Dual-energy X-ray absorptiometry versus quantitative ultrasonography in diagnosing osteoporosis in patients with refractory epilepsy and chronic antiepileptic drug use

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Abstract

Background: The aim of this study was to assess the feasibility of calcaneal quantitative ultrasonography (QUS) as a screening method for increased risk of osteoporosis in a unique population of people with chronic epilepsy, intellectual disability (ID), and chronic use of antiepileptic drugs.

Methods: A total of 205 patients from a long-stay care facility for people with epilepsy underwent dual-energy X-ray absorptiometry (DXA) and QUS of the calcaneus. *T*-scores for both DXA and QUS were calculated and correlated.

Results: A total of 195 patients (95.1%) were successfully measured with DXA and 204 (99.5%) with QUS. High correlations were found between DXA and QUS *T*-scores: $r = 0.666$ (QUS versus *T*-score total femur), $r = 0.631$ (QUS versus *T*-score femur neck) and $r = 0.485$ (QUS versus *T*-score lumbar spine). All correlations were statistically significant ($p = 0.01$).

Conclusion: QUS showed a strong correlation with DXA and proved to be a feasible measuring method in a population with ID and epilepsy. Including osteopenia in the screening process increases the sensitivity of QUS to identify those patients at risk for the development of bone diseases.

Keywords: antiepileptic drugs, bone metabolism, dual-energy X-ray absorptiometry, epilepsy, osteoporosis, quantitative ultrasonography

Introduction

Quantitative ultrasonography (QUS) methods are gaining ground as a reliable technique for measuring bone mineral status in a population [Gluer *et al.* 2004; Hollaender *et al.* 2009]. QUS has a number of advantages over the more commonly used dual-energy X-ray absorptiometry (DXA) scan: it is radiation free, relatively inexpensive, easy to use and portable [Economos *et al.* 2007; Mergler *et al.* 2010]. Furthermore, it has the possibility of independently predicting fracture risk. QUS makes use of the alteration of travelling vibrations when passing through a medium [Baroncelli, 2008]. Information about bone density, structure and composition can be collected by measuring the change in velocity and amplitude when the sound waves travel through bone

tissue. This makes the technique fast and easy to use, even for less mobile or less cooperative individuals. A relative disadvantage of QUS techniques measuring the heel bone is the fact that bone density between left and right foot usually differs [Mergler *et al.* 2010]. However, Roux and colleagues found in a whole population no significant difference between QUS results of right and left feet [Roux *et al.* 1993]. Often the nondominant foot is measured, presuming it has the lowest value of bone density. However, in individuals with intellectual disabilities (IDs) it can be difficult to determine which foot is dominant. Nevertheless, a study investigating feasibility of calcaneal QUS in people with IDs concluded that it is a practical and nonstressful method for measuring bone status [Mergler *et al.* 2010].

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Although feasibility has been ascertained, evidence with respect to validity and sensitivity has not been established for all kinds of populations. Some studies suggest QUS correlates strongly with DXA, holding the potency to independently diagnose osteoporosis [Frost *et al.* 2001; Huopio *et al.* 2004; Jin *et al.* 2010; Stewart *et al.* 2006]. Others find a weaker correlation and reject this potential [Dane *et al.* 2008; Dubois *et al.* 2001; El Maghraoui *et al.* 2009; Lochmuller *et al.* 2003; Shin *et al.* 2005] or propose QUS as a screening method in the absence of or prior to DXA [Gemalmaz *et al.* 2007; Iida *et al.* 2010; Marin *et al.* 2004; Trimpou *et al.* 2010]. In one meta-analysis 25 articles were examined regarding QUS as an identification method for osteoporosis [Nayak *et al.* 2006]. The authors concluded that the determined sensitivity and specificity of QUS were too low to diagnose DXA-determined osteoporosis.

There is an increasing body of evidence on the negative influence of antiepileptic drugs (AEDs) on bone density. Patients on chronic AED therapy may have a reduced bone mineral density (BMD) and an increased risk of fractures [Jancar and Jancar, 1998] even after correction for seizure-related fractures [Desai *et al.* 1996; Vestergaard *et al.* 1999]. Irrespective of the population, DXA is still the gold standard for the measurement of BMD. However, screening a population of epileptic institutionalized patients with DXA demands a great piece of effort from patients and their caregivers. In this specific population many risk factors for low BMD exist. Moreover, this is a population with frequent intellectual and physical comorbidities and therefore would profit most from a portable and noninvasive method that would allow early screening and follow up for the presence of osteoporosis and osteopenia. Also follow-up measurements for the evaluation of the effect of the implemented bone enhancing therapies (physical therapy with weight bearing exercise, calcium and vitamin D supplementation and sometimes also antiresorptive bone therapy) is necessary. In the light of the repeated measurements a method of BMD measurement that is noninvasive, patient-friendly and without radiation load is obligatory. QUS could be a good candidate for screening for low BMD in this population, under the condition that it has a high sensitivity and specificity. To investigate this, we conducted a cross-sectional study to determine the sensitivity and specificity of QUS in a high-risk population consisting of patients with

refractory epilepsy on chronic use of AEDs, using DXA as the gold standard.

Material and methods

Study population/subjects

The study population consisted of patients living in a long-stay care facility for patients with epilepsy. A total of 205 patients were adults of 18 years and older. Almost all patients had a history of refractory epilepsy for which in most patients treatment with several AEDs was necessary. Most of the patients also had some degree of ID.

A cross-sectional study was performed, measuring BMD at lumbar spine and femur with DXA (Hologic) and using QUS of the calcaneus (Sahara, Hologic). In addition, characteristics regarding lifestyle, epilepsy, medication use, history of AED use, fracture history and potential secondary causes of osteoporosis were recorded in a database. The study was approved by the local and regional Ethics Committee and was in accordance with the Code of Ethics (Declaration of Helsinki). Informed consent was obtained from each patient or his/her legal representative.

Methods: BMD by DXA

BMD of the lumbar spine and left femur was measured by DXA and expressed as the amount of mineral (g) divided by the area scanned (cm²). All DXA measurements were performed by the same densitometer (Hologic, Discovery W [S/N 70991]) and were performed between 30 August and 29 September 2009. *T*-scores (number of standard deviations [SD] below peak bone mass) and *Z*-scores (number of SD below age- and sex-matched controls) were calculated for total lumbar spine, femoral neck and total femur using the manufacturers' reference database (reference values supplied by Hologic for the hip and lumbar spine as well as data from the National Health and Nutrition Examination Survey part III (NHANES III) dataset. Manufacturer specific reference population (White) was used to calculate *T*-scores. World Health Organization (WHO) criteria [World Health Organization Study Group, 1994] were used to classify BMD and osteoporosis. A *T*-score of -1.0 and greater is considered normal, a *T*-score between -1.0 and -2.5 is considered low bone mass (osteopenia) and a *T*-score of -2.5 and less is considered osteoporosis. In patients aged 70 years and older also a *Z*-score of

less than -1.0 was considered osteoporosis, because of the increased fracture risk and the advice to consider treatment for osteoporosis in this specific age group [CBO, 2002]. The site with the lowest T -score was included in the diagnosis osteoporosis.

Methods: BMD by QUS

Bone densitometry was performed by quantitative ultrasonography of the heel bone (Sahara, Hologic). Several devices using QUS are available, measuring at different parts of the body. A widely used measuring spot is the calcaneus [Gluer *et al.* 2004; Hollaender *et al.* 2009]. Two quantifiable variables are available: speed of sound (SOS), related to velocity of the ultrasound signal, and broadband ultrasound attenuation (BUA), related to the weakening of the ultrasound signal [Mergler *et al.* 2010, Baroncelli, 2008]. In some techniques an additional variable, stiffness index (SI), can be assessed. Devices such as the Sahara (Hologic) require application of alcohol or gel to the foot, after which the foot can be placed in the device, measuring bone status within half a minute. The calcaneus of the left foot was measured to assess the lowest value of bone density. In three patients (1.5%) the heel bone of the right foot was measured due to anatomical restrictions (severe clubfoot). Derived variables consisted of BUA, SOS, QUI/Stiffness and T -scores using manufacturers' database (Sahara Reference Ranges for White subjects). All QUS measurements were performed directly before or after the DXA measurements. A QUS T -score of -1.0 was taken as the cut-off value to distinguish between osteoporotic and nonosteoporotic patients. This value was based on data reported by Hologic, stating that 82–87% of people with a Sahara T -score of less than -1 are diagnosed with osteoporosis as determined by DXA.

Analysis and statistics

Data are presented as mean $\pm$ SD or as percentages. Tests determining the screening value of QUS in relation to DXA grouped osteopenia and osteoporosis together by using a cut-off value of -1.0 for DXA T -scores. This way not only patients with osteoporosis, but also patients in the risk group of low bone mass can be identified by a follow-up DXA scan. Correlation analysis was performed using a two-tailed Pearson correlation coefficient with a significance level of $p < 0.05$. Furthermore a received operating characteristic

(ROC) curve and the area under the curve (AUC) were calculated to assess the correspondence of QUS with regard to the gold standard of DXA. AUC reflects the discriminatory value of a test; in this case the potential of QUS to discriminate between osteopenic/osteoporotic and nonosteopenic/nonosteoporotic patients as diagnosed by DXA. An AUC of 1 indicates a perfect discrimination and an AUC of 0.5 indicates a very poor discrimination. In addition, discriminant analysis was used. This is a rotating procedure that step-wise searches the best solution to classify the patients according to a gold standard. We used the DXA T -score of the femur (total hip) as the gold standard with a cut-off value of -1.0 , separating osteopenic and osteoporotic patients from the rest of the population. The QUS cut-off T -score of -1 was then used to compare overlaps of classifications. Discriminant analysis gives outcomes for concordance, 'hits' (same diagnosis with both techniques) and 'correct rejections' (same rejection of diagnosis), and measures of discordance, 'misses' (QUS T -score fails the DXA diagnosis) and 'false alarms' (diagnosis with QUS T -score and not with DXA as gold standard). From a clinical perspective it is interesting to further examine the group of 'misses', because they are diagnosed as osteopenic or osteoporotic by DXA, but overlooked by QUS. Therefore, an additional analysis was done comparing the 'misses' with the rest of the population in order to find a possible explanation for the false rejection of these patients. All statistical analyses were done using SPSS for Windows (Rel. 18.0.2, 2010, SPSS Inc., Chicago, IL) and Excel 2003 (Microsoft, Seattle, WA).

Results

The study group consisted of 205 patients: 124 men (60.5%) and 81 women (39.5%). Mean age was 47.0 ± 16.8 years, range 18–88 years. A total of 54.6% of patients were under the age of 50 years. Of the 205 patients 55 (26.8%) were wheelchair-bound, 28 (13.7%) walked with aid and 122 (59.5%) walked without aid. The DXA scan of lumbar spine and/or femur was successfully performed in 195 (95.1%) of the patients and QUS in 204 (99.5%) of the patients. Mean and SD of all QUS variables are shown in Table 1. Correlation analysis showed statistically significant correlations between QUS and the three different DXA T -scores of the lumbar spine, femur neck and total femur (Table 2). Correlations ranged from $r = 0.485$ ($p = 0.01$) for QUS T -score with DXA T -score lumbar spine to $r = 0.666$

Table 1. Quantitative ultrasound parameters.

	BUA	SOS	T-score	QUI
Number	203	203	204	204
Mean (SD)	46.9 (21.3)	1514.6 (30.9)	−2.2 (1.2)	68.8 (20.2)
BUA, broadband ultrasound attenuation; QUI, quantitative ultrasound index; SD, standard deviation; SOS, speed of sound.				

Table 2. Correlation analysis QUS and DXA.

	QUS T-score
DXA T-score Lumbar spine	0.485*
DXA T-score femur total	0.666*
DXA T-score femur neck	0.631*
*Correlation is significant at the 0.01 level (two-tailed). DXA, dual-energy X-ray absorptiometry; QUS, quantitative ultrasonography.	

($p = 0.01$) for QUS T-score with DXA T-score femur total.

Results of the ROC analysis are shown in Figure 1 with the analysis showing an AUC of 0.832. The strength of the relationship between DXA and QUS was additionally tested using discriminant analysis (Tables 3 and 4). This shows a sensitivity of 90.3%, as 90.3% of the patients diagnosed with

osteoporosis or osteopenia based on DXA are also identified as osteoporotic or osteopenic by QUS. Specificity is lower, as 40.8% of the patients in whom the diagnosis was rejected with DXA were also rejected with QUS. In 15 cases the diagnosis of osteoporosis or osteopenia based on DXA could not be confirmed with QUS. Of these 15, 11 (73.3%) were diagnosed as osteopenic and 4 (26.7%) as osteoporotic.

Table 4 shows demographic characteristics of the group classified as misses and the rest of the population. Factors that stand out are gender, number of fractures, drug load and the total duration of epilepsy. Of these variables the number of fractures [$t(170) = -1.48, p = 0.140$], gender [$\chi^2(1, N = 194) = 3.12, p = 0.077$] and the total duration of epilepsy [$t(183) = -1.70, p = 0.090$] showed no significant effect. Drug load, expressed in the presence of epilepsy in years $\times$ the number

Figure 1. Receiver operating characteristic (ROC) curve using quantitative ultrasonography (QUS) T-score as the test variable and the diagnosis ‘osteoporosis or osteopenia/no osteoporosis or osteopenia’ based on dual-energy x-ray absorptiometry (DXA) as the state variable. Area under the curve (AUC) = 0.832.

Table 3. Classification results for low bone mineral density (osteopenia and osteoporosis) as diagnostic outcome.

	Predicted group membership (QUS <i>T</i> -score ≥ -1.0)	
	Osteopenia/osteoporosis	Normal
DXA osteopenia/osteoporosis, <i>n</i> (%)	140 (72.2)	15 (7.7)
DXA normal, <i>n</i> (%)	20 (10.3)	19 (9.8)
The number of correct diagnoses for osteopenia/osteoporosis by QUS is 140. The number of correct rejections is 19. 'False alarms' are found in 20 cases and 'false rejections' in 15. A total of 82% of the patients were correctly classified with QUS based on DXA diagnosis of osteopenia and osteoporosis. DXA, dual-energy X-ray absorptiometry; QUS, quantitative ultrasonography.		

of prescribed AEDs, showed a significant effect ($t(183) = -2.16$, $p = 0.032$) with the group of misses having a smaller drug load than the remainder of the population.

Discussion

The goal of this study was to assess the validity of QUS as a screening method for osteoporosis in a population with chronic epilepsy and AED use. The results show a strong and positive correlation between *T*-scores measured by DXA and QUS. Furthermore, this study demonstrates QUS as a feasible method for measuring bone density in a population with IDs and epilepsy. For 10 (4.9%) patients it was impossible to perform DXA due to anatomical or behavioural restrictions; for one patient QUS could not be performed due to the history of fractures in both feet. In three patients QUS of the right calcaneus was performed because of anatomical deformities of left foot (foot clubbing). Although feasible, using a DXA scanner in this specific population turned out to be a high-effort undertaking, consuming a lot of time in preparation, instruction and application. These results confirm the advantages of QUS over DXA, regarding mobility and ease of use.

The manufacturers of the Sahara QUS device (Hologic) report that 80–82% of patients with DXA determined osteoporosis will score below -1.0 in the Sahara *T*-score. Around 5–10% with nonosteoporotic or nonosteopenic DXA results will score lower than -1 on the Sahara *T*-score and 6–9% with DXA determined osteoporosis will score above 0 on the Sahara *T*-score. Our results, including osteopenia as a diagnostic outcome, are marginally higher on the sensitivity level of the Sahara device in relation to DXA: 90.3% of patients with DXA determined osteoporosis or osteopenia fall under the QUS cut-off value of $T = -1.0$. The specificity was lower than

the sensitivity: at a QUS cut-off *T*-score of -1.0 , 40.8% of patients determined as nonosteoporotic by DXA will be classified as nonosteoporotic by QUS.

The results show a strong correlation between QUS and DXA. However, the correlation is not strong enough to rule out any occurrence of false positives or false negatives when choosing a cut-off value for Sahara *T*-scores. Results show that when the cut-off value is high (-1.0) there will be a large number of false hits, but when decreasing this *T*-value the number of false rejections steadily increases. Therefore, irrespective of the high correlation between DXA and QUS *T*-scores, using a single QUS measurement as a method for screening or diagnosing osteoporosis does not yet seem viable.

However, when screening with QUS, a relative higher number of false positives would be acceptable, given the follow-up examination performed by the gold standard of DXA. In particular, in a specific population of people with epilepsy and IDs, the prevalence of osteoporosis is so high that, despite a low specificity, only a small percentage of patients will be falsely diagnosed with osteoporosis. The same argument is true for the falsely rejected cases, as only 4 of the 15 missed cases were diagnosed with osteoporosis by DXA.

Repeated measurements with QUS in this specific high risk population could greatly increase the validity of QUS as a reliable screening method as it allows follow-up procedures with a portable machine in a noninvasive and patient-friendly manner without involving radiation. In particular, the chronic use of AEDs would make these patients eligible for follow-up screening with a 6-monthly, yearly or 2-yearly screening cycle. One way of approaching this method is repeated screening of a 'risk group' with a QUS

Table 4. Demographic table: misses and rest.

	Misses		Rest	
	<i>n</i>	Mean (SD) or %	<i>n</i>	Mean (SD) or %
Age at screening (years)	15	40.53 (17.75)	179	47.89 (16.64)
18–39	8	53.3	56	31.3
40–49	2	13.3	40	22.3
50–59	2	13.3	35	19.6
60–69	2	13.3	32	17.9
70–79	1	6.7	13	7.3
80–89	0	0	3	1.7
Gender				
Male	6	40	113	63.1
Female	9	60	66	36.9
Body mass index (BMI), kg/m ²	15	23.4 (3.2)	179	25.2 (4.4)
Barthel index	15	11.3 (6.4)	178	12.1 (6.3)
Ambulatory status				
Wheelchair-bound	3	20.0	44	24.6
Walk with aid	2	13.3	24	13.4
Walk without aid	10	66.7	111	62
Intellectual disability (IQ score)				
Normal	0	0	2	1.1
Mild (70–55)	5	33.3	50	27.9
Moderate (40–55)	4	26.7	66	36.9
Severe (25–40)	4	26.7	54	30.2
Profound (<25)	2	13.3	7	3.9
DXA <i>T</i> -scores				
<i>T</i> -score lumbar spine	14	−1.36 (0.99)	175	−0.95 (1.65)
<i>T</i> -score femur neck	15	−1.28 (0.93)	175	−1.73 (1.07)
<i>T</i> -score total femur	15	−1.12 (0.62)	175	−1.39 (1.20)
QUS <i>T</i> -score	15	−0.33 (0.84)	179	−2.29 (1.08)
FRAX				
Major osteoporotic	7	5.72 (2.05)	119	10.03 (9.66)
Hip	7	0.91 (0.83)	118	4.09 (8.51)
Total duration epilepsy (years)	15	34.7 (17.5)	170	42.18 (16.1)
Drugload (years × number of AEDs)	15	83.8 (59.4)	170	116.1 (55.1)
Falls per month				
Seizure related	12	1.4 (2.9)	152	1.7 (7.5)
Seizure unrelated	12	2.0 (3.6)	143	0.9 (3.0)
History of fractures				
Yes	8	57.1	115	68.9
No	6	42.9	46	27.5
Unknown	0	0	6	3.6
Number of fractures	13	0.8 (0.9)	159	1.6 (1.9)
Smoking				
Never smoked	13	86.7	133	74.3
Past smoker	0	0	25	14
Current smoker	2	13.3	21	11.7

AED, antiepileptic drug; DXA, dual-energy X-ray absorptiometry; FRAX, fracture risk assessment tool; IQ, intelligence quotient; QUS, quantitative ultrasonography; SD, standard deviation.

T-score between -1 and 0 . This would lead to coverage of a large number of the 15 patients that were falsely declared healthy in prior QUS measurements.

This study has a number of limitations. First of all we only measured the left foot in our population with QUS. In particular, in a population with IDs it is difficult to determine dominance and thereby higher bone density in a specific foot. In addition, only the use of calcaneal QUS was explored in this research. A different study suggests that phalangeal QUS might be a better method to assess bone loss in epileptic patients [Pluskiewicz and Nowakowska, 1997]. Another factor not taken into account in this study was the supplementation of vitamin D. Pedrera and colleagues report that a group of patients using anticonvulsants regained normal bone status, measured by QUS, within a month after supplementation of high-dose vitamin D [Pedrera *et al.* 2000]. Future studies might take this factor into account when trying to explain variability in measured bone status by QUS.

In conclusion, QUS is a feasible and a noninvasive method for measuring bone status in a population with ID and epilepsy. Moreover, future application of QUS as a screening method for the diagnosis of osteoporosis and osteopenia should be considered. Specifically in institutions with a population with epilepsy, chronic AED use and ID, the benefits of QUS as a screening method seem to outweigh the potential disadvantages. In a population with such a high prevalence of osteoporosis and osteopenia the actual number of misdiagnosed cases stays low. Also, its mobility and ease of use make it a suitable method for repeated measurements, thereby increasing its reliability.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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