the lumbar spine (LS) [L₁-L₄] as well as the femoral neck (FN) and was expressed as the number of grams of bone mineral per square centimetre of bone. The data were also expressed as a Z-score and a T-score. A T-score is the number of standard deviations (SDs) below the mean score for young adult control subjects, while the Z-scores reflects the number of SDs below the mean of age-matched control subjects. Osteopaenia is defined according to the World Health Organization as being present if the T-score is between -1.0 and -2.5 and osteoporosis is defined as a T-score that is < -2.5³. Due to uncertainties within the CF population, the BMD values recommended should be expressed as Z-scores in premenopausal females and males aged under 50 years, and as T-scores thereafter¹. In this study the authors have assessed BMD in terms of score values as the designation “osteoporosis” should be confined to those with a history of fragility fracture and “low

BMD” applied to children or adults with a BMD score below -2¹.

For anthropomorphic evaluation the body mass index (BMI) was used including the cut-off points for each category as stated by World Health Organization data.

Lung function was assessed by spirometry which is carried out on average every two months. FEV₁, expressed as a percentage of normal predicted values, was used considering the best value obtained during the six-month period of the study.

Blood was drawn for biochemistry measurements 25-OHD which is the most accurate measure of the amount of vitamin D in the body. This parameter is assessed routinely in annual review of each patient.

Correlation analysis was the main method of statistical analysis used. The covariance between BMD and other variables measured for the patient population was obtained using the Pearson product-moment correlation, where high correlation, according to the Cohen effect size classification (over 0.5 for a small population within a biomedical environment), was obtained for BMD variance with BMD, FEV₁ and Vitamin D. Where the coefficient was high, the Pearson asymmetry coefficient was calculated to obtain the skewness of the deviation.

Where the correlation analysis yielded a low to medium, according to Cohen coefficient, i.e. less than 0.3, Bayesian credible intervals were applied, such as when comparing Vitamin D to BMI.

Results

Of the 22 patients included in the study, 15 were female and 7 male. Mean age was 26.3 years [14-45].

Table I – Patient characteristics

Age, yrs [min-max]	[14 - 46]
Female gender, %	68% (n=15)
BMI, kg/m ² [min-max]	[15.2 - 33.7]
FEV ₁ , % [min-max]	[17.9 - 98]
25-OHD, ng/ml [min-max]	[3.5 - 27]
Pancreatic insufficiency, %	68% (n=15)
Bacterial colonisation, %	100% (n=22)
Diabetes, %	23% (n=5)
Receiving oral steroids, %	18% (n=3)
Receiving biphosphonates, %	18% (n=3)
Lung transplant pts, %	9% (n=2)

The characteristics of the subjects are shown in Table I.

BMD (Z-score and T-score) ranged from 0.6 to -6 and from 0.5 to -6,7 at LS; at FN the scores ranged from 0.6 to -3.9 and from 0.6 to -4,1. (Fig. 1 and Fig. 2)

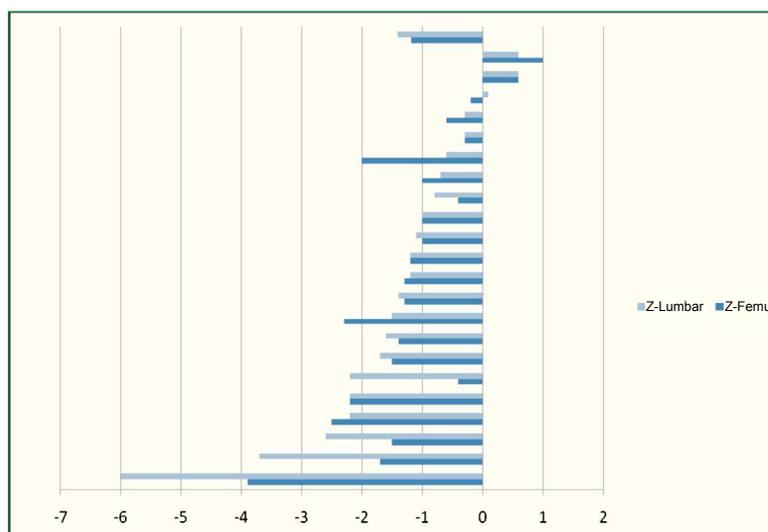
Overall 14 of 22 patients (64%) were found to have reduced BMD at any site. Nine of those subjects (64%) had a Z score between -1 and -2, while five (23%) subjects had very low Z score (<-2) as shown in Fig. 3.

The Z and T score distributions show that average values are below normal range.

As shown in Fig. 1, the Z-score distribution is on average below normal range and a minority of patients have normal BMD.

Average BMI was 21.97 kg/m² and although two patients had low body mass (below 16 kg/m²) most patients had adequate nutritional status (Fig. 4).

Lung function assessment showed that 64% of patients had FEV₁ (percent predicted) below 80% and within this group four patients had a FEV₁ under 40% (Fig. 5).



	Z-Lumbar	Z-Femur
Mean	-1.54	-1.31
Max	0.6	0.6
Mín	-6	-3.9

Fig 1 – Z score distribution



	T-Lumbar	T-Femur
Mean	-1.618	-1.39
Max	0.6	0.6
Min	-6.7	-4.1

Fig. 2 – T score distribution

The mean serum 25-OHD concentration (12.57ng/ml) was at the low end of the normal range (10 to 60 ng/ml)⁵; 4 of 22 patients (18%) had frankly low (< 10 ng/ml) levels. (Fig. 6)

The dietary recall revealed adequate intake of calcium, phosphorus and calories according to the nutritional recommendations laid out in the European Cystic fibrosis Consensus⁶. When analysed individually FEV₁ was positively associated with BMD at the LS and the FN as demonstrated by the Correlation Coefficient (64%) illustrated in Fig. 7. Likewise a positive correlation (CC 60%) was found between 25-OHD and BMD (Fig. 8). No significant correlation was found between BMI and low BMD (CC 12%) as observed in Fig. 9.

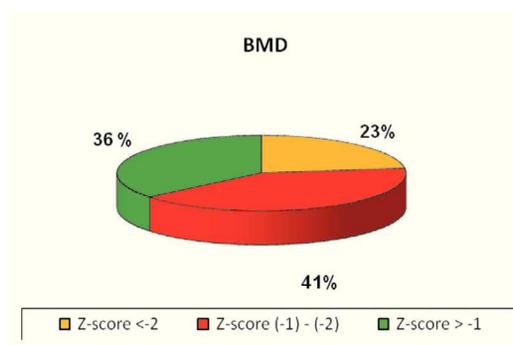
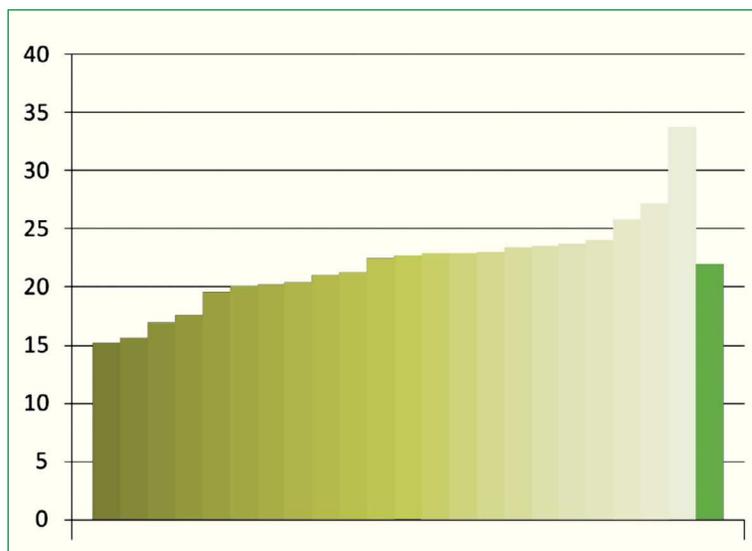
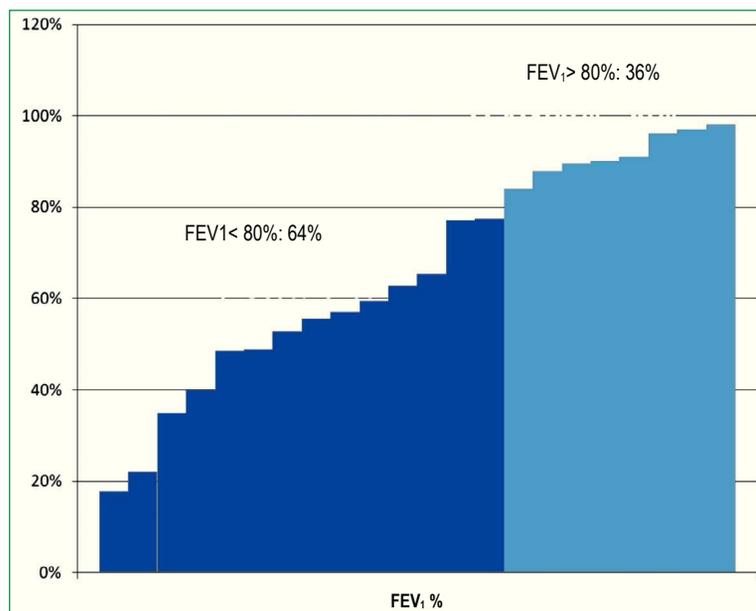


Fig. 3 – BMD assessment



Mean	21.97
Max	33.7
Min	15.2

Fig. 4 – BMI distribution



Mean	66.05 %
Max	98 %
Min	17.9%

Fig. 5 – FEV₁ distribution

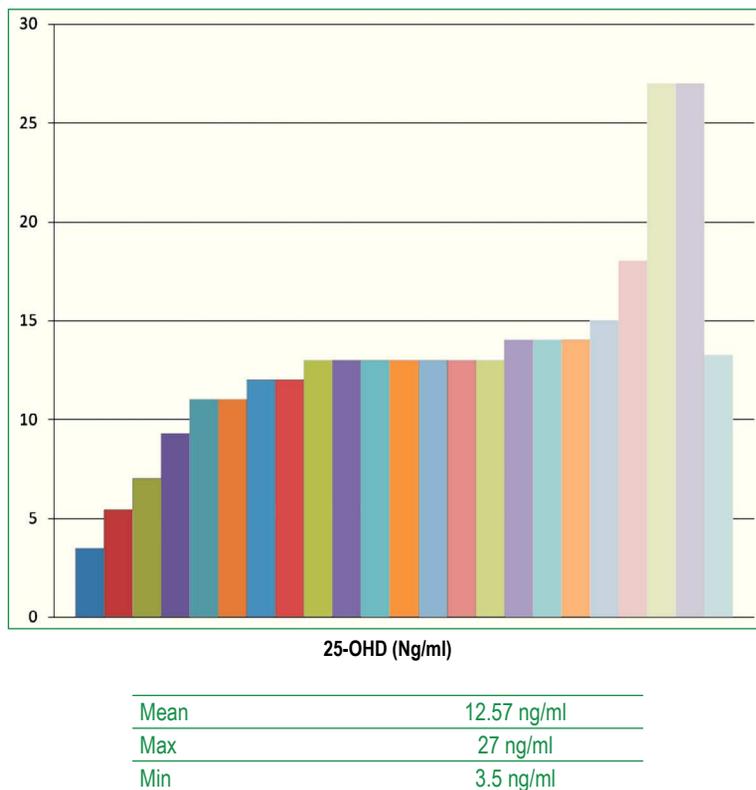


Fig. 6 – Distribution of 25–OHD measurements

Discussion

CF patients both before and after lung transplantation have a complex metabolic disease that is not typical of vitamin D deficiency: osteomalacia. Although bone density is generally reduced in CF adults and there is evidence relating this to vitamin D insufficiency, most studies suggest that CF-related bone disease has a more multifactorial aetiology with additional factors such as disease severity, general malnutrition and pancreatic disease⁷.

Several techniques are available to assess bone mass, including dual energy x-ray absorptiometry (DEXA) which is most commonly used because it is non-invasive, high-

ly reproducible and delivers an extremely low dose of radiation¹. Furthermore, DEXA testing is considered gold standard as it assesses both trabecular and cortical bone.

The overall BMI in our study population was similar to a range of 18 to 21 kg/m² seen in other studies^{5,6}.

This group of patients had an adequate nutritional status and overall no significant correlation with BMD was found. However, on an individual analysis, the patient with lower BMI (15.2 kg/m²) also had the most severe bone loss (Z-score -6 and -3.9 at the LS and FN respectively).

Pulmonary damage due to tissue inflammation post colonisation leads to increased

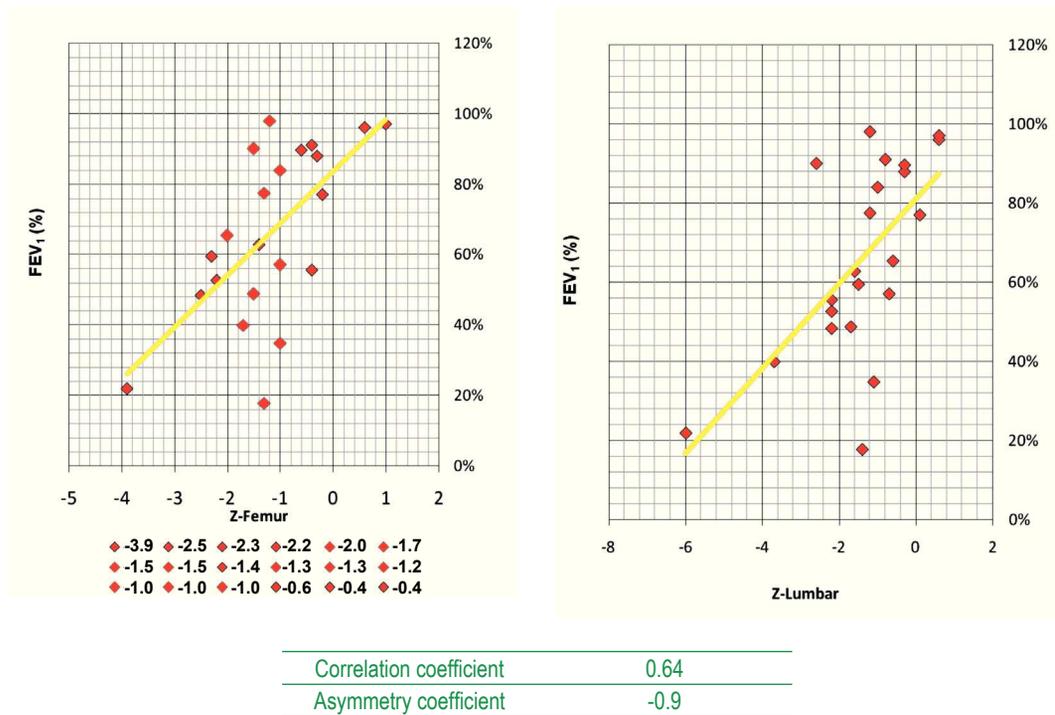


Fig. 7 – BMD / FEV₁ correlation

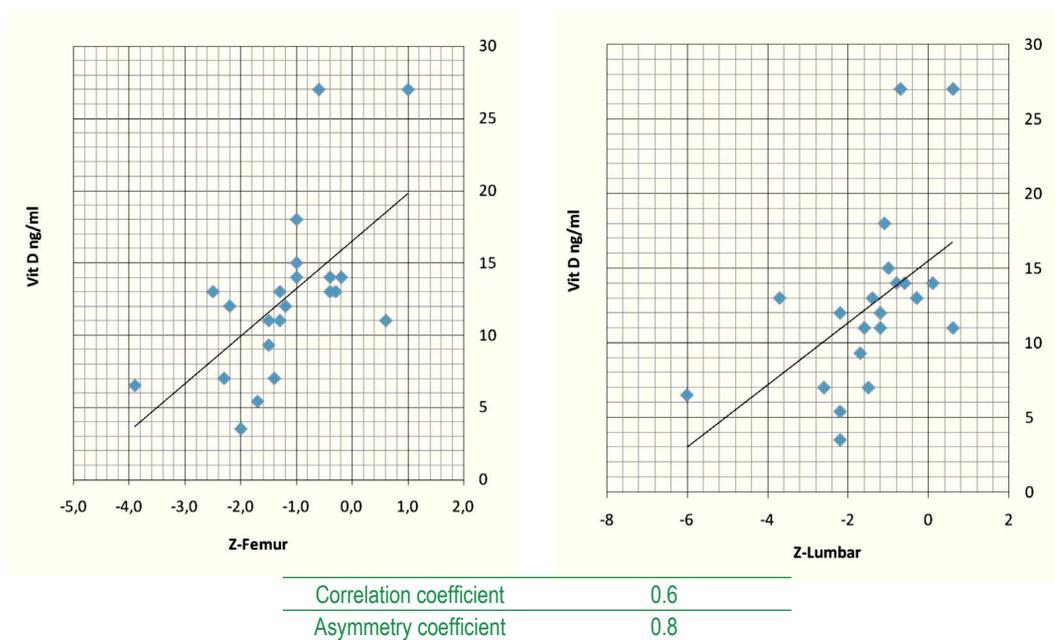


Fig. 8 – BMD / Vitamin D correlation



Fig. 9 – BMI / BMD correlation

cytokines which precedes lung function impairment. These cytokines stimulate bone resorption which may be a contributing factor in the association between disease severity and BMD. Accordingly, FEV₁ was found to be positively correlated with low bone density.

Pancreatic-insufficiency is common in CF patients and this causes malabsorption of fat soluble vitamins (D,E,A and K). Vitamin D deficiency can lead to osteomalacia and secondary hyperparathyroidism increases bone turnover which causes osteoporosis. Most authors quote optimum 25-OHD serum levels as being in the 20-60 ng/ml (50-150 nmol/ L) range^{1,4} and this wide range is due to differences in latitude and season.

The results found in this study suggest that management should be optimised assuring that patients are absorbing adequate amounts of vitamin D. Interestingly five patients with no pancreatic insufficiency had low serum 25-OHD measurements which may be an aspect meriting further investigation.

It seems there is a high prevalence of low BMD in this adolescent and adult group of CF patients and more frequently affecting the femoral neck. Lung disease and low vitamin D are factors that are positively associated with BMD. All preventive measures should be undertaken to ensure bone disease does not progress and management should be optimised whenever necessary⁹. Vitamin D levels should be checked annually and supplementation is recommended in all patients with low BMD. Alternative strategies such as UVB therapy and treatment with bisphosphonates may also be considered.

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