Comparative bone status assessment by dual energy X-ray absorptiometry, peripheral quantitative computed tomography and quantitative ultrasound in adolescents and young adults with cystic fibrosis

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Received 16 June 2011; received in revised form 12 September 2011; accepted 21 October 2011
Available online 26 November 2011

Abstract

Purpose: Quantitative ultrasound bone sonometry (QUS) might be a promising screening method for cystic fibrosis (CF)-related bone disease, given its absence of radiation exposure, portability of the equipment and low cost. The value of axial transmission forearm QUS in detecting osteopenia in CF was therefore studied.

Methods: We investigated the application of QUS in the evaluation of bone status in a group of 64 adolescents (>12 years) and young adults (<40 years) with CF in a comparison with a dual X-ray absorptiometry (DXA) of the whole body and peripheral quantitative computed tomography (pQCT) at 4% and 66% sites.

Results: Mean (SD) Z-scores of speed of sound (SOS), whole body bone mineral content (BMC), radial trabecular bone mineral density (BMD), and radial cortical BMD were respectively −0.31 (0.78), −0.09 (1.28), 0.10 (1.16) and −0.62 (2.88). The pQCT determined bone geometry values (cortical bone area and cortical thickness) were more depressed than the BMD data. QUS had a sensitivity and specificity of respectively 0% and 96% for diagnosing osteopenia (based on a whole body BMC Z-score <−2).

Conclusions: QUS cannot replace DXA, but can screen out patients with normal bone mass. Further and larger studies are needed to examine if QUS may reflect other aspects than bone mass, or if it is possible to improve its sensitivity by supplementing the SOS results with clinical risk factors.

Keywords: Cystic fibrosis; Bone mass; Bone densitometry; Osteoporosis; Quantitative ultrasound bone sonometry

1. Introduction

In adolescents and adults with cystic fibrosis (CF) the high incidence of osteopenic bone disease, called CF-related bone disease, requires monitoring of the skeletal status. [1,2]. The recommendation for regular DXA examinations in CF patients can be questioned since no correlation between DXA and vertebral and/or rib fractures has been observed in cross-sectional studies [3,4]. Furthermore, the interpretation of DXA results, especially in adolescents, is complicated by a frequent delay in pubertal growth and development and the lack of adjusted volumetric bone mineral density (BMD) results by most commercial densitometers.
Although still not a widespread available technique, peripheral quantitative computed tomography (pQCT) not only offers the advantage of measurements of dyspneic patients in a sitting position, but also provides results on bone geometry and gives real volumetric BMD results of separate cortical and trabecular bone measurements at the radius or tibia. Longitudinal DXA and pQCT data are scarce in this population and the policy of regular bone status monitoring with these techniques will result in unwanted additive radiation doses in CF patients, although the effective doses of these bone examinations are among the lowest of doses resulting from commonly used medical X-ray examinations and lower than a standard chest X-ray [5]. An alternative might be the use of quantitative ultrasound bone somometry (QUS), which gives more assessment of the bone quality than bone quantity [6]. The axial transmission ultrasound technique allows the measurement of the sound progression, labeled as the speed of sound (SOS), at several peripheral bone sites. QUS has particular advantages for monitoring of CF related bone disease, since it is a non radiating and easy to use technique, allowing bed-side monitoring without positioning problems, especially when the axial transmission mode is used. We therefore investigated the application of forearm axial transmission QUS in the evaluation of bone status in a group of adolescents and young adults with CF.

2. Methods

All adolescent (>12 years of age) and young adult (<40 years of age) CF patients who attended the Cystic Fibrosis Clinics of the Brussels University hospital (Universitair Ziekenhuis Brussel, Brussels, Belgium) and of the Ghent University hospital (Universitair Ziekenhuis Gent, Ghent, Belgium) were considered for this study, after informed consent. Exclusion criteria were the use of any bone active medication, with the exception of corticoids or routine vitamin D supplementation, being on a waiting list for lung transplantation or already having received a lung transplant. Of the 68 CF eligible individuals, 58 attending the Universitair Ziekenhuis Brussel for their annual screening for complications between mid 2006 and mid 2007, agreed to participate. At the Universitair Ziekenhuis Gent, recruitment was only done during the last 5 months of the study inclusion period due to logistic problems. In total 21 of the 35 eligible patients, who had been programmed for their annual check-up, only 16 patients had complete bone data available for analysis. The Institutional Ethical Review Boards at both University hospitals approved the study.

In both hospitals bone assessment was performed with the same devices. All DXA scans were performed with a Hologic QDR 4500A densitometer (Hologic Inc., Bedford, MA, USA). Whole body measurements were performed in a standardized way and analyzed using the same software (version V8.24a:3). DXA measurement of the whole body was chosen since it allows the determination of the body composition, which is of major importance in the nutritional monitoring of CF patients. Bone mass (BMC) measurements are given as g (hydroxyapatite) and Z-scores using the normative data of Sala et al. [7]. BMD measurements are reported in g/cm² and Z-scores, as delivered by the apparatus. The coefficient of variation (CV) % is <3% for BMC data and <1% for BMD data. QUS measurements were done with an Omnisense 7000P apparatus (Sunlight Ltd, Tel Aviv, Israel) at the distal left radius as described by the manufacturer. SOS measurements were reported in m/s and Z scores (age and gender adjusted standard deviation scores), as delivered by the incorporated software. The CV % with repositioning is <2% for the SOS result. A 2000 Stratec pQCT device (Stratec Medizintechnik, Pforzheim, Germany) was used to perform measurements at the left radius at the distal (4% of fore-arm length) and the proximal (66%) site. Total BMD at the proximal site and trabecular BMD at the distal site were analyzed using the same software version (version 6.00). In addition, at the proximal site total bone cross-sectional bone area and cortical cross-sectional bone area and cortical wall thickness were assessed at the proximal site. Z-scores of the bone mineral density data assessed at the distal site, as calculated by the software of the pQCT device, were used. The Z-scores of the variables measured at the proximal site were calculated with the regression equations developed by Neu et al. [8]. The CV % is 3% for bone geometry data and <2% for BMD data.

At moment of bone analysis, standard anthropometry and spirometry, as well as a liver ultrasound scan were performed. The ultrasound scoring system of Williams et al. was used to allocate patients to a no liver disease group (score <4), a moderate liver disease (score 4–8) and severe liver disease (with portal hypertension) (score >8) [9]. In all but one patient vertebral bone deformities were analyzed at an X-ray of the chest obtained within 6 months of the bone analysis by the semi-quantitative method described by Genant et al. [10].

Statistical analysis was performed using the SPSS (SPSS, Chicago, IL) software program. The results for continuous data are given as mean ± SD and for non-continuous variables are represented as a frequency and a percentage. Comparisons were made by T-tests or ANOVA. Univariate and multivariate statistical tests were applied to explore for associations between the bone measurements.

3. Results

3.1. Clinical data

Table 1 represents the clinical data of the studied population at study enrollment. The study group included 35 males and 29 females with a median (range) age of 20 (12–38) years. Twenty seven patients were younger than 18 years. As shown in Table 1, females had a significantly lower mean relative body height, body mass index (BMI) and Forced Expiratory Volume in the first second (FEV1) values. In total 13 (20%) patients were suffering from severe respiratory insufficiency (FEV1 <50%) and 4 (6%) were undernourished (BMI Z-score <−2). Fourteen (21%) patients were treated for CF-associated diabetes mellitus. The majority of patients (41 in total or 64%) had a normal liver ultrasound scan, while severe liver disease was documented in 9 (14%) subjects. Oral corticoids had been taken for at least during 3 months in the preceding year by 6 patients. None of the adult
women or men had been treated with sex steroids for delayed puberty. Vertebral deformities were observed in 36 (21 males and 15 females) of the 68 studied patients.

3.2. Comparison of the bone data

The results of bone analysis (as a group and by gender) are shown in Table 2. No gender difference in radial SOS Z-scores was present. Females had significantly higher age-adjusted whole body BMC values by DXA than males, but lower radial distal trabecular BMD values and radial proximal bone areas (assessed by pQCT). Of all studied bone parameters, the lowest Z-scores were obtained in females for the cortical thickness results, while in males the lowest bone values were observed for the radial total BMD determinations (Fig. 2). No significant difference in the DXA, pQCT and QUS results was found between patients with or without vertebral fractures (data not shown).

Overall, as a group, CF patients had significantly (p<0.005) decreased SOS Z-scores. A radial SOS Z-score below -2 was found in only 2 patients (Fig. 1). DXA detected respectively 6 and 1 patient with a whole body BMC and BMD Z-score below -2. Abnormal low (Z-score below -2) radial trabecular and cortical BMD results were seen respectively in 2 and 12 subjects, but severely decreased (Z score below -2) cross-sectional total bone area and cortical thickness values were observed in respectively 27 and 14 patients. Using the whole body BMC Z-score below -2 to diagnose low bone mass or osteoporosis and calculating with a cut-off Z-score of SOS of<−2, a sensitivity of 0% and a specificity of 96% were found. Positive and negative predictive values of QUS were respectively 0% and 90% in detecting osteoporosis.

3.3. Parameters influencing bone data

No significant correlation coefficients between the SOS Z-scores and the Z-scores of all the studied bone parameters were found. Absolute SOS results correlated significantly (p<0.05) with radial cortical BMD as assessed by pQCT, both in females (r=0.58) and males (p=0.36) as well as with whole body BMC in females (r=0.44) and males (r=0.39), but after correction for age, the significance of the observed correlations disappeared.

Using linear regression analysis, SOS Z-scores were found to be independent of age and age-adjusted anthropometric data. BMI Z-score correlated positively with cortical area Z-score (r=0.37; p<0.05) and whole body BMD Z-score (r=0.32; p<0.05) in males, but no significant correlation was found in the females. On the other hand only in the female group, age correlated significantly negatively and FEV1 correlated positively (r=0.47; p<0.05) with cortical bone thickness Z-scores (r=−0.55; p<0.005) and FEV1 related significantly negatively and FEV1 correlated positively (r=−0.55; p<0.005) with cortical bone thickness Z-scores (r=−0.55; p<0.005). Patients who had received oral corticoids during the past year had also similar age and gender adjusted bone parameters compared to those without corticoid therapy. The

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Table 1
Mean (SD) clinical characteristics in female and male CF patients.

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Females (n=25)</th>
<th>Males (n=39)</th>
<th>All (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.8 (6.4)</td>
<td>20.5 (5.7)</td>
<td>20.6 (5.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.7 (6.6)</td>
<td>171.2 (9.8)**</td>
<td>168.0 (9.8)</td>
</tr>
<tr>
<td>Height (sds)</td>
<td>−0.58 (1.08)</td>
<td>1.09 (1.27)**</td>
<td>0.44 (1.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.8 (2.5)</td>
<td>20.0 (2.2)</td>
<td>19.9 (2.3)</td>
</tr>
<tr>
<td>BMI (sds)</td>
<td>−0.47 (0.88)</td>
<td>−0.37 (0.89)*</td>
<td>−0.41 (0.89)</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>9/16</td>
<td>5/34</td>
<td>14/50</td>
</tr>
<tr>
<td>Liver disease</td>
<td>15/64</td>
<td>26/85</td>
<td>41/149</td>
</tr>
</tbody>
</table>

Table 2
Mean (SD) bone measurements results in female and male CF patients.

<table>
<thead>
<tr>
<th>Bone measurements</th>
<th>Females (n=25)</th>
<th>Males (n=39)</th>
<th>All (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOS (m/s)</td>
<td>4003 (139)</td>
<td>3935 (126)</td>
<td>3961 (134)</td>
</tr>
<tr>
<td>SOS (sds)</td>
<td>−0.47 (0.88)</td>
<td>−0.37 (0.89)</td>
<td>−0.31 (0.78)</td>
</tr>
<tr>
<td>Whole body BMC (g)</td>
<td>1885 (267)</td>
<td>2353 (484)**</td>
<td>2170 (471)</td>
</tr>
<tr>
<td>Whole body BMC (sds)</td>
<td>0.80 (0.77)</td>
<td>−0.66 (1.2)*</td>
<td>−0.09 (1.28)</td>
</tr>
<tr>
<td>Whole body BMD (g/cm²)</td>
<td>1.08 (0.08)</td>
<td>1.19 (0.13)**</td>
<td>1.14 (0.13)</td>
</tr>
<tr>
<td>Whole body BMC (sds)</td>
<td>0.14 (0.93)</td>
<td>0.65 (1.17)</td>
<td>0.47 (1.32)</td>
</tr>
<tr>
<td>Distal radial trabecular BMD (g/cm²)</td>
<td>174 (41)</td>
<td>236 (36)**</td>
<td>212 (49)</td>
</tr>
<tr>
<td>Distal radial trabecular BMD (sds)</td>
<td>−0.44 (1.26)</td>
<td>0.44 (0.96)*</td>
<td>0.10 (1.16)</td>
</tr>
<tr>
<td>Proximal radial total BMD (g/cm²)</td>
<td>675 (105)</td>
<td>705 (128)</td>
<td>693 (120)</td>
</tr>
<tr>
<td>Proximal radial total BMD (sds)</td>
<td>0.69 (1.21)</td>
<td>0.31 (1.39)</td>
<td>0.46 (1.33)</td>
</tr>
<tr>
<td>Proximal radial cortical BMD (g/cm²)</td>
<td>1063 (120)</td>
<td>1034 (124)</td>
<td>1045 (122)</td>
</tr>
<tr>
<td>Proximal radial cortical BMD (sds)</td>
<td>−0.22 (2.72)</td>
<td>−0.88 (2.92)</td>
<td>−0.62 (2.88)</td>
</tr>
<tr>
<td>Proximal radial total area (mm²)</td>
<td>125 (23)</td>
<td>150 (26)*</td>
<td>140 (34)</td>
</tr>
<tr>
<td>Proximal radial total area (sds)</td>
<td>−0.39 (1.91)</td>
<td>−2.65 (1.88)**</td>
<td>−1.77 (2.18)</td>
</tr>
<tr>
<td>Proximal radial cortical area (mm²)</td>
<td>61 (8)</td>
<td>80 (17)**</td>
<td>72 (17)</td>
</tr>
<tr>
<td>Proximal radial cortical area (sds)</td>
<td>−1.18 (0.88)</td>
<td>0.87 (1.58)**</td>
<td>0.06 (1.68)</td>
</tr>
<tr>
<td>Proximal radial cortical thickness (cm)</td>
<td>1.82 (0.26)</td>
<td>1.82 (0.14)**</td>
<td>1.9 (0.26)</td>
</tr>
<tr>
<td>Proximal radial cortical thickness (sds)</td>
<td>−1.87 (0.66)</td>
<td>−1.1 (0.76)**</td>
<td>−1.4 (0.81)</td>
</tr>
</tbody>
</table>

*p<0.005 between females and males; **p<0.0001 between females and males.
presence of liver disease had no influence on the bone measurements (ANOVA analysis). Diabetic patients (n=14) had significantly (p<0.05) lower Z-scores for proximal radial cortical area (p<0.05), cortical thickness (p<0.005), distal trabecular and total BMD (p<0.05) measurements in comparison with non-diabetic patients.

Fig. 1. Scattergraph of SOS Z-score in relation to whole body BMC Z-score in CF males and females.

Fig. 2. Box plot of Z-scores of the different bone parameters in CF males and females.
4. Discussion

The major aim of this study was to evaluate if QUS could be used as a selective population pre-screen method, in order to maximize the cost effectiveness of referral for DXA examinations and to limit at the same time the radiation dose to CF patients. The observed relatively high negative predictive values in our study suggest that QUS may reliably screen out patients unlikely to have a decreased bone mass by DXA. The absent positive predictive power, however, means that subjects classified as having a low QUS result should have further investigations to confirm the diagnosis of low bone mass. Since QUS and densitometric methodologies do not measure identical properties of bone tissue, it could be expected that these techniques would not capture the same patients. In 2001, for the first time bone quality was investigated by quantitative ultrasound (QUS) at the calcaneus in a cross-sectional sample of 29 CF children between 5 and 16 years of age. In this study QUS results were not different form an age and height matched healthy control group. Although whole body BMC and BMD was measured by DXA, no predictive values were calculated [11]. In a subsequent larger study of 75 adult patients with CF, QUS at the calcaneus had a sensitivity and a specificity of only 57% and 89% respectively for diagnosing osteoporosis, which was based in this study on a femoral neck T score $\leq -2.5$ by DEXA [12]. In our study, whole body bone mass was studied and in accordance with the most recent recommendations, Z-scores were used to define the degree of demineralization, since adolescents and young (<40 years) CF adults were studied and the majority of patients have not yet reached their peak bone mass [1,13]. Our finding of a low to absent sensitivity of QUS does not mean that sonometry has no place at all in evaluating the bone status in CF. Only prospective comparison of these three techniques to predict fractures on the long-term may clarify the future clinical utility of any of these methods in CF patients [14,15]. Up to now, only one study has evaluated both QUS and DXA in vertebral bone fracture prediction in CF patients: phalangeal QUS as opposed to calcaneal QUS and DXA was found to discriminate between adult patients with and without vertebral fractures [4]. In our study, radial QUS was not able to discriminate CF adolescent and young adult CF patients with prevalent vertebral deformities from non-fractured patients.

We found that the majority of CF adolescents and young adults had a normal bone mineral status when examined by DXA, pQCT or QUS. The current study was performed in adolescents and young adults, who benefitted from the most recent therapeutic interventions, with exclusion of patients listed for transplantation, explaining the rather limited degree of lung disease and malnutrition. In most previous studies both the younger and the healthier CF individuals were found to have a normal bone mineralization. In patients with severe lung disease (FEV1 $\leq 30\%$), who are referred for lung transplant, the most severe CF related bone disease is found [16]. Whereas bone mineral data were within normal limits in most of patients in our study, a significant number were at risk for small radial bone sizes. Especially older and less healthy female CF patients were found to be at risk for thin forearm bones. In clinically stable osteopenic adults, bone area, bone formation rate and wall width in bone biopsies were found to decrease up to 50% [17]. The finding of rather small bone size in CF patients is an important issue, since the disturbed radial bone growth will lead to an overdiagnosis of osteoporosis when using DXA for defining osteopenia or osteoporosis.

In our study, for the first time a comparison between SOS and QUS results has been made in CF patients: absolute SOS results were found to correlate with radial cortical BMD values. An earlier study with the same QUS apparatus found that in healthy young adolescents tibial SOS results (the radius site was not investigated in this study) correlated with cortical BMD measured at the same bone site [18]. Another important finding in our comparative study was that in general bone geometry values were found to be more depressed than bone density data. We further evaluated if the degree of bone mineral quantity and quality impairment were related to known conditions of increased bone fragility. CF related diabetes mellitus was found to particular influence both bone size and trabecular BMD in our group of rather well nourished patients. Surprisingly, the influence of diabetes on the bone mineral content has not been well studied in CF patients up to now, despite the fact that more than 50 studies have investigated the clinical correlates of CF bone disease in the past 20 years. However, in a recent Israeli study investigating the consequences of CF related diabetes in adults, a lower BMD at the lumbar spine and femur was evidenced by DXA [19].

There are several limitations to our study. We had a limited number of severely attained patients and only very few had bone abnormalities assessed by QUS, limiting the possibility of detecting severe bone disease. There is however a consensus that it is mandatory to identify CF related bone disease early in its course to allow earlier therapeutic interventions to optimize bone health. Another weakness is the absence of any anamnestic assessment of fractures, although the accuracy of this kind of information is in general poor.

In conclusion, radial QUS identified bone abnormalities in less than 5% of rather well-nourished CF patients in our comparative bone study. The SOS was not influenced by the severity of the lung and liver disease and QUS results were independent of anthropometric data. QUS cannot replace DXA in evaluating whole body bone mass in CF adolescents and young adults, but it can screen out patients with a normal bone mass.

Conflict of interest

The authors have no conflict of interest to disclose.

Acknowledgements

This work was supported by the Belgian Cystic Fibrosis Foundation. Dr. Inge Roggen received a grant from the Belgian Study Group for Pediatric Endocrinology.
References


