Original article

Calcaneous quantitative ultrasound measurements predicts vertebral fractures in idiopathic male osteoporosis

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Abstract

Objectives: The aim of this study was to identify the differences in ultrasound bone variables (QUS) and to test the ability to discriminate male patients with and without vertebral fractures.

Methods: We therefore measured broadband ultrasound attenuation (BUA) and speed of sound (SOS) matched for bone mineral density (BMD) and vertebral deformity in idiopathic male osteoporosis.

Results: One hundred and seventeen men (age 56.6 range 27–78) were divided into three groups (osteoporosis n = 25, osteopenia n = 58 and age-matched control n = 34) according to BMD T-score by WHO criteria. We found 66 patients (56%) with at least one vertebral deformity during the study. BMD and BUA did not differ, while SOS was lower in osteoporosis (p < 0.001) and control group (p < 0.001) between the patients with and without vertebral compression. Strong positive correlation was demonstrated between BUA and BMD (lumbar spine r = 0.44, p < 0.001, femoral neck r = 0.56, p < 0.001, radius r = 0.40, p < 0.001), while similar association between SOS and BMD values was not shown. There was no relationship between the BUA and vertebral fracture risk (Odds ratio: 1.14 95% CI: 0.80–1.61). However, the relative risk of vertebral fracture by SOS was 1.56 (95% CI: 1.08–2.62). Adjusting for age and BMI the risk of vertebral fracture did not change (odds ratio for SOS 1.50 95% CI: 1.02–2.22). After adjustment for BMD SOS was still associated with fracture risk at all measured sites (odds ratio: 1.43, 95% CI: 1.02–2.22; 1.41, 95% CI: 1.02–2.17 and 1.32, 95% CI: 1.02–2.0).

Conclusion: Our results suggest that BUA values are more closely related to density and structure while SOS values are able to predict fractures. © 2006 Elsevier Masson SAS. All rights reserved.

Keywords: Male osteoporosis; Bone quantitative ultrasound; Vertebral fracture risk

1. Introduction

Fragility fractures in men represent a major health problem. Although bone mineral density (BMD) is a good surrogate measure of bone strength, it has been reported that BMD explains only 20% of the variance in fracture number [1]. This observation suggested that other factors that influence bone strength, and which may differ in men and women and at different skeletal sites, such as bone quality and micro-architecture, could play a relevant role in fracture risk [1,2].

The quantitative ultrasound measurement (QUS) is an endorsed diagnostic tool for the assessment of osteoporosis [3,4]. In the past decade there has been a growing interest in assessment of bone status using QUS techniques, which may offer an attractive possible alternative to the dual-energy X-ray absorptiometry (DXA) assessment. Many studies have reported that QUS parameters may reflect not only bone density but also quality properties of bone (elasticity, structure, micro-architecture) that are strictly related to bone strength [5].

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QUS parameters include broadband ultrasound attenuation (BUA), a measure of frequency dependent ultrasound attenuation, and speed of ultrasound (SOS) passing through soft tissue (BUA), a measure of frequency dependent ultrasound attenuation. Nevertheless it is not completely known which parameter and in which extent is sensitive to the bone structure [6,7]. It is hypothesized that BUA has an explanatory power for the mechanical property measurements, while SOS is a possible way of measuring bone elasticity [5]. Several studies, both longitudinal and cross-sectional have demonstrated that for the assessment of the risk of fracture QUS is as suitable as bone densitometry, irrespective of the bone mass [8–10]. To date, only a few studies have assessed QUS in male osteoporosis. Some studies have reported that QUS parameters at the calcaneus and at the fingers can discriminate male patients with fracture from control subjects [9,11–13].

In the present study men with idiopathic osteoporosis were studied using quantitative ultrasound measurement at calcaneus. The difference between the ultrasound bone variables was identified and SOS proved its ability to discriminate patients with vertebral fractures from unfractured men, independently of their bone mineral density.

2. Methods

2.1. Participants

One hundred and seventeen men (age 27–78 years) referred to our Osteoporosis Ambulance in Flór Ferenc Country Hospital for examinations to diagnose metabolic osteopathy were enrolled into the study. Ten of them had experienced at least one fragility fracture during the previous 10 years. Fragility fractures were defined as a history of wrist (n = 5), pelvis or hip (n = 4) or vertebral (n = 1) fracture resulting from mild to moderate trauma (typically a fall to the floor from standing height or less), that occurred within ten years, confirmed by medical record. Patients with secondary causes of osteoporosis and those with reduced testosterone level and/or clinical symptoms of hypogonadism were excluded. In particular, we excluded patients with hypercalcaemia or vitamin D deficiency (defined as having serum 25-OH-vitamin D concentration of less than 20 ng/ml) or with parathyroid hormone (PTH) serum levels of more than 65 pg/ml. Other exclusion criteria were: presence of disorders known to affect mineral metabolism (thyroid dysfunction, liver or kidney diseases), a history of alcohol abuse (>400 g/week), habitual smoking (>20 cigarettes/day), intake of drugs known to interfere with calcium metabolism, such as corticosteroids, thyroid hormone, heparin, anti-convulsants The study was approved by the Institutional Research and Ethics Committee and all patients gave informed consent.

2.2. Study design

Medical history was taken and complete physical examination was performed to assess the health status of the volunteers. Height and weight were measured with participants wearing light clothing and no shoes and body mass index (BMI) was calculated as kilograms per square meter (kg/m²). Blood was taken for complete hematological and biochemical analysis to exclude patients with any significant abnormalities. Levels of serum gonadal hormones (total testosterone, total estradiol, LH and FSH), serum thyroid-stimulating hormone (TSH), parathyroid hormone and 25-OH-vitamin D levels were measured by radioimmunoassay methods to exclude men with significant gonadal dysfunction, thyroid, or parathyroid disease and osteomalacia. Postprandial blood glucose, serum lipid levels, and biochemical test of liver function were checked by routine methods on an Olympus AU600 auto-analyser (Olympus Ltd, Japan). Serum calcium, phosphorus, and 24-h urinary output of calcium were measured by atomic absorption spectrophotometer. An individual was considered having hypercalciuria when the 24-h urinary calcium value was ≥0.1 mmol/kg per day on the 20 mmol/day calcium intake. All patients had normal multichannel blood chemistries.

The participants were divided into three groups. We followed the WHO criteria [14], because NORA study [15] revealed that women with low BMD (T-score ≤1.0) had a similar relative risk for fracture regardless of age. No similar data were published in males; however, the above-mentioned study emphasizes the clinical importance of osteopenia. Osteoporosis group consisted of 25 men with primary osteoporosis if bone mineral density (BMD) was below −2.5 at one or more measured sites. Fifty-eight men with osteopenia were included into the second group if BMD was between −1.0 and −2.5 at one or more measured sites, too. Thirty-four age-matched men were classified as control if BMD was within the normal range.

2.3. Measurement of bone mineral density

Lumbar spine (L2–4) and left femoral neck BMD (g/cm²) were measured by dual energy X-ray absorptiometry (LUNAR-DPX-L, Lunar Co., Madison, WI). The equipment was calibrated every day. The variation coefficient was 0.32% and 0.91%, respectively. Each scan was analysed by same operator using the manufacturer’s recommended procedures for analysis.

Bone density of the non-dominant radius was measured by single photon absorptiometry using NK-364 device (Gamma Co., Budapest, Hungary). Bone mineral content was given in g/cm; precision error (expressed as the coefficient of variation, CV%) was 0.68%. Both equipment provided automatic T-scores for the measured results which is derived from the difference between the measured value and the best mean value of young adults from the same gender expressed as a deviation from the normal value. T-scores were generated using peak gender-matched reference data from Caucasian males. Measurements were performed by the same assistant.

2.4. Quantitative ultrasound of the bone

QUS measurements were performed on the left heel by DTU-ONE (Osteometer, Hörsholm, Denmark). QUS device measures BUA (db/MHz) and SOS (m/s) at the heel in a small region of the calcaneus of 0.2 cm². This circular region of
interest is automatically chosen by software at a region of lowest ultrasound attenuation. Broadband ultrasonic frequencies range from 300 to 650 kHz. During the examination, the foot is placed in a room temperature water bath. The water temperature is automatically checked before each patient scan; SOS is corrected for temperature, whereas BUA is not. Precision errors were found as 1.28% for BUA and 0.1% for SOS, respectively. Measurements were performed by the same assistant.

2.5. X-ray measurement and roentgenmorphometry of bones

Lateral thoracic and lumbar spine radiographs were taken according to a standard protocol [16] at the time of the densitometry measurement. Tube to film distance was 120 centimetres and X-ray beam was focused on thoracic (Th) 7 and lumbar (L) 2 vertebrae. Both images were obtained with the subject in a lateral position. They were analysed by trained investigator who was unaware of the patient’s status. A vertebral fracture was defined as a reduction of at least 20% in the anterior, middle or posterior vertebral height. The criteria were thus: (1) in anterior wedge deformity, ratio of anterior/posterior height < 80%; (2) in concavity deformity, ratio of middle/posterior height < 80%; and (3) in compression deformity, ratio of posterior height/posterior height of the adjacent vertebra < 80%. The variation coefficients of vertebral heights were 1.42% in anterior height, 1.74% in central height and 2.44% in posterior height.

2.6. Statistical analysis

Analyses were performed using SPSS version 10.0 for Windows (Chicago, IL). For all characteristics there were determined the mean, the standard error and the 95% confidence intervals for the estimation of the mean values, too. ANOVA test after Bonferroni correction was used for intergroup comparisons. Independent sample t test was used to compare BUA and SOS values of patients with or without fractures. Correlation coefficients were applied to evaluate the relationship between bone mineral density and QUS variables. Receiver operating characteristic (ROC) analysis was performed, and we calculated the areas under the curve (AUC) in order to determine the ability of QUS and DXA parameters to discriminate subjects with or without vertebral fractures. Adjusted multiple regression models were used to determine the influence of QUS variables for fracture risk. Results are expressed as the Odds ratio of vertebral fracture with 95% confidence interval (CI). A result was considered statistically significant if the derived p value was less than 0.05.

3. Results

The clinical characteristics of participants are shown in Table 1. There were no age differences among the three groups, while the body mass index was lower in the osteoporosis group than in the osteopenia (p = 0.001) and in the osteoporosis group than in the controls (p < 0.001). Difference was not found between group of the osteopenia and the control (p = 0.247). BUA was significantly lower in patients with low bone mineral density (osteoporosis vs. osteopenia p = 0.027; osteoporosis vs. control p < 0.001; osteopenia vs. control p = 0.004). However, SOS values didn’t show differences between the three groups.

Vertebral deformities were identified in 66 subjects (56%). As much as 286 vertebral compression were detected. The distribution of the deformities is shown in Table 2. In the osteoporosis group 73 vertebral fractures were detected in 16 patients, while in the group of osteopenia 160 compressions were verified in 35 patients. Fifteen patients (23%) in control group were also found having vertebral deformities (number of deformities was 53).

We compared bone mineral density at the three measured sites and QUS variables between men with and without vertebral deformities in all three groups. As seen in Table 3, there were no significant differences in bone mineral density at any sites and at any groups between men with and without vertebral deformities. Similarly, there were no any differences in the BUA values either in osteoporosis (41.2 ± 2.3 vs. 38.9 ± 2.2 dB/MHz) or in control (49.4 ± 1.7 vs. 52.4 ± 1.8 dB/MHz) group between subgroups of men with vertebral fracture and without vertebral fracture (Fig. 1). The SOS values were significantly lower in fractured men than in unfractured men with osteoporosis (1546.0 ± 4.2 vs. 1532.6 ± 4.1 m/s, p = 0.05). SOS values in 18 men, who had vertebral compression in control group, were lower than in 22 healthy, control men (1561.4 ± 2.8 vs. 1536.2 ± 3.8 m/s, p = 0.01). The similar tendency of difference was not significant in the osteopenic group.

Table 1

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Osteoporosis</th>
<th>Osteopenia</th>
<th>Control</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>58</td>
<td>34</td>
<td>117</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.1 ± 2.1</td>
<td>56.7 ± 1.1</td>
<td>56.0 ± 1.5</td>
<td>117</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 0.84</td>
<td>27.1 ± 0.47*</td>
<td>28.7 ± 0.72#</td>
<td>117</td>
</tr>
<tr>
<td>LBMD (g/cm²)</td>
<td>0.900 ± 0.002</td>
<td>0.998 ± 0.001*</td>
<td>1.153 ± 0.003#</td>
<td>117</td>
</tr>
<tr>
<td>FBMD (g/cm²)</td>
<td>0.710 ± 0.001</td>
<td>0.866 ± 0.007*</td>
<td>1.031 ± 0.002#</td>
<td>117</td>
</tr>
<tr>
<td>RBMC (g/cm)</td>
<td>1.032 ± 0.003</td>
<td>1.096 ± 0.002*</td>
<td>1.210 ± 0.008#</td>
<td>117</td>
</tr>
<tr>
<td>BUA (dB/MHz)</td>
<td>39.7 ± 1.6</td>
<td>45.2 ± 0.9*</td>
<td>50.9 ± 1.2#</td>
<td>117</td>
</tr>
<tr>
<td>SOS (m/s)</td>
<td>1546.2 ± 21.9</td>
<td>1546.4 ± 2.5</td>
<td>1550.2 ± 3.7</td>
<td>117</td>
</tr>
</tbody>
</table>

Age, body mass index (BMI), bone mineral density (BMD) at lumbar spine (LBMD), femoral neck (FBMD) and bone mineral content at radius (RBMC), broadband ultrasound attenuation (BUA) and speed of sound (SOS). Values are expressed as mean ± SE. *Significant difference between osteoporotic group vs. osteopenic group (p < 0.05). #Significant difference between osteopenic group vs. control group (p < 0.05). |Significant difference between osteoporotic group vs. control group (p < 0.05).

Table 2

| Number of patients with (VF+) and without vertebral fracture (VFØ) |
|------------------|----------------|----------------|----------------|----------------|
| Osteoporosis     | Osteopenia    | Control        | All patients   |
| Number of patients | 16          | 9            | 35           | 23            | 15 | 66 | 51 |
| Number of deformities | 73         | 160          | 53           | 286           |

VF+: patients with vertebral fractures, VFØ: patients without vertebral fracture.
We further analyzed the relation between ultrasound variables and bone mineral density. A strong positive correlation was documented between BUA and BMD at all measured sites. Correlation coefficients were within the range of 0.43 and 0.55. However, no association was found between SOS and BMD values (Table 4). Table 5 shows the values of the areas under the ROC curves for all parameters relative to subjects with and without fractures.

The ability of QUS to determine vertebral fracture risk was also assessed (Table 6). We could not find any connection between the BUA and the vertebral fracture risk (Odds ratio: 1.14 95% CI: 0.80–1.61). However, there was a strong positive association the SOS parameter and the vertebral fracture rate among our control subjects was an unexpected result. Several studies have looked at the incidence of clinically diagnosed vertebral fractures in population samples of men [18,19]. Direct comparison with our study is difficult because of the differences in study design and the restricted area of spinal assessment. As expected, the absolute incidence of fracture is lower than in observed in our study, reflecting the fact that only a proportion of vertebral fractures come to clinical attention.

Previous studies observed that among all measured regions of densitometry the total hip region was the preferred site to predict vertebral fracture risk in young and middle-aged men [20]. In this study patients with normal bone mineral density were found to have vertebral deformity. This finding inspired us turn to get non-mass bone features, which are independent from bone mineral density, at least partly.

Bone fragility shows a high correlation with bone mass, but as much as 25–30% of observed variation in bone strength may be due to qualitative features such as structure and elasticity of bone material [1,21–23]. Bone densitometry is an established, worldwide-accepted method to measure bone mass and predicts osteoporosis fracture risk [4]. However,
BUA correlate with DXA at all measurement sites, but SOS containing homogeneous patient groups shows that calcaneal (porosity, etc.) and by bone mass [6]. The EPIDOS and SOF influenced by the structural characteristic of tabecular bone [26]. BUA, on the contrary, seems to be more to be influenced by mineral density and the elastic character-

On the other hand, quantitative ultrasound became more and more accepted as reflecting some qualitative properties of bone. In 1996 it was officially declared that QUS is an alternative diagnostic technique for assessment of osteoporosis [3]. Several studies have shown that ultrasound variables correlate moderately with BMD measured by DXA at different sites [24], but strongly when measured on the same site [23]. It has been demonstrated that QUS is as suitable as densitometry for the assessment of the risk of fracture, irrespective of the bone mass [8], because QUS provides information on the so-called non-mass characteristics of bones [8,4,25]. SOS seems to be influenced by mineral density and the elastic characteristic of bone [26]. BUA, on the contrary, seems to be more influenced by the structural characteristic of tabecular bone (porosity, etc.) and by bone mass [6]. The EPIDOS and SOF studies, two large scale prospective, longitudinal studies were the first investigating the effectiveness of bone ultrasound at the calcaneus with regards to fracture risk prediction. The relative risks for fractures obtained for BUA and SOS are 2.0 and 1.7, respectively [8,27]. In contrary, it is still unclear which ultrasound variable and in which extent is able to predict fracture risk in idiopathic male osteoporosis. The anthropometric features did not reveal a negative influ-

Time and place for QUS: The study was conducted with grants from OTKA (T038067) and ETT (226/2003).

### Table 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBMD</td>
<td>0.61</td>
<td>0.50–0.72</td>
</tr>
<tr>
<td>FBMD</td>
<td>0.59</td>
<td>0.48–0.71</td>
</tr>
<tr>
<td>RBMC</td>
<td>0.64</td>
<td>0.53–0.75</td>
</tr>
<tr>
<td>BUA</td>
<td>0.51</td>
<td>0.39–0.62</td>
</tr>
<tr>
<td>SOS</td>
<td>0.74</td>
<td>0.64–0.83</td>
</tr>
</tbody>
</table>

Bone mineral density (BMD) at lumbar spine (LBMD), femoral neck (FBMD) and bone mineral content at radius (RBMC), broadband ultrasound attenuation (BUA) and speed of sound (SOS).

none of the densitometric techniques enable a qualitative evaluation of bone tissue.

On the other hand, quantitative ultrasound became more and more accepted as reflecting some qualitative properties of bone. In 1996 it was officially declared that QUS is an alternative diagnostic technique for assessment of osteoporosis [3]. Several studies have shown that ultrasound variables correlate moderately with BMD measured by DXA at different sites [24], but strongly when measured on the same site [23]. It has been demonstrated that QUS is as suitable as densitometry for the assessment of the risk of fracture, irrespective of the bone mass [8], because QUS provides information on the so-called non-mass characteristics of bones [8,4,25]. SOS seems to be influenced by mineral density and the elastic characteristic of bone [26]. BUA, on the contrary, seems to be more influenced by the structural characteristic of tabecular bone (porosity, etc.) and by bone mass [6]. The EPIDOS and SOF studies, two large scale prospective, longitudinal studies were the first investigating the effectiveness of bone ultrasound at the calcaneus with regards to fracture risk prediction. The relative risks for fractures obtained for BUA and SOS are 2.0 and 1.7, respectively [8,27]. In contrary, it is still unclear which ultrasound variable and in which extent is able to predict fracture risk in idiopathic male osteoporosis. The anthropometric features did not reveal a negative influ-

### Table 6

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted BUA</td>
<td>1.14 (0.80–1.61)</td>
</tr>
<tr>
<td>SOS</td>
<td>1.56 (1.08–2.62)</td>
</tr>
<tr>
<td>Adjusted for age and BMI</td>
<td>1.50 (1.02–2.22)</td>
</tr>
<tr>
<td>SOS</td>
<td>1.43 (1.02–2.22)</td>
</tr>
<tr>
<td>Adjusted for age, BMI and L2-L4 BMD</td>
<td>1.41 (1.02–2.17)</td>
</tr>
<tr>
<td>SOS</td>
<td>1.32 (1.02–2.01)</td>
</tr>
</tbody>
</table>

BUA: broadband ultrasound attenuation; SOS: speed of sound; BMI: body mass index; BMD: bone mineral density; BMC: bone mineral content.

seems to be an independent parameter. These clinical data are in good parallelism with the conclusions of previous experimental studies [29,30]. The ability of QUS to discriminate between fracture and non-fracture group has been reported by other researchers [30,31]. Cross sectional studies in female populations have demonstrated competence of QUS to discriminate between healthy and fractured people [32,33]. Only a few prospective studies on fracture discrimination in men have been published so far [34–36]. Our findings agree with these previous studies. In men measurements taken with calcaneal QUS devices were able to indicate the presence of vertebral fractures. Our results also suggest that ultrasounds measure properties intrinsic to the bone structure that are independent of bone mass, because lower SOS was measured among patients suffering from vertebral deformity within the group of patients with normal bone density. It seems to be an important observation that only SOS but not BUA differed significantly between fractured and non-fractured men. This observation could suggest that the deterioration in bone quality — especially the decreased elasticity — could play an independent role in the process of vertebral deformation in males, even in case of normal amount of bone mass reflected by BMD and partly BUA as well.

Finally, we observed the ability of QUS to predict vertebral fractures risk. The ability of QUS measurements to indicate increased fracture risk has been demonstrated for some devices [3] but remained doubtful when compared with DXA [8,37]. It has been shown in two large prospective studies that calcaneal QUS has similar power in hip fracture prediction to peripheral DXA measurements [38,39]. Few data are available on widely used QUS and its ability to discriminate between healthy and osteoporotic subjects with documented vertebral fractures [31,40]. The main finding of our study was that vertebral deformity proved to be connected to both ultrasound parameters but with different Odds ratios. The relative risk of vertebral fracture for each 1 SD reduction was 1.14 in calcaneal BUA and 1.56 in SOS. The anthropometric features did not reveal a negative influence on BUA nor on SOS. After adjustment for BMD at all measured sites SOS was still associated with an increased risk for vertebral fracture, unlike BUA. This evaluation of the data again suggests the importance of changes in bone elasticity resulting in more fragility.

However, our study has several limitations. First of all, it was a retrospective study concerning fractures and we did not use a computerized technique to define vertebral deformity. It is likely, however, that the results were not modified because of measurement, our variation coefficients being within a 1.42–2.44 range. A second limitation of our study could be the moderate number of cases. Our conclusion could be more powerful using the direct measurement of BMD at the calcaneus site.

### Acknowledgements

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