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Quantitative ultrasound for monitoring bone status in institutionalized adults with refractory epilepsy and intellectual disability: A 7-year follow-up study

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ABSTRACT

Purpose: Long-term exposure to anti-epileptic drugs has been shown to decrease bone mineral density (BMD). The aim of this 7-year follow-up study was to explore changes in bone status, using quantitative ultrasound (QUS) and Dual-energy X-ray Absorptiometry (DXA) in adults with refractory epilepsy and intellectual disability (ID) residing at a long-term care facility. Both measurements can be challenging to conduct in this population.
Methods: In 2009 and 2016, a total of 126 patients (18–79 years) underwent QUS of the heel and DXA of lumbar spine (LS) and hip (femoral neck (FN) and total hip (TH)). Subgroup analysis was performed for patients with (group A, n = 53) and without (group B, n = 73) bisphosphonate use during follow-up.
Results: Overall, weak to moderate correlations between changes in DXA and QUS parameters were found. For group A, correlations varied from r = .31 to .59, whereas correlations did not exceed r = .40 in group B. Patients in group A showed a larger increase or a smaller decrease in BMD for all DXA regions during follow-up ($p < .001$ for ΔLS and ΔFN BMD, $p = .001$ for ΔTH BMD). For change in QUS parameters, no significant difference between groups was found.
Conclusion: In this study we demonstrated the limited use of QUS in the monitoring of bone status in our study population. Although correlations between changes in QUS parameters and axial DXA are positive and mostly significant, QUS only explains little of the variability in DXA values and is inadequate for measuring treatment response in this population.

1. Introduction

Worldwide, approximately 50 million people suffer from epilepsy [1]. Although most patients benefit from treatment with anti-epileptic drugs (AEDs), a minority of patients does not respond to AEDs even with adequate dosage in either mono- or polytherapy [2].

Long-term exposure to (particularly enzyme-inducing) AEDs has been shown to decrease bone mineral density (BMD) [3,4]. A high prevalence of osteoporosis and osteopenia (32% and 48%, respectively) has been found in patients with refractory epilepsy and intellectual

Abbreviations: AEDs, anti-epileptic drugs; BMD, bone mineral density; BUA, broadband ultrasound attenuation; DXA, dual-energy X-ray absorptiometry; Est.heel, estimated heel; FN, femoral neck; IC, informed consent; ID, intellectual disability; LSC, least significant change; LS, lumbar spine; nLSC, negative least significant change; pLSC, positive least significant change; QUS, quantitative ultrasound; SD, standard deviation; SE, standard error; SOS, speed of sound; TH, total hip

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disability (ID) residing in a long-term care facility [5].

The current gold standard for diagnosing osteoporosis is Dual-energy X-ray Absorptiometry (DXA). However, its feasibility is limited in institutionalized patients with epilepsy, who often suffer from intellectual and physical comorbidities. The required transport of the patient to a radiology facility and patient cooperation can be challenging in this population.

An alternative method of assessment of bone status is Quantitative Ultrasound (QUS). Best measured at calcaneal site [6], QUS is relatively low-cost, quick and easy to use, portable and free of radiation. Nonetheless, correlations between calcaneal QUS and axial DXA parameters in identifying low BMD are only moderate at best [7–11]. Although suitable for fracture risk prediction [12], QUS is not considered a suitable replacement for DXA in diagnosing osteoporosis [13]. To our knowledge, correlations in a population of patients with epilepsy (and ID) were only published by our research group in a cross-sectional study. These correlations between calcaneal QUS and axial DXA parameters were classified as moderate to strong [14].

Institutionalized patients with epilepsy (and ID) are at increased risk of low BMD and fractures due to chronic AED use, cumulative drug load [15], seizure-related trauma, and, in many cases, because of limited mobility. Therefore, adequate monitoring of bone status is of utmost importance in this specific group. Currently, there are no guidelines on monitoring bone status in patients with epilepsy.

The aims of this study are *(1)* to explore changes in bone status using two bone imaging techniques (DXA vs QUS) in patients with refractory epilepsy, chronic AED use and intellectual disabilities, and *(2)* to explore the effect of bisphosphonates on these changes. Based on the hypothesis of a positive correlation, we determine the correlation between changes in calcaneal QUS (as the method of interest) and axial DXA (as the gold standard) parameters over 7-year follow-up.

2. Material and methods

2.1. Patients

In 2009, all adult patients (n = 261) of a long-term care facility for people with epilepsy and ID were invited to participate in this study. All of the patients have a history of epilepsy and long-term AED use, caused by a variety of factors (i.e. structural, genetic, infectious, metabolic, immune or unknown). Most of the patients (98.4%) also have an intellectual disability, ranging from mild to profound (see Table 1).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local medical ethical committee of Kempenhaeghe, Heeze in the Netherlands. Patients and/or their legal representatives gave informed consent prior to inclusion. For safety reasons, female patients had to declare not to be pregnant at the time of the study.

Participants underwent calcaneal QUS measurements and DXA measurements of hip and lumbar spine (L1-L4) in 2009 (T0) and 2016 (T1). Standard operating procedures from the manufacturer's manual were followed. During measurements, patients were accompanied by a nurse and/or family member. Measurements would not take place if a patient showed signs of resistance.

If indicated after baseline measurement, patients started treatment with bisphosphonates, calcium and/or cholecalciferol, in accordance with the Dutch guidelines [16].

2.2. Measurement by DXA

Trained radiographers carried out DXA measurements (Hologic Discovery/W at T0, Hologic Discovery/A at T1) in September 2009 and October and November 2016. All patients' measurements of lumbar spine (LS), total hip (TH) and femoral neck (FN) were compared with an age-, race- and sex-matched reference database provided by the manufacturer. If possible, patients were measured at the left hip. In case of non-matching (left and right) hip measurements, patients were excluded from hip analyses.

DXA measures BMD in g/cm^2 and converts it to a T-score (the number of standard deviations (SD) below peak bone mass) and Z-score (number of SD below age- and sex-matched controls). The World Health Organization defines osteoporosis as a T-score of $\leq$-2.5 SD, based upon the lowest T-score of FN, TH or LS [17]. A T-score between -1.0 and -2.5 SD is defined as osteopenia, a T-score of $\geq$-1.0 SD as normal.

Vertebral fracture assessment and BMD imaging analysis were done by one author (JB), who screened all lumbar DXA scans for deformation according to the Genant classification [18] of vertebral fractures. Fractured vertebra and vertebrae significantly affected by artefacts were excluded from BMD analysis. In case of exclusion of more than two vertebrae [19], patient's LS DXA was excluded from analysis. When in doubt, a second researcher was consulted for consensus (JvdB).

2.3. Measurement by QUS

A duo of trained operators carried out QUS measurements of the calcaneus using the non-imaging Sahara Clinical Bone Sonometer by Hologic at both T0 and T1. All QUS measurements were performed within six months after DXA measurements. If possible, patients were measured at the left heel. In case of non-matching (left and right) heel measurements, patients were excluded from the study. The lower leg of the seated patient was immobilized by a positioning aid to minimize movement artefacts and maximize reproducibility. Quality control was assessed daily with a phantom.

The Sahara device assesses bone by measuring the propagation of ultrasound waves between two transducers at varying frequencies. At a fixed region of interest in the midcalcaneus, it measures the speed of sound (SOS, in m/s) and broadband ultrasound attenuation (BUA, in dB/MHz) of an ultrasound beam passed through the calcaneus. Subsequently, it combines these results linearly to obtain a third parameter: Estimated heel Bone Mineral Density (Est. heel BMD, g/cm^2). The lower these values, the lower the bone status.

2.4. Data analysis

Statistical analyses were done by one author (SC) using IBM® SPSS® Statistics 24 (SPSS, RRID: SCR_002865). All data were entered into the database (JB) and verified (SC). Data were tested for normal distribution. The statistical significance level was set at $p < .05$.

2.4.1. DXA versus QUS

Changes in BMD and QUS parameters during follow-up were expressed as Δ[parameter] in absolute units. We computed two-tailed Pearson's correlation coefficients r to assess the relationship between changes in calcaneal QUS parameters and axial DXA parameters; r^2 shows the percent of variance in the DXA values explained by the QUS values.

2.4.2. Treated versus untreated patients

To determine the effect of bisphosphonate treatment on densitometer values, we performed a subgroup analysis for two groups. Group A was defined as the patients who have been treated with any type of bisphosphonate at any point of time between T0 and T1. Group B consisted of patients who were not in need of bisphosphonate treatment.

Unpaired T test, chi-squared test and Mann-Whitney U test were used to compare clinical data and the measured variables. Two-tailed paired T tests were used to compare the changes with baseline values within the same group.

2.4.3. Least significant changes

To distinguish between an apparent measurement change that is within the range of error of the test versus one that is statistically

Table 1
Baseline characteristics of all patients (Total), patients treated (Group A) and patients not treated with bisphosphonates (Group B).

	Total (n = 126)		Group A (n = 53)		Group B (n = 73)		*p* value
	n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	
Age (years)		44.6 ± 15.4		50.7 ± 14.5		40.3 ± 14.7	< .001**
Sex							.658
Male	78	61.9	34	64.2	44	60.3	
Female	48	38.1	19	35.8	29	39.7	
BMI (kg/m2)		25.6 ± 4.16		25.0 ± 3.42		26.1 ± 4.59	.129
< 18.5	2	1.6	1	1.9	1	1.4	
18.5-24.99	57	45.2	27	50.9	30	41.1	
25-29.99	45	35.7	19	35.8	26	35.6	
≥30	22	17.5	6	11.3	16	21.9	
Intellectual disability (IQ score)							.751
Normal	2	1.6	2	3.8	0	0	
Mild (55-70)	36	28.6	15	28.3	21	28.8	
Moderate (40-55)	49	38.9	20	37.7	29	39.7	
Severe (25-40)	32	25.4	12	22.6	20	27.4	
Profound (< 25)	7	5.6	4	7.5	3	4.1	
Barthel scale							.096
20	16	12.7	5	9.4	11	15.1	
15-19	45	35.7	18	34.0	27	37	
10-14	32	25.4	10	18.9	22	30.1	
5-9	17	13.5	9	17.0	8	11.0	
0-4	16	12.7	11	20.8	5	6.8	
Ambulatory status							.003*
Immobile	13	10.3	10	18.9	3	4.1	
Independent in wheelchair	15	11.9	9	17.0	6	8.2	
Walk with aid (verbal/physical)	8	6.3	3	5.7	5	6.8	
Walk without aid	90	71.4	31	58.5	59	80.8	
Epilepsy duration (years)		38.9 ± 13.8		43.1 ± 12.5		35.9 ± 14.0	.004*
Cholecalciferol and/or calcium use							< .001**
Yes	86	68.3	46	86.8	40	54.8	
No	40	31.7	7	13.2	33	45.2	
Number of AEDs used							.613
0	6	4.8	4	7.5	2	2.7	
1	11	8.7	6	11.3	5	6.8	
2	40	31.7	13	24.5	27	37.0	
3	49	38.9	23	43.4	26	35.6	
4	18	14.3	7	13.2	11	15.1	
5	2	1.6	0	0	2	2.7	
SOS (m/s)		1519.6 ± 27.3		1506.0 ± 22.2		1529.3 ± 26.5	< .001**
BUA (dB/MHz)		50.3 ± 19.5		41.1 ± 17.2		56.9 ± 18.4	< .001**
Est. heel BMD (g/cm^2)		0.382 ± 0.117		0.323 ± 0.096		0.425 ± 0.112	< .001**
LS BMD (g/cm^2)		0.966 ± 0.158		0.875 ± 0.149		1.031 ± 0.131	< .001**
FN BMD (g/cm^2)		0.710 ± 0.136		0.621 ± 0.100		0.770 ± 0.124	< .001**
TH BMD (g/cm^2)		0.842 ± 0.156		0.735 ± 0.126		0.914 ± 0.132	< .001**

*p < .05, **p < .001. SD = standard deviation, AEDs = anti-epileptic drugs, SOS = speed of sound, BUA = broadband ultrasound attenuation, Est. heel BMD = estimated heel bone mineral density, LS = lumbar spine, FN = femoral neck, TH = total hip.

significant, we used a Least Significant Change (LSC) as reported in literature. If necessary, the LSC with 95% confidence interval was determined by multiplying the precision error (calculated as root mean square SD) by 2.77 [20]. LSCs in g/cm^2 of 0.0232 for LS, 0.0335 for FN and 0.0306 for TH in the Discovery/A densitometer were reported [21]. For the Discovery/W, LSCs in g/cm^2 of 0.046 for LS, 0.034 for FN and 0.024 for TH were reported [22]. LSCs of 8.587 dB/MHz, 16.066 m/s and 0.05817 g/cm^2 were calculated from reported short term precision errors for BUA, SOS and Est. heel BMD respectively [23]. Percentages of patients' changes exceeding the LSC for each of the parameters were calculated for each group.

3. Results

The results of 126 patients, 18–79 years, were analyzed and reported in this study (Fig. 1). One patient had missing data for SOS and BUA.

During follow-up, 53 patients received bisphosphonate treatment (group A), whereas 73 patients did not (group B). Patients in group A had a significantly higher age, worse ambulatory status, longer epilepsy duration and higher rates of cholecalciferol and/or calcium use (Table 1). All baseline QUS and DXA values were significantly lower in group A than in group B (p < .001). Sixteen different AEDs were used by our study population at T0 (Table 2).

Boxplots of changes in bone data measured with DXA and calcaneal QUS during follow-up are presented in Fig. 2. Both group A and group B demonstrated a significant mean change in SOS and BUA compared to baseline (p < .001), but not in Est. heel BMD. All mean changes in DXA parameters compared to baseline reached significance for both groups (p = .002 for ΔLS BMD and p= < .001 for ΔFN and ΔTH BMD in group B; p = .042, .040 and .001 for ΔFN BMD, ΔTH BMD and ΔLS BMD in group A).

When mean changes between groups are compared, patients in group A show a larger increase or a smaller decrease in BMD for all DXA regions during follow-up (p < .001 for ΔLS and ΔFN BMD, p = .001 for ΔTH BMD). A significantly higher proportion of patients had a FN and LS BMD increase exceeding the pLSC (p < .001 and p = .004, respectively) and a significantly lower proportion had a BMD decrease exceeding the nLSC (p = .001 for ΔLS BMD, p < .001 for ΔFN and ΔTH BMD) in group A than in group B (Table 3). There was no difference in change in QUS parameters between group A and B, including the proportion of patients exceeding the pLSC or nLSC.

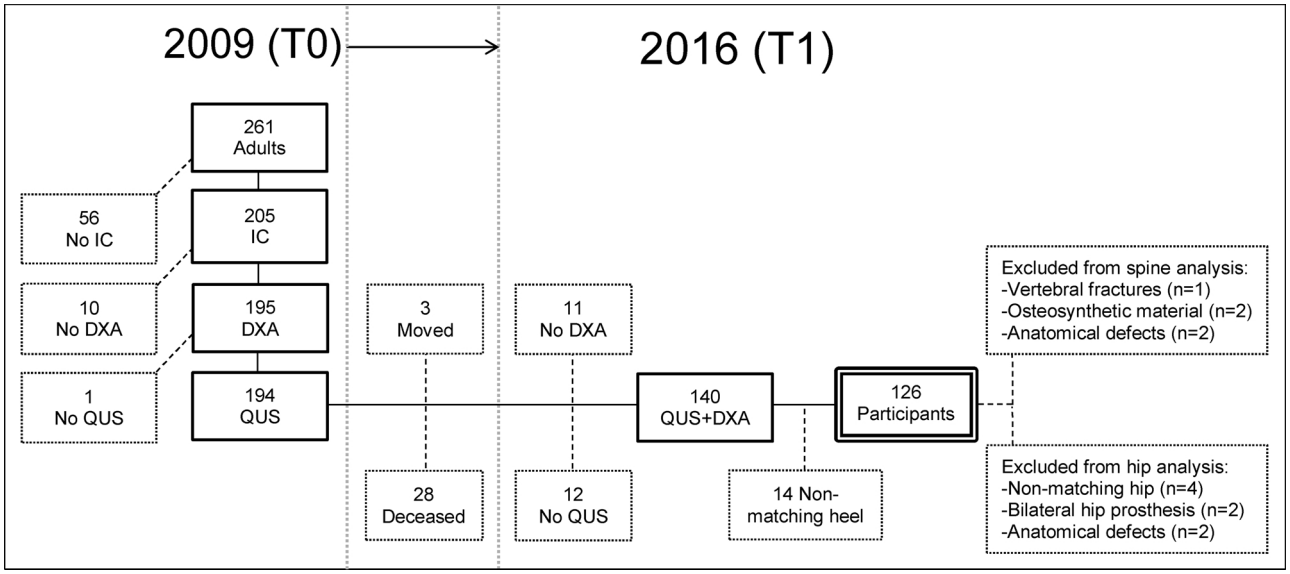

Fig. 1. Flowchart of participants.
IC = Informed Consent, DXA = Dual-energy X-ray Absorptiometry, QUS = Quantitative Ultrasound

Table 2
Types of anti-epileptic drugs used (n = 126).

	n	%
Carbamazepine	77	61.1
Valproic acid	53	42.1
Lamotrigine	46	36.5
Phenytoin	31	24.6
Levetiracetam	24	19.0
Clonazepam	22	17.5
Topiramate	18	14.3
Oxcarbazepine	16	12.7
Phenobarbital	15	11.9
Gabapentin	6	4.8
Pregabalin	5	4.0
Ethosuximide	3	2.4
Zonisamide	2	1.6
Felbamate	1	0.8
Lacosamide	1	0.8
Rufinamide	1	0.8

Correlations are presented in Table 4. ΔBUA and ΔEst. heel BMD were positively correlated with all DXA measurements for group A (r = .31-.59; p = .033- < .001). As for ΔSOS, only ΔLS BMD was significantly correlated in this group (r = .37; p = .009). In group B, ΔSOS did not correlate significantly with any of the DXA values. ΔBUA and ΔEst. heel BMD only correlated with changes in hip DXA measurement (ΔFN BMD and ΔTH BMD)(r = .31-.40; p = .009-.001). Overall, best correlations were seen for changes in hip DXA and ΔBUA.

Within group A, ΔLS BMD and ΔTH BMD were significantly larger for patients starting bisphosphonate treatment after T0 measurement (p = .034 and .024, respectively) than for patients already on treatment. For ΔFN BMD this difference was borderline significant (p = .054). The mean duration of treatment before T0 for patients already on treatment at T0 (n = 24) was 52 months (± 35 months). No significant difference was found between patients ending treatment ≥ two years prior to T1 measurement and patients ending treatment thereafter, and between patients receiving bisphosphonates more or less than five years within follow-up.

4. Discussion

This cohort study shows that compared to DXA, QUS performs inadequate in monitoring changes in bone status in patients with refractory epilepsy, chronic AED use and intellectual disabilities during seven years of follow-up.

4.1. DXA versus QUS

Overall, we observed weak to moderate [24] correlations between changes in DXA and QUS parameters. Our study results were similar to that of Trimpou et al. [25], who performed multiple measurements in seven years. Frost et al. [26] used the Sahara device to find moderate correlations between changes in QUS and DXA measurement variables after two years. Interestingly, a four-year study of monitoring alendronate therapy revealed correlations as high as r = .64 and .52 for ΔSOS and ΔBUA with ΔLS BMD [27]. This may be caused by the homogeneity of their study population, consisting of postmenopausal women without intake of drugs known to interfere with bone metabolism, who were all receiving calcium supplements due to osteoporosis.

One possible explanation for the moderate correlations we observed is differences in properties measured. After all, QUS has been widely suggested to provide information on bone structure in addition to bone density, as measured by DXA [28]. Moreover, the heterogeneity of the calcaneus in both density and structure could affect measurement results in different regions of interest [28]. We used a non-imaging QUS device with fixed transducers. Because of the inhomogeneous aspect of the calcaneus, rotation and shift of the foot can have great impact on BUA and SOS with repeated measurement [29]. Using an imaging device that provides accurate control of positioning has been suggested to aid in overcoming positioning errors, though no proof could be found to support this advantage of imaging [13].

4.2. Treated versus untreated patients

Whereas all DXA measurements' response to bisphosphonate therapy was a bone gain or prevention of bone loss for patients in group A, for QUS we found no difference between both groups. The poor precision of QUS (compared to DXA) may require longer time intervals to detect significant changes in bone status, also known as monitoring time interval. Indeed, the LSC for QUS measurements has been found to be three times that of DXA measurements [26]. One would expect that our 7-year follow-up covered this monitoring time interval. However, from our results it appears that bisphosphonates affect bone density, and not so much bone structure; or perhaps the effect of

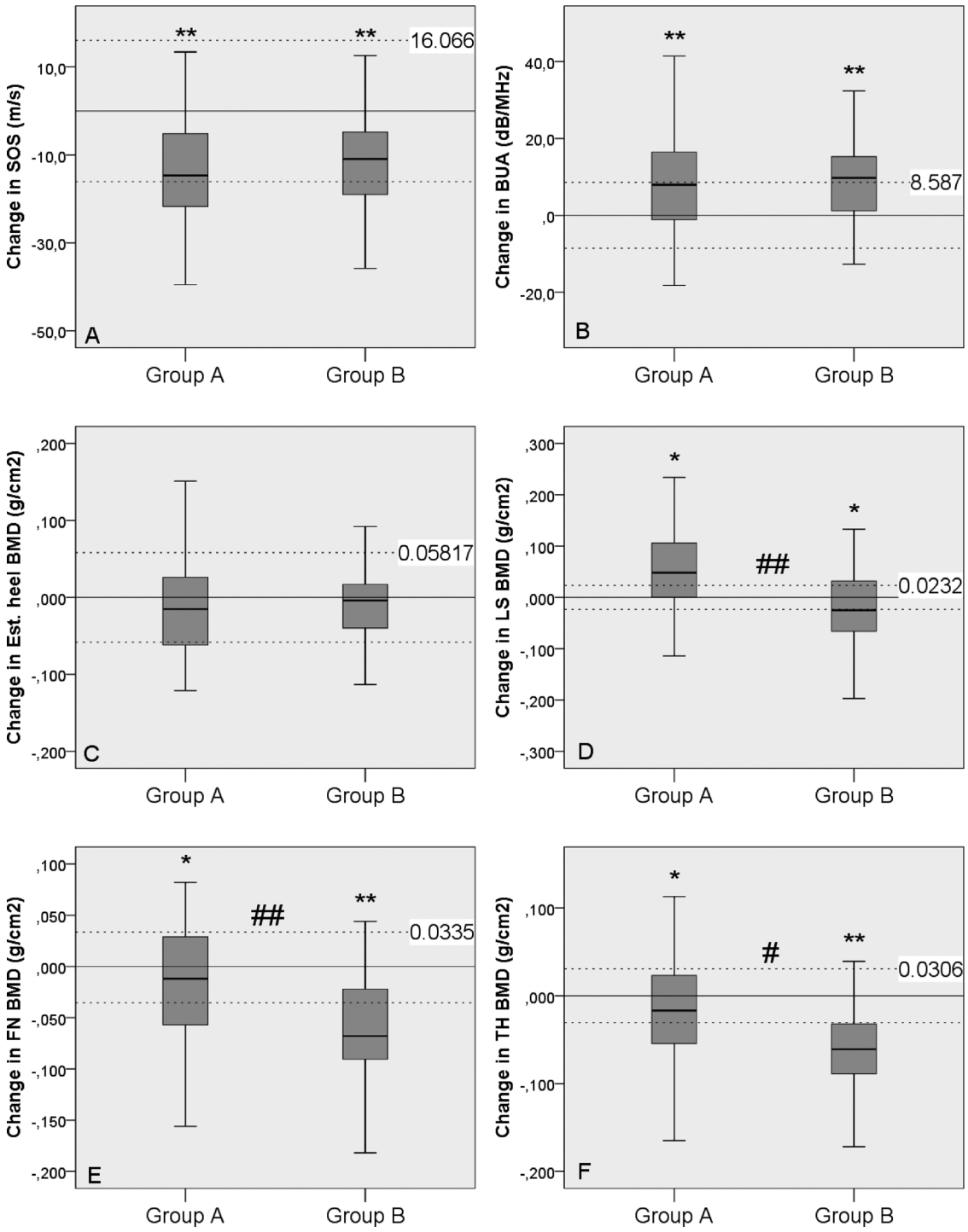

Fig. 2. Absolute changes of bone data measured in patients treated (group A) and patients not treated with bisphosphonates (group B) for A.) Speed of sound, B.) Broadband ultrasound attenuation, C.) Estimated heel BMD, D.) Lumbar spine BMD, E.) Femoral neck BMD and F.) Total hip BMD.
Positive and negative Least Significant Changes are shown as interrupted lines. *p < .05, **p < .001 versus baseline, #p < .05, ##p < .001 between groups. SOS = speed of sound, BUA = broadband ultrasound attenuation, Est. heel BMD = estimated heel bone mineral density, LS = lumbar spine, FN = femoral neck, TH = total hip

bisphosphonates on bone density lasts longer. The latter is supported by the fact that Frost et al. [26] did find a significant difference in QUS parameter change between treated and untreated groups after one and two years of follow-up, just like Gonnelli et al. [27] did after four years. Nevertheless, ΔLS BMD was also the best responder to treatment in several other studies [26,30]. This may be caused by the high percentage of trabecular bone in vertebrae, which due to its high surface-to-volume ratio has a higher turnover rate than cortical bone. As mentioned earlier, patients in group A were more often wheelchair-bound; their body position may result in a higher bone turnover rate and higher bisphosphonate response in the spine, compared to the hip.

Although a smaller mean decrease in FN and TH BMD was found in group A than in group B, one would expect a bone gain in treated patients in all DXA parameters. The decrease in FN and TH BMD we found despite treatment is probably the result of contributing risk factors, such as ongoing AED use, limited mobility and little sun exposure. Why

Table 3
Mean changes with standard errors (SE) and number *n* (%) of patients treated (group A) and patients not treated with bisphosphonates (group B), exceeding the positive or negative Least Significant Change (pLSC and nLSC, respectively) for each of the QUS and DXA parameters.

		Group A (n = 53)			Group B (n = 73)		
	LSC	Mean change ± SE	n (%) exceeding pLSC	n (%) exceeding nLSC	Mean change ± SE	n (%) exceeding pLSC	n (%) exceeding nLSC
SOS (m/s)	(-)16.066	−13.581 ± 2.691	5 (9.6)	22 (42.3)	−10.863 ± 1.913	5 (6.8)	29 (39.7)
BUA (dB/MHz)	(-)8.587	7.325 ± 1.801	24 (46.2)	7 (13.5)	8.968 ± 1.327	40 (54.8)	6 (8.2)
Est.heel BMD (g/cm^2)	(-)0.05817	−0.015 ± 0.010	8 (15.1)	14 (26.4)	−0.005 ± 0.007	11 (15.1)	15 (20.5)
LS BMD (g/cm^2)	(-)0.0232	0.043 ± 0.012**	31 (62.0)**	11 (22.0)*	−0.029 ± 0.009	21 (29.6)	36 (50.7)
FN BMD (g/cm^2)	(-)0.0335	−0.020 ± 0.010**	10 (21.3)*	14 (29.8)**	−0.063 ± 0.007	3 (4.2)	45 (63.4)
TH BMD (g/cm^2)	(-)0.0306	−0.021 ± 0.010*	8 (17.0)	19 (40.4)**	−0.064 ± 0.008	5 (7.0)	54 (76.1)

*p < .05, **p < .001 in comparison with group B. LSC = least Significant Change, SE = standard error, SOS = speed of sound, BUA = broadband ultrasound attenuation, Est. heel BMD = estimated heel bone mineral density, LS = lumbar spine, FN = femoral neck, TH = total hip.

Table 4
Correlation coefficients *r* (p values) between absolute changes (Δ) in QUS and DXA parameters over 7 years for patients treated (group A) and patients not treated with bisphosphonates (group B).

	ΔSOS	ΔBUA	ΔEst. heel BMD
$\Delta LS\ BMD_A$	.37* (.009)	.38* (.008)	.43* (.002)
$\Delta FN\ BMD_A$	.15 (.333)	.47* (.001)	.31* (.033)
$\Delta TH\ BMD_A$	.22 (.148)	.59** (< .001)	.42* (.003)
$\Delta LS\ BMD_B$	.13 (.290)	.14 (.243)	.15 (.213)
$\Delta FN\ BMD_B$	.22 (.065)	.40* (.001)	.34* (.004)
$\Delta TH\ BMD_B$	.20 (.088)	.37* (.002)	.31* (.009)

*p < .05, **p < .001. SOS = speed of sound, BUA = broadband ultrasound attenuation, Est. heel BMD = estimated heel bone mineral density, LS = lumbar spine, FN = femoral neck, TH = total hip.

ΔBUA showed an increase in values in both groups remains unexplained. Several studies [26,30] also demonstrated that changes in BUA can be opposite to that of SOS, others contradicted this [27].

4.3. Least significant changes

We did not determine precision errors for QUS or DXA, nor did we carry out cross-calibration for DXA. Precision errors vary across different devices and parameters measured and are affected by intra-system performance stability (calibration shift or drift), inter-system changes, the patients being tested, and by the technologist's skill level [13,19,31,32]. Thus, precision errors of similar systems reported in literature could not be used to calculate a generalized LSC for inter-system quantitative comparisons in our study. Consequently, an accurate interpretation of repeated measurements was not possible. Yet, to give a rough impression of treatment response, we used LSCs that were based on the Discovery/A [21]. Nevertheless, performing precision assessment would be virtually impossible in our study population. First of all, we did not want to repeat measurements and expose patients to ionizing radiation unnecessarily. Secondly, compared to a community based population, it is more likely that patients are unable to maintain position required for making bone density images – thereby increasing short-term precision errors.

Frost et al. [26] studied postmenopausal women who started bisphosphonate and/or estrogen therapy at baseline and reported that all axial DXA and calcaneal QUS measurements showed a significant response to treatment after 2 years. However, only 23.5% and 5.9% of the women displayed changes in BUA and SOS that exceeded the LSC, whereas 94.1% exceeded the LSC for LS, 50% for TH and 6.3% for FN BMD. Note that the LSCs used in this study were derived from long-term precision errors. The difference from our observations could be explained by our longer follow-up duration as well as our choice to combine de novo patients and patients already on bisphosphonate treatment at T0 into group A. However, since our LSCs were extracted from literature and not calculated from our own study population, a reliable comparison is not possible.

4.4. Challenges in patients with intellectual and physical comorbidities

Our study is unique in the way that it did not exclude patients who were taking medication known to influence bone metabolism, i.e. AEDs, and who were of limited mobility. Consequently, it is difficult to compare study results to other studies. Some factors specific for our study population may have affected test results. For instance, behavioral problems associated with ID may have led to movement errors. In order to offer a familiar surrounding and to reduce the need for traveling (for some patients a very stressful event), measurements were done at the residential facility. Moreover, anatomical defects made interpretation of scans difficult in some cases. On the other hand, medication compliance (to bisphosphonates) is considered high in this population, since the caregivers administer all medication.

4.5. Strengths and limitations

Our study is limited by the fact that measurements at T0 and T1 were not performed using the same DXA device, thereby affecting precision. To mitigate this disadvantage, DXA bone densities were compared by means of differences in absolute BMD rather than T-score, thereby avoiding differences in reference databases of the two densitometers [32]. Also, we analyzed both series of scans using the same software version (13.5.3).

As for the ultrasound, several manufacturers and types of devices exist. The only validated site for the use of QUS is the heel [6,13]. The Sahara device is among the most and best tested heel devices and more proven effective than others [33,34], justifying its use in our study.

QUS and DXA measurements did not take place on the same day, due to personnel capacities. QUS measurements were performed within six months after DXA measurements (on average 67 ± 32 days). When it comes to the total follow-up time, we do not expect this extra time interval to have affected bone status and therefore measurement results.

Another limitation is that we assigned every patient that had been treated with bisphosphonates between T0 and T1 to group A. This included patients that received ongoing treatment at T0 and those who discontinued treatment before T1. It is possible that the first group had reached a plateau for BMD increase before T0 measurement, while the latter group may have (partially) lost treatment success after discontinuation before T1 measurement. Indeed, we observed a difference in changes in DXA values between patients starting and already on treatment at T0, similarly to Frost et al. [26].

We did not control for possible confounders such as cumulative drug load, genetic syndromes, comorbidities, physical mobility or nutritional status. A review by Beerhorst et al. [35] suggests several risk factors for bone disease in patients on chronic AED therapy, such as polytherapy, treatment duration and type of AED used. Also impaired physical mobility and institutionalization are mentioned to be especially important in a population of patients with chronic epilepsy.

A strength of this study is the relatively large sample size for this specific population. Another strength is that all DXA scans were analyzed by one author. Lastly, this is one of the few studies of this subject with a follow-up duration of as much as seven years.

5. Conclusion

In this 7-year follow-up study we demonstrated the limited use of QUS in monitoring osteoporosis in adult inpatients with refractory epilepsy, chronic AED use and intellectual disabilities. Although correlations between changes in QUS and axial DXA parameters are positive and mostly significant, changes in QUS only explain little of the variance in DXA values. Also, QUS is inadequate for measuring treatment response in our population. Despite QUS' advantages of being low-cost, portable and radiation free - which make it more feasible to use in our population – the results of this study implicate that the use of DXA in monitoring treatment effects remains warranted.

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