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ORIGINAL ARTICLE

Bone mineral density, pulmonary function, chronological age, and age at diagnosis in children and adolescents with cystic fibrosis☆

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KEYWORDS
Bone mineral density;
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Abstract

Objective: To assess bone mineral density in patients with cystic fibrosis (CF), and to correlate it with possible intervening variables.

Methods: Children and adolescents diagnosed with CF, aged 6 to 18 years, followed at the outpatient clinic were included in the study. First, demographic data were collected and, subsequently, patients underwent a spirometric test. All patients answered the Cystic Fibrosis Quality of Life Questionnaire (CFQ) and underwent the six-minute walk test (6MWT) and bone densitometry (DXA).

Results: A total of 25 CF patients were included, of which 56% were males. The mean age was 12.3±3.4 years; mean height was 149.2±14.4 cm; and mean weight was 44.4±13.9 kg. Most results on pulmonary function and bone mineral density (BMD) were within normal limits. The mean forced expiratory volume in one second (FEV_1) was 92.5±23.6 (% of predicted), mean forced vital capacity (FVC) was 104.4±21.3 (% of predicted), and mean BMD z-score was 0.1±1.0. BMD was moderately correlated with FEV_1 ($r = 0.43$, $p = 0.03$) and FVC ($r = 0.57$, $p = 0.003$). Regarding chronological age and age at diagnosis,

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a moderate and inverse correlation was also found (r = −0.55, p = 0.004 ; r = −0.57, p = 0.003, respectively). However, no significant correlations were found with the data from CFQ, 6MWT, and body mass index.
Conclusion: Most patients had BMD within normal limits and presented a positive correlation with pulmonary function, as well as a negative correlation with chronological age and age at diagnosis.

PALAVRAS-CHAVE
Densidade mineral óssea;
Fibrose cística;
Função pulmonar

Densidade mineral óssea, função pulmonar, idade cronológica e idade de diagnóstico em crianças e adolescentes com fibrose cística

Resumo
Objetivo: Avaliar a densidade mineral óssea de pacientes com fibrose cística (FC) e correlacioná-la com possíveis variáveis intervenientes.
Métodos: Foram incluídos crianças e adolescentes com diagnóstico clínico de FC, idade entre seis e dezoito anos, e em acompanhamento ambulatorial. Primeiramente, foram coletados os dados demográficos, para posterior realização do teste espirométrico. Todos os pacientes responderam ao questionário de qualidade de vida em FC (QFC) e realizaram o teste de caminhada dos seis minutos (TC6) e o exame de densitometria óssea (DXA).
Resultados: Foram incluídos 25 pacientes fibrocísticos, sendo 56% do sexo masculino. A média de idade foi de 12,3 ± 3,4 anos, altura de 149,2 ± 14,4 cm e peso de 44,4 ± 13,9 kg. A maioria dos dados de função pulmonar e de densidade mineral óssea (DMO) encontrou-se dentro dos limites de normalidade. A média do volume expiratório forçado no primeiro segundo (VEF_1) foi de 92,5 ± 23,6 (% do previsto), capacidade vital forçada (CVF) de 104,4 ± 21,3 (% do previsto) e o escore z da DMO de 0,1 ± 1,0. A DMO correlacionou-se de forma moderada com o VEF_1 (r = 0,43; p = 0,03) e com a CVF (r = 0,57; p = 0,003). Em relação à idade cronológica e à idade de diagnóstico, também foi encontrada uma correlação moderada e inversa (r = −0,55; p = 0,004 / r = −0,57; p = 0,003, respectivamente). Entretanto, não foram encontradas correlações significativas com os dados do QFC, TC6 e índice de massa corporal.
Conclusão: A maioria dos pacientes avaliados apresenta DMO dentro dos limites de normalidade e possui correlação positiva com a função pulmonar e negativa com a idade cronológica e a idade de diagnóstico.

Introduction

With improved treatment and better understanding of cystic fibrosis (CF), the life expectancy of these patients has increased.[1] However, as the age of survival increases, other complications start to become apparent such as liver disease, diabetes mellitus, and low bone mineral density.[2] Of these, the last is the most emergent problem, due to increased risk of fractures and possible impact on these patients' quality of life.[3]

Many studies have shown that there may be a decrease in bone mineral density (BMD) in children and young adults,[4-6] reporting that osteopenia can be found in 28% to 47% of this population, and osteoporosis in 20% to 34%.[7] As a whole, bone disease in CF patients probably appears or worsens around puberty and continues deteriorating during adulthood with a variety of risk factors. The use of corticosteroids, hypogonadism, decreased physical activity, decreased muscle mass, growth alterations, malnutrition, low absorption of calcium, vitamins D and K deficiency, and chronic pulmonary infection could be involved in the pathogenesis.[8,9] Moreover, puberty is a critical period for bone mineralization and requires special care so that optimum peak bone mass can be attained.[10] Thus, BMD gains are decreased even in young children with mild CF, suggesting the role of other pathophysiological mechanisms, such as the negative impact of cystic fibrosis transmembrane conductance regulator (CFTR) protein dysfunction on bone formation.[11]

BMD also appears to be associated with decreased lung function and lower exercise capacity.[12] Thus, effective strategic measures are necessary to optimize bone health, such as BMD monitoring by bone densitometry (DXA), and preventive care from infancy through adolescence.[13]

However, there is little evidence of these associations in the pediatric population, justifying studies that aim at a better understanding of the correlations between bone mass and intervening factors in children and adolescents with CF. Moreover, there is still little information on associations with quality of life indices and functional capacity in this age group, making it difficult to understand the influence of these parameters on BMD.

Therefore, considering that decrease in BMD has been reported in the pediatric population and the absence of information on the associations of BMD with possible intervening variables in this population, particularly with exercise capacity and quality of life indices, this study aimed to evaluate BMD in children and adolescents with CF, and to correlate it with possible intervening variables. A better understanding of these associations in the pediatric population may help to establish the best conduct and early therapeutic interventions in patients with CF.

Material and methods

This was a cross-sectional study, whose sample consisted of patients with clinical diagnosis of CF confirmed through the sweat test and/or genetic assessment, and followed at the CF clinic of the Hospital São Lucas of the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS). The study sample was aged between 6 and 18 years, had clinically stable disease, and had cognitive capacity to perform all procedures. Patients who failed to perform the lung function test or who were receiving systemic corticosteroids for more than 15 consecutive days were excluded. The research protocol was initiated only after approval by the Research Ethics Committee of PUCRS (CEP-PUCRS) under No. 09/04683, and an informed consent form was read and signed by patients and/or guardians.

Firstly, data were collected regarding patient identification (name, medical record number, age, gender), weight, and height. Selected patients underwent interdisciplinary clinical assessment and subsequent pulmonary function test (spirometry) as routine outpatient care. The questionnaires for quality of life questionnaires were applied during the physical therapy team assessment and, at the end of the interdisciplinary clinical assessment, patients were referred for the six-minute walk test (6MWT) and DXA examination.

Pulmonary function test

Assessment of pulmonary function was performed by spirometry using a KOKO spirometer (Louisville, CO, USA). The evaluated spirometric parameters included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), Tiffeneau index (FEV_1/FVC), and forced expiratory flow 25% and 75% of FVC ($FEF_{25\%-75\%}$). Calibration was performed before each test session according to the manufacturer's instructions. In order to perform the spirometric test, patients should not have had exacerbation of respiratory symptoms, nor have used short-acting bronchodilator 4 hours before the test or long-acting bronchodilator 12 hours before the test. A resting period of 5 to 10 minutes was required before each test.

After instructions and previous training, the children were instructed to start the exam. The spirometric test was described in detail to each patient, with emphasis on maximum inspiration followed by a maximal fast expiration, following the criteria established by the American Thoracic Society (ATS).[14] All spirometric tests were performed individually, in the standing position, with the use of a nose clip. For best presentation of results, spirometric values were expressed in absolute values and percentages of the predicted values.[15]

Bone densitometry

DXA for the assessment of bone mineral content was performed by dual-energy X-ray absorptiometry of the lumbar column segment (L1 to L4) in a Hologic Discovery Wi DXA scanner. Bone mineral content (g) (BMC) and bone mineral density (g/cm^2) were evaluated. To undergo DXA, the participants were advised to wear light clothing to prevent absorption by any material that could create an artifact. Thus, for acquisition of lumbar spine images, the patient was placed in the supine position on the examination table with legs supported by a cushion, forming an angle of 90° at the coxofemoral joints and 90° at the knees, and asked to remain still, without the need for sedation. The examination lasted approximately 2 minutes. The diagnosis of BMD was attained through standardized results using the z-score and the classification according to the International Society for Clinical Densitometry, in which low BMD occurs when z-score is #< −2, adjusted for age, gender, and height.[16]

Six-minute walking test

The 6MWT was performed according to the guidelines of the American Thoracic Society (ATS).[17] As in the lung function tests, patients remained at rest for at least 30 minutes before starting the test. The parameters evaluated pre-and post-test included heart rate (HR) and oxygen saturation (SpO_2) using a pulse oximeter (PalmSAT 2500, Nonin Medical – Plymouth, Minnesota, USA), blood pressure (CE0050, Tycos/Welch Allyn – Skaneateles Falls, New York, USA), respiratory rate (RR) (counted as chest wall excursions per minute), and score in the modified Borg scale to measure the perceived intensity of dyspnea.

Patients were instructed to walk as fast as possible without running, being allowed to slow down, stop, or rest, if necessary. Thus, they were instructed to walk as far as possible for six minutes in a 30-meter long enclosed corridor with a flat and hard surface, marked at every meter. The child received the stimuli recommended by ATS at every minute. At the end of the six minutes, the

Table 1 Characteristics of the study sample.

Assessed variables	
Age (years)	12.3±3.4
Gender	
Male	56%
Anthropometric data	
Weight (kg)	44.4±13.9
Height (cm)	149.2±14.4
BMI (absolute)	19.5±3.3
BMI (percentage)	56.7±29.4
Pulmonary function (% of predicted)	
FEV_1	92.5±23.6
FVC	104.4±21.3
$FEF_{25\%-75\%}$	79.8±33.2
Bone mineral densitometry (lumbar column)	
BMC (g)	33.7±13.6
BMD (g/cm²)	0.7±0.1
z-score	0.1±1.0

BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of forced vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.
Results shown as mean and standard deviation.

child was requested to stop at that exact place, so that the researcher could collect the data. The criteria for test discontinuation were manifestations of fatigue and intense dyspnea by the participant, SpO2 < 80%, or refusal to continue the test. Distance was calculated by counting the total number of laps performed at the end of the test and expressed in meters. The normalization of the walked distance was performed using reference equations and expressed by z-score.[18,19]

Cystic Fibrosis Quality of Life Questionnaire

The quality of life assessment was performed using the Cystic Fibrosis Quality of Life Questionnaire (CFQ), translated and validated to be used in Portuguese.[20] The CFQ contains 35 questions for the age groups of 6 to 13 years, 50 questions for ages older than 14, and 44 questions for the parents. This instrument covers nine domains of quality of life, three symptom scales, and one item related to health perception: physical, body image, emotional, social/school, social role, vitality, nutrition, treatments, digestive, respiratory, weight, and health factors. The answers to each question are quantified and can reach a maximum of 100 points; the higher the final score, the better the quality of life.

Statistical analysis

Data normality was assessed using the Shapiro-Wilk's test. For all variables with normal distribution, data were shown as mean and standard deviation. For the CFQ results, which showed some domains with asymmetric distribution, data were expressed as median and range. Data on BMD and on 6MWT were expressed as z-scores, and spirometry results were shown as percentage of predicted value. Pearson's correlation test or Spearman's test were used to assess possible correlations of intervening variables with BMD, according to their distribution. All data processing and analyses were performed using the Statistical Package for Social Sciences (SPSS) version 18.0 (SPSS Inc. – USA). In all cases, differences were considered significant when $p < 0.05$.

Results

A total of 25 patients with CF were included, with a mean age of 12.3±3.4 years, of which 56% were males. The sample characterization with anthropometric data, pulmonary function, and BMD are shown in Table 1. Most patients (84%) had pancreatic failure and needed enzyme replacement therapy. Regarding the classification of BMD z-score in this sample, no participant showed z-score below the normal range (-2), 11 (44%) had values between −1 and zero, two (8%) presented values between -1 and -2, and 12 (48%) had values above normal (higher than zero). As for the CFQ evaluation, scores above 70 were obtained for all assessed domains, except for the weight and vitality domains, which presented scores of 61.1 and 66.7, respectively. The data are shown in Table 2 and, in general, indicate that the assessed children were within the normal range.

When correlating FEV_1 data and z-score values obtained in the DXA test, a moderate correlation coefficient was observed ($r = 0.43$, $p = 0.03$). When FVC data were analyzed with the BMD z-score values, a significant result was obtained ($p = 0.003$) with a correlation coefficient of 0.57, demonstrating that the better lung function, the better the bone density (Fig. 1). When analyzing the results of age at diagnosis with BMD z-score, significant correlation was found, with an inverse and moderate correlation coefficient ($r = -0.57$, $p = 0.003$), showing that the older the age at diagnosis of CF, the lower the BMD values. Likewise, age showed a significant inverse and moderate correlation ($r = -0.55$, $p = 0.004$), indicating that as the age increases, bone density decreases (Fig. 2).

Conversely, data obtained through the CFQ in its specific domains showed no significant correlations with the z-score values of BMD in either case. Moreover, there was no significant correlation between BMD and distance walk in the 6MWT, nor with the calculated BMI values.

Discussion

The results of the present study showed that most assessed patients had BMD values within the normal range; only two patients (z-score between −1 and −2) would have treatment indication according to the management recommendations for CF patients.[21] In addition, they presented a positive correlation with lung function and an inverse correlation with chronological age and age at diagnosis. The findings of normal BMD in this study may be attributed to the fact that patients showed

Table 2 Quality of life assessment through the Cystic Fibrosis Quality of Life Questionnaire and correlation with bone mineral density.

Assessed domains	Mean±SD	Median (range)	Correlation with BMD (r)	p-value
CFQ physical	77.8±13.9	77.8 (14.0-100.0)	−0.26	0.19
CFQ food	84.9±18.1	88.9 (18.1-100.0)	−0.22*	0.28
CFQ treatment	81.8±19.5	88.9 (19.0-100.0)	0.08*	0.67
CFQ respiratory	75.6±18.6	75.6 (19.0-100.0)	0.12	0.54
CFQ role	90.3±12.3	91.7 (12.3-100.0)	0.66	0.15
CFQ vitality	66.7±22.4	62.5 (22.4-100.0)	0.43	0.39
CFQ emotional	80.3±13.6	86.7 (13.6-100.0)	0.91	0.67
CFQ social	72.0±15.6	71.4 (16.0-95.0)	−0.19	0.35
CFQ body	85.8±17.1	88.9 (17.1-100.0)	0.22	0.28
CFQ health	73.2±26.2	77.8 (22.2-100.0)	−0.54	0.20
CFQ weight	61.1±32.8	66.7 (0.00-100.0)	0.39	0.43
CFQ digestion	86.7±16.0	100.0 (16.0-100.0)	−0.20*	0.92

BMD, bone mineral density; CFQ, Cystic Fibrosis Quality of Life Questionnaire; SD, standard deviation.
*Spearman correlation. Pearson's correlation was used in the domains that are not indicated.

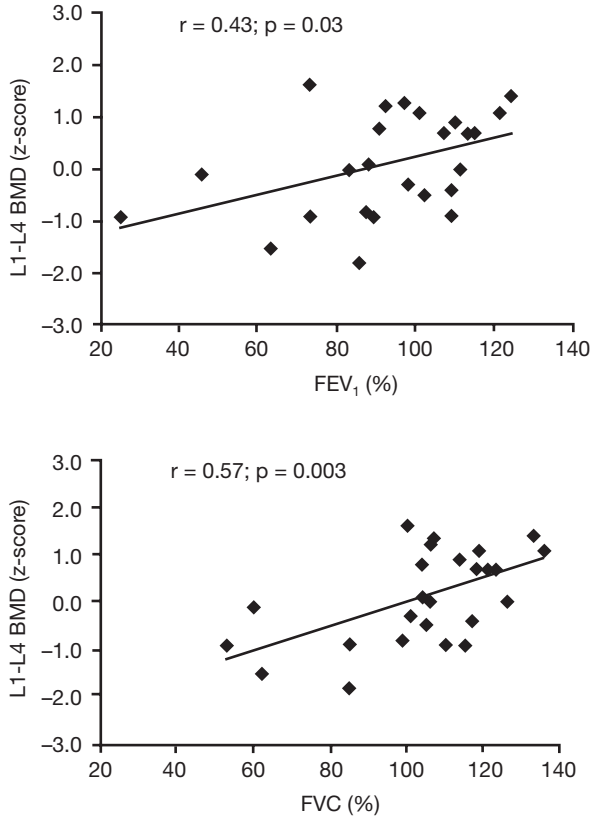

Figure 1 Correlation between bone mineral density (BMD) z-score and pulmonary function: FEV1 (forced expiratory volume in one second) in the upper chart and FVC (forced vital capacity) in the lower chart.

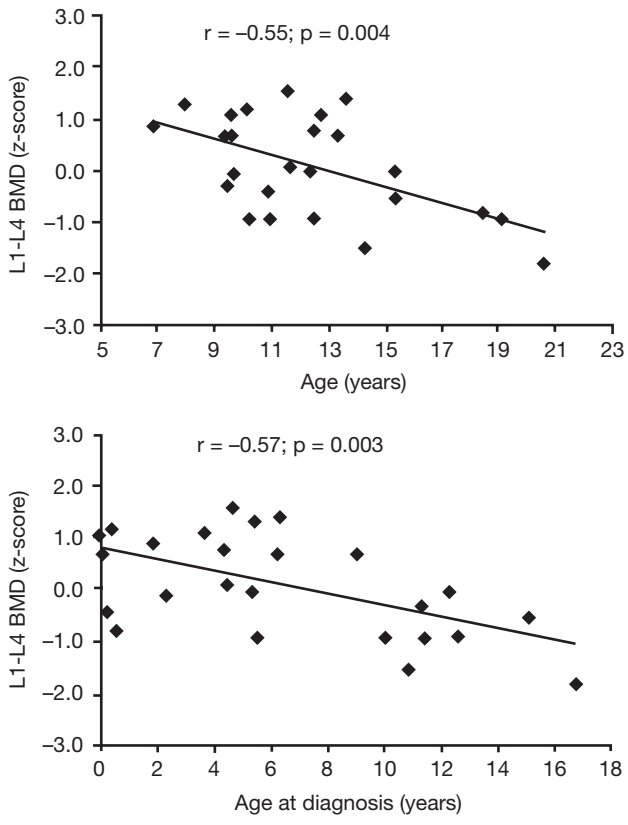

Figure 2 Correlation between bone mineral density (BMD) z-score and chronological age (years) of patients evaluated in the upper chart and the age at diagnosis (years) in the lower chart.

young mean age and also mild pulmonary impairment.[22,23] Previous studies also reported normal BMD values, and attributed these findings mainly to the preservation of nutritional status and low pulmonary impairment. However, several studies[6,9,24] reported BMD deficiency in children and linked this decrease to nutritional impairment, number of hospitalizations, worse lung function, gonadal dysfunction, and treatment with steroids.

These conflicting results appear to be related, at least in part, to differences in the characteristics of the studied patients and other intrinsic factors, such as those mentioned above. Moreover, differently from what occurs in the pediatric population, evidence of decreased bone mass in adults appears to be more present and to have been increasing, due to increased patient survival.[4,12]

As expected, the results of lung function demonstrated a positive correlation between FVC and FEV_1, with z-score values obtained from DXA examination, indicating that the worse the lung function, the lower the BMD indices. These results are in agreement with several authors who demonstrated FEV_1 as a robust marker of lung disease severity, establishing a direct association with bone mass at all ages.[12,13] Previous studies have demonstrated that impaired lung function is associated with increased presence of inflammatory mediators, leading to an impact of cytokines and interleukins on the mineralization of bone content, as there is increased bone resorption in periods of pulmonary exacerbation.[7,25]

Unlike healthy children and adolescents, who present an increase in bone mass with increasing age, patients with CF may have a reduction in BMD.[13] The results of the present study are consistent with these findings, showing that chronological age has an inverse correlation with bone density, indicating that as age increases, bone density decreases, emphasizing the importance of following these patients as they enter adolescence and adulthood. Studies in healthy populations have shown that healthy children have a constant gain in bone mass, extending from birth until they reach a peak in late adolescence or early adulthood. Thus, the higher the bone mass gained during childhood and adolescence, the lower the likelihood of fractures.[26,27]

However, delayed puberty in CF patients may play an important role in peak bone mass, leading to reduced bone mineral content and to an increased risk of fractures in these patients.[28] In this regard, some studies have shown that CFTR can directly modulate the reproductive endocrine axis, causing some puberty delays to be a direct consequence of the alteration in this protein function, as there can be alterations in the hypothalamic-pituitary-gonadal axis.[13]

Furthermore, the present study also showed an inverse correlation with age at diagnosis, showing that the older the age at which the diagnosis is made, the lower the bone density values, which demonstrates the importance of neonatal screening and of early diagnosis that would enable the rapid inclusion of these patients in referral centers for disease treatment and monitoring.

To the authors' knowledge, this is the first study in the pediatric population that evaluated the association between BMD and specific domains of the CFQ questionnaire. However, there were no significant correlations with any of the specific domains of the questionnaire. The results indicate a healthy perception by patients in most domains assessed. Quittner et al.,[29] in their CFQ validation study, showed that the scores obtained in the different domains were positively correlated with lung function, indicating that the healthiest children had the highest scores in the CFQ.

The slightly altered pulmonary function and BMD within the normal range observed in the present patients could be related to this absence of correlation. Moreover, there was no specific correlation with the physical activity domain of the questionnaire, or with the distance walked in the 6MWT. There are no studies in the pediatric population that have correlated BMD with exercise capacity, both through the 6MWT or VO_2max. Conversely, studies[12,30] conducted in the adult population showed a positive correlation with exercise capacity through submaximal and maximal tests, indicating that as the exercise capacity increases, the greater are the values of BMD.

The assessment of physical fitness through maximum tests could better reflect the aerobic fitness of a group of patients that show little involvement in comparison to submaximal tests, and could justify, in part, the lack of correlation with BMD in the assessed children and adolescents, constituting a limitation of this study. Furthermore, the evaluation of a sample with only 25 patients, most with low pulmonary involvement and good nutritional status, can also be additional limiting factors. Future studies evaluating children with more compromised lung function and worse nutritional status could contribute to a greater knowledge on the subject.

In conclusion, the results of the present study demonstrate that most patients have BMD within normal limits and that there is a positive correlation with lung function, and an inverse correlation with chronological age and age at diagnosis. A better understanding of the associations and of the evolution of bone health is of clinical and scientific relevance for the treatment and monitoring of children and adolescents with cystic fibrosis.

Conflict of interest

The authors have no conflicts of interest to declare.

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