Osteoporosis and fractures in institutionalized patients with refractory epilepsy and intellectual disability

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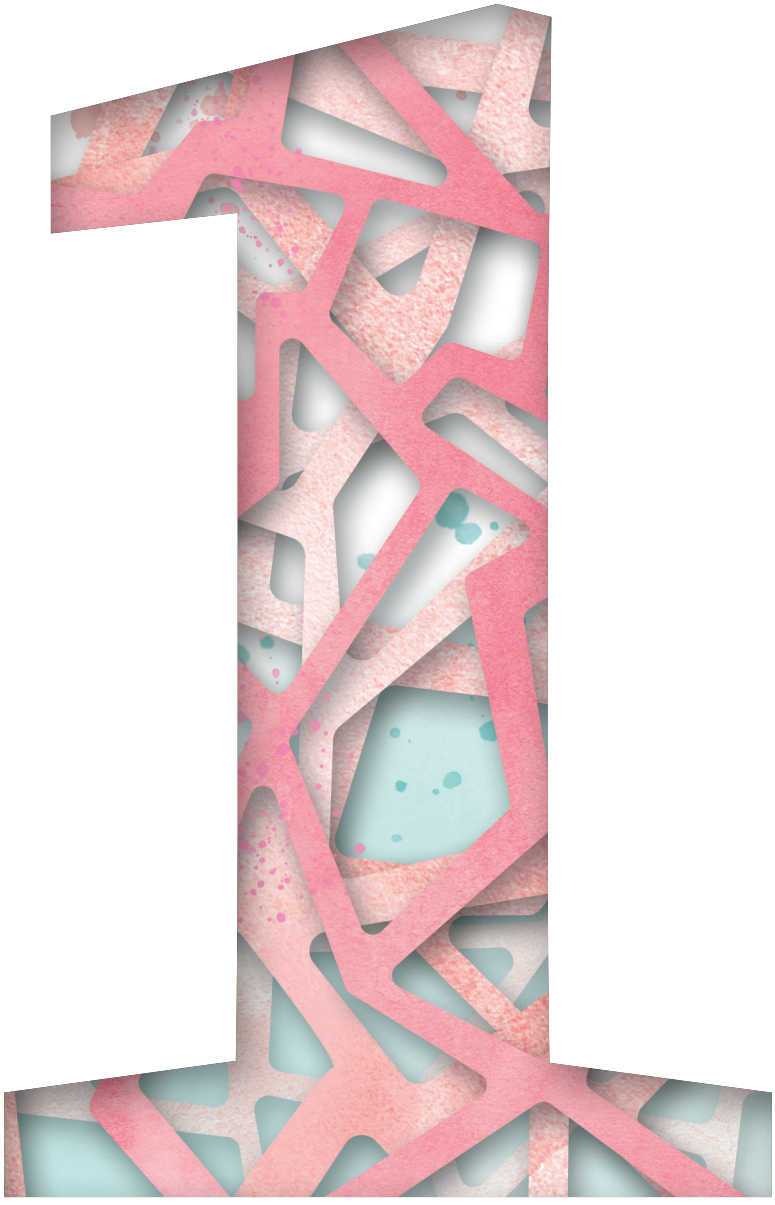

General introduction

INTRODUCTION

Epilepsy and antiseizure medication

Epilepsy is one of the most common neurological diseases; globally, an estimated 50 million people are affected[1]. In the Netherlands, each year approximately 11,000 new patients are diagnosed[2]. In 2017, the total cost of epilepsy in the Netherlands was estimated at 304.1 million euro, which accounts for 0.35% of the total costs in health care[3]. About 29.5 million euro are costs of medication, the number one treatment of epilepsy. Even though antiseizure medication can effectively control seizures in 70% of the patients with epilepsy, a minority continues to have refractory seizures[1]. Seizures increase the risk of injury, hospitalization and mortality and decrease the quality of life[4]. Additionally, several medical, psychiatric and cognitive disorders are highly prevalent in patients with epilepsy[5]. In a childhood epilepsy cohort, 21.2% of the patients was diagnosed with some degree of intellectual disability, predominantly severe to profound[6]. The co-existence of epilepsy increases with increasing severity of intellectual disability; it is estimated that the prevalence of epilepsy is at least twenty times higher in patients with intellectual disability than in the general population[7,8].

Despite beneficial effects on the amount and/or severity of seizures, antiseizure medication may cause side effects, such as fatigue, sedation, ataxia, gastro-intestinal problems and/or bone mineral disorders[9]. In 1968, Kruse[10] found X-ray evidence of osteomalacia in 15% of young patients with epilepsy. In addition, he reported a reduced serum concentration of calcium and phosphate and a raised serum concentration of alkaline phosphatase. Two years later, his findings were confirmed in adult patients with epilepsy in the study of Richens and Rowe[11]. They hypothesized that the abnormalities they found were the result of vitamin D deficiency. Later that year, Dent *et al*.[12] treated two patients with epilepsy using a combination of ultraviolet light and vitamin D supplementation and saw a rapid healing of osteomalacia in both of them. In addition to the described biochemical abnormalities, a decreased bone mineral density (BMD) has been reported in patients on antiseizure medication[13-16], especially when used in polytherapy[17]. In the first reports about bone diseases and antiseizure medication, the focus was on enzyme-inducing antiseizure medication such as phenytoin, phenobarbital and primidone. It is suggested that the induction of the cytochrome P450 enzyme in the liver, results in an increased catabolism of vitamin D, which leads to a lower biologically active vitamin D, resulting in decreased intestinal absorption of calcium and secondary hyperparathyroidism[18,19]. However, also newer, non-enzyme-inducing antiseizure medication have been reported to affect bone and decrease BMD, in human[19-24] and animal studies[23,25-28].

Bone imaging, Osteoporosis and Fractures

With its origins in the 1960s, dual-energy X-ray absorptiometry (DXA) has become the gold standard for measuring BMD[29]. For DXA, patients are required to lie in specific horizontal positions, without moving. DXA is primarily used to scan the lumbar spine and hip. Bone mineral density is reported in gram/cm^2 and in T- and Z-scores. Normative BMD values are provided by the manufacturer of the DXA scanner, based on the NHANES III database[30]. A Z-score is the number of standard deviations below or above the average peak BMD of individuals of the same age and sex. A T-score is the number of standard deviations below or above the average peak BMD of healthy young individuals of the same sex. A T-score ≥-1 equals a normal BMD, a T-score between -1 and -2.5 indicates low BMD or osteopenia. A severe form of low BMD, osteoporosis, is indicated by a T-score ≤-2.5[29]. According to the official definition, osteoporosis is characterized by "a low bone mass and microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture"[31].

When using DXA for the measurement of BMD, it is known that for each standard deviation decrease in BMD at the hip and/or spine, the relative risk of fractures increases by approximately 1.5 and the risk of major osteoporotic fractures (MOF; at the proximal humerus, forearm, hip and vertebrae) by 2.6[32,33]. Incident fractures, especially after the age of 50, are associated with an increased risk of subsequent fractures and an increased mortality rate[34]. Seizures[14,35] and (seizure-related) falls[36] may lead to both vertebral and non-vertebral fractures in patients with epilepsy. It is estimated that the risk of non-vertebral fractures is two to six times higher than in patients without epilepsy[14-16]. However, most studies about osteoporosis and fracture risk in patients with epilepsy, only focused on outpatients.

Using DXA, lateral images of the thoracic and lumbar spine (T4 to L4) can be obtained for vertebral fracture assessment (VFA). In general, vertebral fractures (VFs) are the most frequent osteoporotic fractures[37-39] and in two third of the patients, VFs occur asymptomatic[40-42]. VFs can be graded by morphometric assessment according to the method of Genant *et al.*[43], as mild (20-24% reduction in height), moderate (25-40% reduction in height) or severe (>40% reduction in height).

Several aspects may lead to a poor quality of DXA scans and a low accuracy and/or precision of the measurement. One of the most critical aspects is positioning of the patient[44]. In two retrospective studies, involving a standard care outpatient population, 12% to 83% of the scans showed improper patient positioning[45,46]. In patients with both behavioral and physical comorbidity, these percentages might even be higher. Contractures, scoliosis, movement, osteosynthetic material, intracorporal medical devices et cetera, might disrupt

DXA outcomes[47]. A more feasible and noninvasive method to measure BMD is the use of quantitative ultrasound of the heel (QUS). QUS is portable and quick and easy to use. In the study of Beerhorst *et al.*[48], strong and positive correlations had been found between DXA and QUS T-scores in adult patients with epilepsy and intellectual disability. It was concluded that QUS as a screening method for the diagnosis of osteopenia and osteoporosis was feasible and confirmed the advantages of QUS over DXA regarding mobility and ease of use.

A relatively recent development is assessment of the Trabecular Bone Score (TBS). TBS is a score that indicates the microarchitecture of the bone[49]. It can be calculated through a software application that can be installed on a DXA computer and can be run simultaneously with DXA scans[50]. No additional scanning time is required. For the analysis, a 2D image with pixel-to-pixel gray-level variations is generated by projecting the trabecular microstructure of the bone onto a plane. A 3D structure is estimated using a variogram (calculated as the sum of the squared gray-level differences between pixels at a specific distance). TBS (unitless) is then calculated as the slope of the log-log transform of the variogram, where the slope characterizes the rate of gray-level amplitude variations[50]. A TBS value of 1.310 or above is considered as normal microarchitecture, a TBS value between 1.230 and 1.310 as partially degraded microarchitecture and values below 1.230 as degraded microarchitecture[51]. In patients with primary osteoporosis and several types of secondary osteoporosis (diabetes, primary hyperparathyroidism, rheumatoid arthritis, adrenal incidentaloma, chronic kidney disease, HIV and in individuals on long-term glucocorticoid therapy), it has been shown to enhance fracture risk prediction[52,53].

While quite some research has been carried out on DXA measurements in patients on chronic antiseizure medication, much less is known about the use of VFA, QUS and TBS in this group especially vulnerable for low bone quality and fractures.

Refractory epilepsy and intellectual disability

Fractures can significantly reduce quality of life[54], especially in patients who are already dependent on others for their daily living. Even minor fractures can severely impact one's life and impair the last bit of independence. In patients with refractory epilepsy and intellectual disability who are admitted in residential care, several other factors may contribute to the risk of low bone quality and fractures, besides the chronic use of antiseizure medication, seizures and (seizure-related) falls. Intellectual disability[55,56], leading to severe neurological impairments[57] and immobility[56,58] are shown to be associated with low BMD, as well as a limited sunlight exposure[59], feeding difficulties and malnutrition[57,60]. Visual impairments, a decreasing physical ability, paretic conditions, impulsiveness, previous falls, incontinence and the non-use of assistive equipment may further increase the risk of falling[61].

"Oscar is a 48-year-old male patient of the department of Residential Care at Epilepsy Center Kempenhaeghe, who was diagnosed with epilepsy at the age of 1, after suffering an encephalitis. On a daily basis, Oscar has tonic seizures with a generalized onset. Due to the refractoriness of his seizures, he is treated with carbamazepine, phenobarbital and valproate. Oscar has a profound intellectual disability, is unable to speak or communicate and has limited vision. Additionally, he is quadriplegic and confined to a wheelchair. He has never been able to walk. One morning, Oscar was lying in bed restlessly. When touching his upper leg, he moaned. After a physical exam, Oscar was sent to the hospital. On an X-ray, a fracture of his right femur was discovered."

Epilepsy Center Kempenhaeghe is a specialized expertise center and tertiary clinic for epilepsy, sleep medicine and neurocognition in the Netherlands and provides both cure and care facilities. It has a large department of Residential Care for patients with epilepsy and intellectual disabilities. In the past, several relatively young (male) patients of the department of Residential Care at Epilepsy Center Kempenhaeghe had sustained fractures during minimal impact trauma. After referral to an internist-endocrinologist, the majority of these patients had been diagnosed with osteoporosis[62]. In 2009, it was then decided to evaluate the skeletal health of all the patients living at the long-stay care department by DXA and laboratory evaluation[48,63]. The results were revealing; 80% was diagnosed with low BMD (osteopenia or osteoporosis) and 65% had a deficient serum 25-hydroxy vitamin D3 level (<50 nmol/L)[63]. Patients who were diagnosed with osteoporosis, started treatment with oral bisphosphonates, as recommended by the national guideline 'Osteoporosis and fracture prevention'[64,65].

At that time, it was decided to reexamine patients after several years, including several bone imaging techniques (VFA, QUS, TBS) in order to evaluate individual treatment and fracture incidence.

Aim and outline of this thesis

In institutionalized patients with refractory epilepsy and intellectual disability there are several knowledge gaps in the literature regarding longitudinal changes of BMD, the application of other bone imaging techniques such as QUS and TBS, the incidence of clinical fractures and morphometrically assessed vertebral fractures.

Therefore, the aim of this thesis was to study fracture incidence in this specific group of patients and to examine the skeletal status using DXA, VFA, QUS and TBS.

In **Chapter 2** we evaluated bone status in *children* between the age of 5 and 17 years in the department of Residential Care. Bone mineral density was measured using DXA, blood samples were taken and historical fractures were gathered through the medical files.

In **Chapters 3-6** we studied bone status in (subgroups of) *adults* between the age of 18 and 88 years, who are residing in the department of Residential Care.

In **Chapters 3 and 4** we determined the prevalence and incidence of clinical fractures and morphometric vertebral fractures between 2009 and 2016.

In **Chapter 5** we explored changes in bone status over seven years of follow-up, using both DXA and QUS. In a subgroup analysis we tried to examine the effect of bisphosphonate treatment on densitometry values.

In **Chapter 6** we assessed TBS over seven years of follow-up and we studied the association between incident fractures and TBS.

Finally, **Chapter 7** provides a general discussion of the results and a summary of the conclusions of this thesis.

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Bone mineral density and fractures in institutionalized children with epilepsy and intellectual disability

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SUMMARY

Objective

Long-term use of antiseizure drugs is associated with a low bone mineral density (BMD) and an increased fracture risk. The literature regarding institutionalized children on chronic antiseizure drugs is limited. Therefore, the aim of this cross-sectional study is to evaluate the prevalence of low BMD and the history of fractures in institutionalized children with epilepsy and intellectual disability (ID).

Methods

A dual-energy X-ray absorptiometry (DXA) of lumbar spine (L1-L4) and hip was performed in 24 children, residing in a long-stay care facility in the Netherlands. Additionally, serum concentrations of albumin, calcium and 25-hydroxyvitamin D were determined. Data on fractures were retrospectively extracted from the medical files.

Results

Ages of the children (14 male, 10 female) ranged from 5-17 years with a mean age of 13.0 (±3.2). The criteria of the International Society for Clinical Densitometry (ISCD) were used for classification of bone mineral disorders. Eight (33.3%) children had a normal BMD (Z-score >-2.0). Of the sixteen children with a low BMD (Z-score ≤-2.0), three were diagnosed as osteoporotic, based on their fracture history. Ten children (41.7%) were reported to have at least one fracture in their medical history. Serum concentrations of albumin-corrected calcium (2.28-2.50 mmol/L) and (supplemented) vitamin D (16-137 nmol/L) were within the normal range.

Conclusion

This study demonstrated that 67% of institutionalized children with epilepsy and ID had low BMD and 42% had a history of at least one fracture, despite supplementation of calcium and vitamin D in accordance with the Dutch guidelines.

INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting people of all ages. Worldwide, approximately 50 million people are diagnosed with epilepsy[1]. Treatment often consists of life-long therapy with antiseizure drugs. However, antiseizure drugs are shown to be associated with a decreased bone mineral density (BMD) and an increased fracture risk[2-4], especially when used in polytherapy[5,6]. As the peak bone mass of humans is reached between the age of 20 and 30 years, childhood is a critical period for bone mass development. Exposure to antiseizure drugs during this period may lead to a lower peak bone mass and as a result, an increased fracture risk later in life[7]. Children with epilepsy who are institutionalized may be more prone to several other risk factors which could affect BMD, such as feeding difficulties and malnutrition[8,9], severe neurological impairments[8], immobility[10,11] and less sunlight exposure[12]. Additionally, BMD is found to be significantly lower among persons with intellectual disability[11,13]. The literature regarding BMD and fractures in institutionalized children on chronic antiseizure drugs is limited.

Therefore, the aim of this study is to evaluate the prevalence of low BMD and the history of fractures in institutionalized children with epilepsy and intellectual disability.

MATERIAL AND METHODS

Study population and design

This cross-sectional study included children (<18 years) from a long-stay care facility for people with epilepsy and intellectual disability in the Netherlands. All children have epilepsy, caused by a variety of factors (i.e. genetic, structural, metabolic, immunologic, infectious or unknown) and some degree of intellectual disability, ranging from mild to profound. All children were of the same ethnicity (white).

The study was approved by the local medical ethical committee (METC *16.04*) and informed consent was obtained from the legal representatives (in most cases parents) of the children. During measurements, all children were informed verbally and guided by a familiar nurse and/or family member. Procedures were stopped when a child refused to cooperate or showed significant signs of resistance.

Data collection

In November 2016, all 33 children were invited to undergo a dual-energy X-ray absorptiometry-scan (DXA) of hip and lumbar spine (L1-L4) and blood samples were taken. Of these, 26 children (78.8%) participated. The legal representative(s) of two children had refused because of the presence of anxiety/agitation. In the other five children the reasons for refusal were not reported.

Demographic and epilepsy characteristics

Demographic and epilepsy characteristics were collected through the medical records. Demographic characteristics included age (years), sex (male/female), intellectual disability (mild/moderate/severe/profound), Tanner stage (pre-pubertal/pubertal/post-pubertal), weight (kg), height (m), nutritional status (regular food/tube-fed), mobility (not able to walk/walk with aid/walk without aid), current use of calcium, vitamin D and bisphosphonates and Barthel index (0-20).

The Barthel index is a ten-item scale which assesses a person's daily functioning in activities of daily living (ADL). A score of 0 means total dependency on others and the maximum score of 20 implies complete independency in ADL. As for Tanner stages, the most recent (<6 months) assessments of the pediatrician were used for classification; stage 1 (G1/M1) was classified as pre-pubertal, stages 2 to 4 as pubertal and 5 (G5/M5) as post-pubertal[14,15]. In girls, onset of breast development (M2) before the age of eight was considered as early puberty and after the age of twelve as late puberty. In boys, onset of testicular enlargement (G2) before the age of nine was considered as early puberty and after the age of fourteen as late puberty[16]. Furthermore, body mass index (BMI)

was calculated by dividing weight by the square of height and was classified using the WHO child growth references 5-19 years. A cut-off score for thinness was a BMI less than -2SD. Overweight and obesity were classified using cut-off scores of >+1SD and >+2SD, respectively[17].

All epilepsy characteristics in the medical records, had been established by neurologists. All children had been diagnosed with epilepsy in the past, based on the presentation of seizures and/or diagnostic tests. Collected data for this study, included cause of epilepsy (genetic, structural, metabolic, immunologic, infectious or unknown), age of onset, duration and current antiseizure drug use.

Bone mineral density

All measurements were made with the same densitometer (Hologic, Discovery A [S/N 80847]). BMD was expressed as the amount of mineral (g) divided by the area scanned (cm^2) and as Z-scores. Z-scores compare data of the children with age-, race- and sex-matched normative data provided by the manufacturer.

The criteria of the International Society for Clinical Densitometry (ISCD) were used to classify bone mineral disorders[18]. A Z-score equal to or below -2.0 was considered as low BMD.

The diagnosis of osteoporosis was made based on the following criteria[18]:

- Low BMD (Z-score ≤-2.0) AND a clinically significant fracture history:
    1. Two or more long bone fractures under the age of 10 years,
    2. Three or more long bone fractures under the age of 19 years.

Serum concentrations

Blood samples were taken (simultaneously with periodical laboratory testing in January/February) and serum concentrations of calcium (mmol/L), albumin (g/L) and 25-hydroxyvitamin D (nmol/L) were defined. Serum concentrations of calcium were corrected for albumin if the level of albumin was below 35 g/L.

Fractures

Information on clinical fractures was retrospectively extracted from radiology reports in the medical records. All clinical fractures were classified according to the ICD-10. Fractures of hip/femur (S72.0-S72.2), spine (S12, S22.0-S22.1, S32.0-S32.2, S32.7-S32.8), forearm/wrist (S52) and upper arm/humerus (S42.2-S42.4) were considered as major osteoporotic fractures. No vertebral fracture assessments (VFA) were performed.

Statistical analysis

Data are presented as means (±SD) or as frequencies (percentages). Differences in serum concentrations of albumin-corrected calcium and 25-hydroxyvitamin D between groups (fractures yes/no and low/normal BMD) were compared using the Student *t*-test (parametric) or Mann-Whitney *U*-test (nonparametric), after checking for normality (histogram, Q-Q plots, boxplot).

All statistical tests were two-tailed with a level of significance of $p<.05$. Statistical analyses were conducted using SPSS version 26 (IBM Corporation, UK).

RESULTS

Demographic and epilepsy characteristics

From a total of 26 children, two were excluded due to unreliable scans of hip and lumbar spine (movement during the scans). Therefore, 24 children (14 male, 10 female) were successfully measured by DXA at the hip and/or lumbar spine. In one child, hip measurements were missing due to movement and in five children lumbar spine was not measured, due to osteosynthesis material (n=1) or movement during the scan (n=4).

Demographic characteristics are summarized in Table 1. Age ranged from 5 to 17 years (mean 13.0±3.2) and residence duration from 3 months to 12 years (mean 5.1±3.5 years). Four children (16.7%) were wheelchair-dependent. The rest were able to walk, with (n=5) or without aid (n=15). None of the children were completely independent in ADL (Barthel index ranged from 0 to 17 with a median of 8.5). In all six children (25.0%) with a feeding tube, tube-feeding was used in combination with regular food. One child was diagnosed with early puberty. As for bone status, none of the children were previously diagnosed with osteoporosis or treated with bisphosphonates.

Age of onset of epilepsy ranged from birth to 4 years and 4 months (mean 1.3±1.3 years). Duration of epilepsy, at the time of the study, ranged from 4 years to 17 years and 4 months. All children were on antiseizure drugs (Table 2; mean number of drugs 2.6±1.1). Four children (16.7%) were on monotherapy (valproic acid (2x), topiramate, oxcarbazepine). Eleven children (45.8%) were prescribed one enzyme-inducing antiseizure drug and 22 (91.7%) were prescribed one or more non-enzyme-inducing drugs.

Bone mineral density

Based on the Z-scores (Table 3), eight children (33.3%) had a normal BMD and sixteen children (66.7%) a low BMD (Z-score ≤-2.0). In view of the fracture history, three of the latter group (12.5%) were considered as osteoporotic according to the criteria of the ISCD[18]. They were 8, 10 and 17 years old at the time of BMD measurements.

Table 1. Demographic characteristics of 24 children with epilepsy and intellectual disability

	n (%)	Mean (SD)
Sex		
Male	14 (58.3)	
Female	10 (41.7)	
Age (in years)		13.0 (3.2)
Duration of residency (in years)		5.1 (3.5)
Intellectual disability		
Mild (IQ 55-70)	2 (8.3)	
Moderate (IQ 40-55)	8 (33.3)	
Severe (IQ 25-40)	8 (33.3)	
Profound (IQ <25)	6 (25.0)	
Tanner stage		
Unknown	3 (12.5)	
Pre-pubertal	9 (37.5)	
Pubertal	6 (25.0)	
Post-pubertal	6 (25.0)	
BMI category*		
Thinness (<-2SD)	1 (4.2)	
Normal weight	19 (79.2)	
Overweight (>+1SD)	4 (16.7)	
Nutritional status		
Regular food	18 (75.0)	
Regular food (plus tube-fed)	4 (16.7)	
Tube-fed (plus regular food)	2 (8.3)	
Mobility		
Not able to walk	4 (16.7)	
Walk with aid	5 (20.8)	
Walk without aid	15 (62.5)	

*Classification according to the WHO Child growth references 5-19 years

Table 2. Etiology of epilepsy and the use of antiseizure drugs in 24 children with epilepsy and intellectual disability

		n (%)
Etiology of epilepsy		
Genetic		12 (50.0)
Structural		3 (12.5)
Infectious		2 (8.3)
Unknown		7 (29.2)
Number of antiseizure drugs		
One		4 (16.7)
Two		7 (29.2)
Three		7 (29.2)
Four		6 (25.0)
Enzyme-inducing*		
Strong	Carbamazepine	1 (4.2)
	Phenobarbital	1 (4.2)
Weak	Oxcarbazepine	2 (8.3)
	Topiramate	7 (29.2)
Non-enzyme-inducing*		
	Acetazolamide	1 (4.2)
	Clobazam	11 (45.8)
	Clonazepam	1 (4.2)
	Ethosuximide	1 (4.2)
	Lamotrigine	4 (16.7)
	Levetiracetam	7 (29.2)
	Perampanel	3 (12.5)
	Stiripentol	2 (8.3)
	Valproic Acid	19 (79.2)
	Zonisamide	4 (16.7)

*Antiseizure drugs are used in various combinations: due to polytherapy and/or the use of both enzyme- and non-enzyme inducers, total numbers add up to more than 100%.

Table 3. Bone mineral density (BMD) and Z-scores (n=24)

	n	BMD (in g/cm²)	Z-score	Low BMD (Z-score ≤-2.0)
		Mean (SD)	Mean (SD)	n (%)
Lumbar Spine (L1-L4)	19	0.725 (0.151)	-1.0 (1.3)	4 (21.1)
Femoral Neck	23	0.594 (0.116)	-2.5 (1.2)	15 (65.2)
Total Hip	23	0.667 (0.142)	-2.3 (1.2)	15 (65.2)
			Total	16 (66.7)

Serum concentrations

Except for one child, all (95.8%) were on vitamin D supplementation at the time of the study with a mean duration of 4.7 years (±3.1). Ten children used a combination of vitamin D and calcium. In one child (4.2%) albumin was below 35 g/L. Mean serum concentration of albumin-corrected calcium and 25-hydroxyvitamin D were 2.41 (±0.06) mmol/L and 87.2 (±33.3) nmol/L, respectively. Three children had a 25-hydroxyvitamin D concentration below 50 nmol/L (16, 41 and 48 nmol/L). One of them (41 nmol/L) was not on vitamin D supplementation at the time of the study. The child with the lowest serum concentration had a normal BMD and no historic fractures.

Serum concentrations of albumin-corrected calcium and 25-hydroxyvitamin D did not differ between children with a low or a normal BMD and no differences in serum concentrations were found between children with and without fractures.

Fractures

Ten children (41.7%) were reported to have had at least one fracture in their medical history. According to the medical files, seven children had suffered one fracture (humerus, forearm (3x), femur, lower leg, toe), one child had suffered two fractures (finger, toe) and one child nine fractures (forearm, thumb, fingers (3x), lower leg, talus, foot, great toe). One child had sustained multiple fractures, caused by a trauma incident, but they were not further specified. Of the eight children diagnosed with a normal BMD, one child (12.5%) had a history of fracture versus nine of the sixteen children with a low BMD (56.3%).

Three fractures had been caused by an accidental trauma (16.7%); one finger had been fractured during a ballgame, one finger had been caught between the door and one foot had been fractured by bumping it to a doorframe. Seven fractures (38.9%) had been caused by a fall (humerus, forearm (3x), thumb, femur, lower leg), of which at least three (forearm, thumb, lower leg) were the result of a seizure. Circumstances of the eight remaining fractures (forearm, finger (2x), lower leg, talus, great toe, toe (2x)) were not reported (44.4%).

Five fractures (27.8%) are considered as major osteoporotic fractures, based on their locations (humerus, forearm (4x)). Four of these five (the cause of one fractured forearm was unknown), had been caused by a low-level fall from standing height or less.

DISCUSSION

In this study, we found a high prevalence of low BMD (67%) and historic fractures (42%) in institutionalized children with epilepsy and intellectual disability.

The total number of fractures during lifetime, though, might be slightly underestimated as all children lived at home before they moved to the care facility. Age at admittance in the care facility ranged from 1.0 to 13.8 years. Fractures (especially minor ones) that occurred before institutionalization may not have been documented in the medical files. Nevertheless, at least 41.7% of the children had suffered from one or more fractures during their lives. This is higher than what Simm *et al*.[19] found (34.8%) in children with at least one year of antiseizure drug exposure, but they excluded children who suffered from neurodevelopmental disorders or immobility. Overall, in the Netherlands, the incidence of fractures in children between 6 and 16 years of age is estimated at 40% for males and 28% for females[20]. In our study, those percentages were 50% and 30%, respectively. However, three-quarter of our study participants has not yet reached the age of 16. In addition, the peak of fractures for males lies around the age of 15 and for females around the age of 12[21]. Half of our study participants (eight males younger than 15 and four females younger than 12) have not yet reached the age of peak fracture incidence. This implies that it may be expected that the proportion of children with a fracture until the age of 16 in our cohort will further increase.

In our study, circumstances of eight fractures were not reported. In those cases, we are not able to differentiate between low and high impact fractures. Overall, based on the locations, five fractures (27.8%) were considered major osteoporotic fractures. The other had been minor fractures, involving mainly fingers and toes. In children that already suffer from multiple physical disabilities, even minor fractures may have a major impact on daily living and cause pain, discomfort, stiffness and further limitations.

In the study of Shiek Ahmad *et al*.[22], half of the falls (49%) had been caused by a seizure and about one-third of the fractures (31%) in persons on antiseizure drugs had been seizure-related. In our study, seven fractures were reported to be caused by a fall (38.9%). At least three of these falls had been the result of a seizure. Presumably, many seizures go unwitnessed and it is difficult to determine whether a fall is seizure-related or not. For this reason, it is hard to determine whether a fracture is a result of a seizure or of the fall itself. Grzonka *et al*.[23] performed a systematic review of the literature regarding fractures as a direct consequence of convulsive seizures in adults and identified 39 studies. Most frequently reported in these studies were bilateral posterior fracture-

dislocations of the shoulders, thoracic and lumbar vertebral compression fractures, skull and jaw fractures and bilateral femoral neck fractures. In our study, none of these fractures were reported, suggesting that the fractures might be more likely to be a consequence of the fall, rather than the seizure itself although seizure-related fractures may occur at other locations in adults than in children.

Gniatkowska-Nowakowska[24] observed a group of 126 children with epilepsy. During 5 years, 17% of the children on monotherapy had suffered a fracture, versus 49% of the children on add-on therapy. In our study, percentages of children with fractures for mono- and polytherapy were 25.0 and 45.0% respectively, but this should be interpreted with caution due to the small number of children on monotherapy in our study (n=4).

The combination of bone mineral disorders (osteopenia/osteoporosis) and the use of antiseizure drugs has first been described around 1970[25-27] and included cytochrome P450-inducing antiseizure drugs, such as carbamazepine, phenobarbital, phenytoin and primidone. But also newer antiseizure drugs with minimal or no enzyme-inducing effects seem to have an effect on bone metabolism, even though not all results are consistent[28-30]. In our study, no conclusions can be drawn regarding the effects of enzyme-inducing versus non-enzyme-inducing drugs, as only one child used carbamazepine and one child phenobarbital. The rest of the children were on antiseizure drugs with minimal (topiramate/oxcarbazepine) to no enzyme-inducing effects.

A low BMD was found in 67% of the children. In the same care facility, the prevalence of low BMD in adults was 80% and one third was diagnosed with osteoporosis[31]. As childhood is a critical period for bone mass development, the proportion of children with low bone mass (67%) or osteoporosis (12.5%) is alarming. Similar percentages of children on antiseizure drugs with osteoporosis were found by Gniatkowska-Nowakowska[24] (7.1%) and Coppola *et al.*[32] (14.6%), although both studies applied different classification methods and did not include fracture history in the diagnosis.

A complicating factor in diagnostics is the accuracy of the DXA scans. Mergler *et al.*[33] studied a group of children with severe neurological impairment and ID and found a mean number of 5.3 distorting factors and artefacts per child. The most frequently occurring factors they identified were movement during measurement, scoliosis, contractures, gastrostomy catheters, aberrant body composition and a height below the 5th centile for age. In our study, two children were excluded due to movement during the scans, ten children had a form of scoliosis, six children had a gastrostomy catheter and five children had a height below the 5th centile. The presence of contractures and aberrant body composition were not reported or assessed in our study. However, one

child was diagnosed with early puberty which could have affected the results of the DXA. As distorting factors and artefacts can lead to both over- and underestimation of BMD, it is uncertain how this influenced the outcomes in our study. Most of the factors that were identified will be more likely to affect BMD of the spine than BMD of the hip.

In a meta-analysis including nine studies, a significant association was found between antiseizure drug treatment and a decreased 25-hydroxyvitamin D, in persons without vitamin D supplementation[34]. In our study, 25-hydroxyvitamin D levels had been measured in the middle of the winter, when they are at the lowest and we identified only three children with a level below 50 nmol/L. The rest of the children had a sufficient level of serum vitamin D (56-137 nmol/L), but it has to be noted that except for one child, all (95.8%) were on vitamin D supplementation at the time of the study. The higher tendency for vitamin D supplementation may be explained by a previous study undertaken in the care facility. Between 2012 and 2014, Snoeijen-Schouwenaars *et al*.[35] studied the effects of vitamin D supplementation. Some of the children participated in that study, as well as in the current study. Presumably, the previous study led to an increased awareness among general practitioners regarding supplementation. Vitamin D supplements were prescribed, as part of standard care, in doses which were at least equal to the amount recommended by the Dutch guidelines. Eight fractures (44.4%), in four children, occurred after the prescription of vitamin D (ranging from 8 months to 9 years and 4 months).

Serum concentrations of albumin-corrected calcium (2.28-2.50 mmol/L) of the children were within the normal range, similar with the findings in other studies[24,36,37]. However, those studies excluded institutionalized children or children with physical and/or intellectual disabilities.

Limitations

Despite our best efforts to contribute to the literature regarding BMD and fractures in institutionalized children on chronic antiseizure drugs, we acknowledge several limitations of our study.

First of all, it was a cross-sectional study at a single institute. The number of participants was small and they represent a complex, heterogeneous population with differences regarding sex, age, nutritional status, mobility, type and number of antiseizure drugs, etc. As all children have a different background and medical history, we cannot rule out additional factors that may have affected bone mineral density and/or the number of fractures, such as the influence of genetic syndromes and comorbidity, or the possibility of physical abuse before institutionalization. Due to these uncertainties

in background and medical history and the heterogenicity of our study group, our findings may not be completely generalizable to other institutionalized children with epilepsy and intellectual disability.

Although the main focus of our report was on the chronic use of antiseizure drugs, we emphasize the multifactorial nature of the causes of osteoporosis and recognize several other risk factors in our study group. For instance, physical activity. Nine children (37.5%) were not able to walk independently and the median score on the Barthel index was 8.5. Even though these parameters do not necessarily reflect a child's activity level, they may imply a lower physical activity.

Despite limitations regarding heterogenicity of the study group and generalizability, our results should be taken seriously. Screening of BMD in children with epilepsy is not part of routine care in the Netherlands. Although a DXA could be helpful to identify children who are at risk for fractures, it should only be performed when the results impact further treatment. However, there is a lack of evidence regarding treatment of low BMD in children. In adults, the first-choice treatment for low BMD (T-score ≤-2.5), is the use of bisphosphonates[38]. For children, caution is advised with regard to prescribing bisphosphonates, due to the limited data on the (late) effects and the duration of treatment[39,40]. Consequently, prophylactic bisphosphonate therapy (treating low BMD in the absence of fractures) is not recommended[40].

Regardless of DXA results, it is advised to take safety measures to prevent falls and to educate caregivers. These interventions, as well as a careful (re-)evaluation of prescribed antiseizure drugs and the feasibility of lifestyle changes, should be part of the care plan. In order to optimize bone health in children who are at risk of fractures, physical activity, especially weight-bearing exercises[41] and an adequate calcium and vitamin D intake remain important[12]. But above all, more research is needed towards optimal treatment options. We undertook this study to contribute to the literature and to raise awareness about the risk of bone mineral disorders in children on chronic antiseizure drugs.

CONCLUSION

The prevalence of a low BMD in institutionalized children with epilepsy and intellectual disability is found to be high (67%). Osteoporosis might already be present at a very young age (the youngest in our study was 8 years), despite vitamin D supplementation in accordance with the Dutch guidelines. This study emphasizes the need for more understanding of this complex population, in order to adequately manage bone mineral problems. Further research in a larger population, with more accurate fracture data and a focus on treatment is needed, to gain more insight and establish optimal treatment options in children who are at risk of bone mineral disorders.

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Incidence of clinical fractures: a 7-year follow-up study in institutionalized adults with epilepsy and intellectual disability

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SUMMARY

Objective

To determine the incidence of clinical fractures over seven years of follow-up, in adults with epilepsy and intellectual disability, residing in a long-stay care facility.

Methods

In 2009, all institutionalized adult patients (n=261) were invited to undergo a Dual-energy X-ray Absorptiometry (DXA) measurement and a Vertebral Fracture Assessment (VFA). Participants were followed over seven years or until date of discharge (in case of moving from the care facility) or date of death. The patients' medical files were screened for radiology reports and staff notes, to identify clinical fractures. Fracture incidence rates (IR) were determined and compared for subgroups, by calculating incidence rate ratios. Hazard ratios were calculated to identify factors associated with fracture risk, using Cox Proportional Hazards analyses.

Results

A total of 205 patients (124 male, 60.5%) aged between 18 and 88 years (median 48, IQR 34-60) were enrolled. At baseline, 92 patients (44.9%) were diagnosed with osteopenia and 65 (31.7%) with osteoporosis. Between 2009 and 2016, 30 patients (14.6%) deceased and 3 patients (1.5%) left the care facility.

During follow-up, 156 clinical fractures were reported in 82 patients (40.0%). Thirty-eight patients (18.5%) had at least one major osteoporotic fracture. Overall, the IR was 11.6 fractures per 100 person-years. Fracture risk was significantly lower in patients who were wheelchair dependent than in patients who were able to walk (p<.001).

Conclusion

This study demonstrated that 40% of institutionalized adults with epilepsy and intellectual disability had at least one clinical fracture during seven years of follow-up, despite adequate anti-osteoporosis treatment.

INTRODUCTION

Epilepsy is a chronic, neurological disorder characterized by recurrent seizures, affecting approximately 0.4-1.0% of the global population. In the majority of the patients, seizures can be successfully controlled with antiseizure drugs[1]. In about 30% of the patients, the seizures remain refractory. Despite benefits of antiseizure treatment (decrease in number and/or severity of seizures), chronic use of antiseizure drugs is known to affect bone health, which was first reported around 1970[2-4]. Since then, meta-analyses including multiple studies, have shown an association between the use of antiseizure drugs and an increased fracture risk[5,6]. Most of the studies included ambulatory, independently-living adults with epilepsy. In institutionalized patients, fracture rates might even be higher, as they are more likely to suffer from severe comorbidities, refractory seizures and fall-related incidents. In addition, a poor nutritional status, a lack of sunlight exposure and immobility have been shown to be related to a low bone mineral density (BMD)[7-10]. Studies regarding clinical fractures and fracture risks in institutionalized adult patients on chronic antiseizure drugs are of older age and mostly limited to the use of phenobarbital and phenytoin[11-14].

Therefore, the main objective of this study is to determine the incidence of fractures over seven years of follow-up, in adults with epilepsy and intellectual disability, residing in a long-stay care facility.

MATERIAL AND METHODS

Study population

This retrospective cohort study was performed at the long-stay care department of Epilepsy Center Kempenhaeghe, a tertiary care facility for people with epilepsy in the Netherlands. All patients had a diagnosis of epilepsy, caused by structural, genetic, infectious, metabolic, immune or unknown factors and most of the patients (99.0%) had a degree of intellectual disability (mild, moderate, severe or profound).

In 2009, all 261 adult patients (aged 18 years or older) were asked to participate in a study regarding bone status (METC: NL26095.068.09)[15,16]. Forty-seven patients (or their legal representatives) declined the invitation and nine patients (or their legal representatives) did not respond. A total of 205 patients (or their legal representatives) gave informed consent (78.5%) and were included in the study. No further in- or exclusion criteria were applied.

Study design and data collection

In 2009, all participants had a bone mineral density measurement using dual-energy X-ray absorptiometry (DXA) with vertebral fracture assessment (VFA) (Hologic Discovery W/A). BMD was expressed in g/cm^2 and T-scores. A T-score is the number of standard deviations (SD) below peak bone mass, according to the manufacturer's reference database. DXA is the gold standard for diagnosing a normal bone density (a T-score ≥-1.0 SD), osteopenia (a T-score of -1.0 to -2.5 SD) and osteoporosis (a T-score ≤-2.5 SD) as defined by the World Health Organization[17].

For each individual in this study, data collection started on the day of the DXA scan (between August 31st and September 29th, 2009) and ended after seven years of follow-up (between October 5th and November 30th, 2016). When a patient deceased, or left the care facility during the study period, data collection was stopped on the day of death or discharge. The patients' medical files at the care facility and the radiology reports of the hospital patients were referred to, were screened to extract clinical fractures. In addition, fracture-related search terms (i.e. '#', 'breuk', 'gebroken', 'fractu*') were used to screen notes and documents from nursing staff and general practitioners. All clinical (symptomatic) fractures were classified according to the ICD-10. Major osteoporotic fractures (MOF) were defined as: fractures of proximal humerus (S42.2-S42.4), forearm (S52), hip (S72.0-S72.2) and vertebrae (S12, S22.0-S22.1, S32.0-S32.2, S32.7-S32.8)[18]. In this study, we only included *symptomatic* vertebral fractures (VFs). *Asymptomatic* prevalent vertebral fractures (as diagnosed by VFA) in our study population were previously reported[19]. Of the 184 patients with a VFA at baseline, 77 (41.8%) were diagnosed with a prevalent vertebral fracture.

Patient characteristics (age, sex, length, weight, intellectual disability and ambulatory status) and (history of) medication use (antiseizure drugs, calcium, and vitamin D supplements and bisphosphonates) were extracted from the patients' medical files. Patients were treated with calcium and vitamin D and additionally with bisphosphonate (BP) therapy (oral or intravenous) in case of osteoporosis or a vertebral fracture grade two or three, according to the Dutch guideline at that time[20,21]. None of the patients received denosumab, strontium ranelate, raloxifene, teriparatide, or recombinant parathyroid hormone (PTH). All medication (including supplementation of calcium and vitamin D) was administered by nurses and/or taken under direct supervision.

Statistical analysis

The primary outcome of this study is the incidence of clinical fractures over seven years follow-up. Data are presented as means (±SD), medians (interquartile range, IQR), or frequencies (percentages). Differences between patients with and without complete follow-up were analyzed using Student's *t*-test (parametric) or Mann-Whitney U-test (nonparametric) for continuous variables, and Pearson's Chi-Square test for categorical variables. The incidence rate (IR) was calculated as the total number of clinical fractures during follow-up, divided by the sum of each patients' time at risk. Fracture incidence rates for subgroups were compared by calculating incidence rate ratios (IRR) using *R* version 4.0.3 (The R Foundation for Statistical Computing, Austria). Hazard ratios (HR) were calculated to identify factors associated with fracture risk, using Cox Proportional Hazards analyses. All outcomes were analyzed using SPSS version 27 (IBM Corporation, UK) and statistical tests were two-tailed with a level of significance of .05.

RESULTS

A total of 205 patients (124 male, 60.5%) aged between 18-88 years (median 48, IQR 34-60) were enrolled in the study. Duration of follow-up ranged from 1 to 87 months (median 85.3, IQR 84.7-85.9). Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics (in 2009) of 205 patients with refractory epilepsy and intellectual disability

	n (%)	**Median (IQR)**
Sex		
Male	124 (60.5)	
Female	81 (39.5)	
Age (in years)	205	48 (34-60)
Intellectual disability		
None (IQ ≥70)	2 (1.0)	
Mild (IQ 55-70)	56 (27.3)	
Moderate (IQ 40-55)	72 (35.1)	
Severe (IQ 25-40)	61 (29.8)	
Profound (IQ <25)	14 (6.8)	
Ambulatory status		
Wheelchair dependent	58 (28.3)	
Walk with aid	25 (12.2)	
Walk without aid	122 (59.5)	
Body Mass Index (kg/m^2)		
Underweight (<18.5)	7 (3.4)	
Normal weight (18.5-25)	96 (46.8)	
Overweight (25-30)	73 (35.6)	
Obese (≥30)	29 (14.1)	
Number of antiseizure drugs		3 (2-4)
None	8 (3.9)	
1	16 (7.8)	
2	42 (20.5)	
3	78 (38.0)	
4	54 (26.3)	

Table 1. Continued

		n (%)	Median (IQR)
5		3 (1.5)	
6		4 (2.0)	
Enzyme-inducing*		171 (83.4)	
Strong	Carbamazepine	123 (60.0)	
	Phenobarbital	21 (10.2)	
	Phenytoin	45 (22.0)	
Weak	Oxcarbazepine	27 (13.2)	
	Topiramate	28 (13.7)	
Non-enzyme-inducing*		176 (85.9)	
Acetazolamide		1 (0.5)	
Clobazam		81 (39.5)	
Clonazepam		34 (16.6)	
Ethosuximide		4 (2.0)	
Felbamate		1 (0.5)	
Gabapentin		9 (4.4)	
Lacosamide		1 (0.5)	
Lamotrigine		76 (37.1)	
Levetiracetam		40 (19.5)	
Pregabalin		6 (2.9)	
Valproic acid		88 (42.9)	
Vigabatrin		1 (0.5)	
Zonisamide		3 (1.5)	
Seizure frequency			
None		21 (10.2)	
Less than 1 a year		10 (4.9)	
1 a month to 1 a year		28 (13.7)	
1 a week to 1 a month		49 (23.9)	
1 a day to 1 a week		80 (39.0)	
More than 1 a day		17 (8.3)	

IQ=Intelligence quotient, IQR=Interquartile Range
*Due to polytherapy and/or the use of both enzyme- and non-enzyme-inducing antiseizure drugs, total numbers add up to more than 100%.

Antiseizure drugs
At baseline, 150 patients (73.2%) used both enzyme-inducing and non-enzyme-inducing drugs. During follow-up, 103 patients (50.2%) had a switch in prescribed antiseizure drugs; 78 patients (38.0%) started at least one other antiseizure drug and 75 patients (36.6%) stopped at least one antiseizure drug they were using at baseline. Twenty-eight patients (13.7%) stopped at least one enzyme-inducing drug (12 carbamazepine, 9 phenytoin, 2 phenobarbital, 2 oxcarbazepine, 1 topiramate and 2 phenytoin+topiramate) and four patients (2.0%) switched from one enzyme-inducing drug to another enzyme-inducing drug. In addition, six patients (2.9%) started an enzyme-inducing drug (3 phenytoin, 1 carbamazepine, 1 oxcarbazepine, 1 topiramate). Further, a total of 169,028 epileptic seizures (median 275 seizures per patient during follow-up, IQR 55-1060) were reported. Half of the patients (47.3%) had one or more seizures a week.

Bone mineral density and treatment
In 2009, all patients underwent a DXA scan. In ten patients (4.9%) the scan failed due to physical impairments (n=4), lack of cooperation (n=4) or the inability to lie still (n=2). Ninety-two patients (44.9%) were diagnosed with osteopenia and 65 (31.7%) with osteoporosis. The remaining 38 patients (18.5%) had a normal BMD.

At baseline, 22 patients (10.7%) used calcium supplementation, 11 patients (5.4%) vitamin D and 14 patients (6.8%) had a combination of calcium and vitamin D.

Forty-two patients (20.5%) already received bisphosphonate therapy at the start of the study and in 41 patients (20.0%) treatment with anti-osteoporosis medication was initiated during the follow-up period.

Clinical fractures
Between 2009 and 2016, 82 patients (40.0%) sustained 156 clinical fractures, of whom 38 (18.5%) had at least one MOF (16 hip, 16 vertebrae, 9 forearm and 5 proximal humerus). Details on individual fracture sites are shown in Table 2. Seventy-one fractures (45.5%) were reported after a fall and at least 39 fractures (25.0%) were caused by a seizure; between 0.02-0.1% of the reported seizures led to a fracture.

Eight fractures (5.1%) were caused by an accident or trauma and three fractures (1.9%) had been reported to occur spontaneously. For the remaining 35 fractures (22.4%), the circumstances were not reported in the medical records. The median time to the first fracture was 33.5 months (IQR 18.4-54.1).

Table 2. Clinical fractures and fracture locations in patients with refractory epilepsy and intellectual disability (n=205)

Fractures	**Patients (%)**	
None	123 (60.0)	
1	50 (24.4)	
2	10 (4.9)	
3	11 (5.4)	
4	7 (3.4)	
5	3 (1.5)	
10	1 (0.5)	
MOF	**Patients (%)**	
None	167 (81.5)	
1	31 (15.1)	
2	6 (2.9)	
3	1 (0.5)	
ICD-10	**Fracture location**	**Fractures (%)**
S02.0-S02.9	Skull / facial bones	9 (5.8)
S12.0-S12.9	Neck	3 (1.9)
S22.0-S22.9	Rib(s) / sternum / thoracic vertebrae	13 (8.3)
S32.0-S32.8	Lumbar vertebrae / pelvis	7 (4.5)
S42.0-S42.9	Shoulder / upper arm	31 (19.9)
S52.0-S52.9	Forearm	9 (5.8)
S62.0-S62.8	Wrist / hand	15 (9.6)
S72.0-S72.9	Femur	17 (10.9)
S82.0-S82.9	Lower leg (incl. ankle)	33 (21.2)
S92.0-S92.9	Foot	19 (12.2)
Total		**156 (100.0)**

MOF=Major osteoporotic fracture

Total person-time in this study was 1342.8 years, leading to an IR of 11.6 fractures per 100 person-years, or one fracture every 8.6 person-years. In Table 3 the IRRs for subgroups are shown. The IR was significantly lower in patients who were wheelchair dependent than in patients who were able to walk (p<.001). The IR was significantly higher in patients diagnosed with osteoporosis vs patients with normal BMD (p=.004) and during bisphosphonate therapy vs not during therapy (p=.003).

Table 3. Fracture incidence rates (IR) per subgroup and incidence rate ratios (IRR) for comparisons between subgroups

	Subgroup	n Patients	n Fractures
Sex	Male	124	97
	Female	81	59
Age	18-49 years	112	85
	≥50 years	93	71
Mobility	Able to walk	147	142
	Wheelchair dependent	58	14
BMI category	Underweight	7	2
	Normal weight	96	79
	Overweight	73	61
	Obese	29	14
Diagnosis (at baseline)	Normal BMD	38	20
	Osteopenia	92	65
	Osteoporosis	65	71
BP treatment	Not during treatment		81
	During treatment		75
Seizure frequency	Seizure-free	21	7
	Less than 1 a year	10	5
	1 a month to 1 a year	28	26
	1 a week to 1 a month	49	42
	1 a day to 1 a week	80	62
	More than 1 a day	17	14

BMD=Bone mineral density, BMI=Body Mass Index, BP=Bisphosphonates, CI=Confidence interval, IR=Incidence rate, IRR=Incidence rate ratio, P-Ys=Person-years
$^{*}p<.05$, $^{**}p<.01$

	P-Ys	IR per 100 P-Ys	IRR (95% CI)	*p*
	812.6	11.9	-	
	530.2	11.1	0.93 (0.67-1.29)	.671
	764.7	11.1	-	
	578.1	12.3	1.10 (0.81-1.51)	.535
	966.4	14.7	-	
	376.3	3.7	0.25 (0.15-0.44)	<.001**
	41.0	4.9	0.39 (0.10-1.58)	0.172
	631.4	12.5	-	
	476.4	12.8	1.02 (0.73-1.43)	0.892
	193.9	7.2	0.58 (0.33-1.02)	0.055
	250.0	8.0	-	
	595.5	10.9	1.36 (0.83-2.25)	.223
	432.1	16.4	2.05 (1.25-3.37)	.004**
	850.2	9.5	-	
	492.5	15.2	1.60 (1.17-2.19)	.003**
	115.5	6.1	-	
	71.3	7.0	1.16 (0.37-3.65)	.803
	192.8	13.5	2.23 (0.97-5.13)	.054
	303.1	13.9	2.29 (1.03-5.09)	.037*
	549.4	11.3	1.86 (0.85-4.07)	.113
	110.8	12.6	2.09 (0.84-5.17)	.104

After adjustment for age, sex, femoral neck BMD, prevalent VF and seizure frequency (Table 4), mobility was the only factor that remained significantly associated with fracture risk with a lower risk (HR 0.32, [95% CI 0.16-0.64], $p<.001$) in wheelchair dependent patients.

Table 4. Multivariate analysis for the risk of fracture during seven years of follow-up in patients with refractory epilepsy and intellectual disability (n=205)

	Adjusted HR (95% CI)[a]	***p***
Sex		
Male	1.00	
Female	1.00 (0.62-1.61)	.987
Age	1.00 (0.98-1.02)	.967
Mobility		
Able to walk	1.00	
Wheelchair dependent	0.32 (0.16-0.64)	<.001**
BMD (FN) at baseline	0.19 (0.03-1.33)	.095
Prevalent VF at baseline		
No	1.00	
Yes	1.41 (0.85-2.32)	.181
Seizure frequency		
Seizure-free	1.00	
Less than 1 a year	0.84 (0.21-3.40)	.803
1 a month to 1 a year	1.14 (0.36-3.61)	.827
1 a week to 1 a month	1.19 (0.38-3.69)	.770
1 a day to 1 a week	0.97 (0.30-3.15)	.953
More than 1 a day	0.85 (0.19-3.91)	.835

BMD=Bone mineral density, CI=Confidence interval, FN=Femoral neck, HR=Hazard ratio, VF=Vertebral fracture

[a]Adjusted for age, sex, mobility, BMD of femoral neck at baseline, prevalent VF at baseline and seizure frequency

*$p<.05$, **$p<.01$

Lost to follow-up

Between 2009 and 2016, 30 patients (14.6%) deceased and 3 patients (1.5%) left the facility. Patients who deceased were significantly older ($p<.001$) than patients who completed follow-up and had a significant lower BMD of femoral neck and total hip ($p<.01$). No significant differences were found between the two groups, regarding BMD of lumbar spine ($p=.339$), sex ($p=.651$), BMI ($p=.876$), ambulatory status ($p=.055$), prescribed number of antiseizure drugs ($p=.206$) or prevalent vertebral fractures ($p=.605$) at baseline.

DISCUSSION

Over seven years follow-up, 40.0% of institutionalized adult patients with epilepsy and intellectual disability had suffered from at least one clinical fracture, of whom 38 (46.3%) had at least one MOF. A total of 156 fractures, including 46 (29.5%) major osteoporotic fractures, had been reported during the follow-up period. Fracture risk was significantly lower in patients who were wheelchair dependent as compared to those who were able to walk. In multivariate analyses, no significant differences were found regarding age, sex, seizure frequency, BMD of femoral neck and the presence of a prevalent VF at baseline.

In a large Dutch population-based study in people of 45 years and older, a fracture incidence rate of 2.1 per 100 person-years was found[22]. In our younger study population (mean age 46.8±16.6 vs 64.7±9.4 in men and 66.5±10.9 in women) the fracture incidence rate was at least five times higher. Schoufour *et al*.[23] studied fractures over a three-year follow-up period in patients with intellectual disability aged 50 years and over. Of the 651 patients with complete follow-up data, 97 (15%) sustained one or more fractures, resulting in an IR of at least 5.0 fractures per 100 person-years. Previously published studies in comparable study populations, reported fracture incidences similar to ours, between 7.1 and 14.2 per 100 person-years[11-14]. These studies included institutionalized adult patients with epilepsy, however the degree of mobility and the severity of physical disabilities were underreported and none of these studies reported treatment with bone agents such as bisphosphonates. In addition, these studies were of older age (1977-1999) and did, for that reason, include patients using older (enzyme-inducing) antiseizure drugs, mostly phenobarbital and phenytoin. In our study also newer (non-enzyme-inducing) antiseizure drugs were included, often in polytherapy.

Over the years, several laboratory, preclinical and clinical studies have focused on fracture risk associated with the use of enzyme- vs non-enzyme-inducing antiseizure drugs. Despite numerous attempts to unravel the pathophysiological mechanisms behind the increased fracture risk, these are still not fully understood. It is certain however, that multiple mechanisms exist and that bone mineral disorders are not limited to the use of enzyme-inducing drugs[24,25]. In our study, about three-quarter of the patients used both types of antiseizure drugs and half of all patients had at least one switch in prescribed antiseizure drugs during follow-up. Therefore, we are not able to draw conclusions regarding fracture risk associated with the use of either enzyme- or non-enzyme inducing antiseizure drugs.

Of all seizures that were reported during our study (n=169,028), at least 39 resulted in a fracture (0.02-0.1%). This is comparable to what Nakken *et al*.[26] found (0.1%) in institutionalized adult patients with intellectual disability and therapy-resistant

epilepsy. Note that these studies are probably not very comparable, due to improved techniques in detecting nocturnal seizures which may have increased the number of reported seizures in our study.

As for fracture locations, Grzonka *et al*.[27] focused on fractures as a direct consequence of generalized convulsive seizures and/or status epilepticus. Fractures of the shoulders (bilateral; 33%), thoracic/lumbar vertebrae (29%), skull/jaw (8%) and (bilateral) femoral neck (6%) were most frequently reported. In our study, these percentages were 7.7%, 0%, 15.4% and 7.7%, respectively. None of the seizure-related fractures in our patients had been bilateral. In our study, fractures of the lower leg/foot (13/39) and clavicle (9/39) were the most frequently reported seizure-related fracture sites. Some fractures in our study participants may have been the result of a fall, rather than the seizure itself, explaining possible differences in fracture locations as compared to the meta-analysis of Grzonka *et al*.[27].

Additionally, we would like to consider other causes of falling than seizures. The most common side effects of antiseizure drugs are dizziness and ataxia, resulting in an unsteady gait and impaired balance function[28,29]. Additional risk factors for falling in patients with disabilities, are visual impairments, a decreasing physical ability, paretic conditions, impulsiveness, previous falls, incontinence and the non-use of assistive equipment[30]. In our study, almost half of the fractures (45.5%) had been reported after a fall. In line with the aforementioned factors, we found a lower risk of fractures in patients who were wheelchair dependent than in patients who were able to walk. Based on our findings, we recommend educating caregivers about fracture risks and to raise more awareness about safety measures and fall prevention.

We followed a large group of adult patients with epilepsy over seven years and started (individual) anti-osteoporosis treatment according to the Dutch guidelines. In total, 75 fractures (48.1%) had occurred during treatment with bisphosphonates. This may raise questions about the effectiveness of the bisphosphonate therapy, but a plausible explanation is that it may reflect the severity of the bone mineral problems in those who receive treatment.

To our knowledge, there are only few studies describing the efficacy of anti-osteoporosis treatment in patients on antiseizure drugs[31-33]. Lazzari *et al*.[31] performed a randomized controlled trial in male veterans with epilepsy. Due to ethical reasons, patients with osteoporosis had been excluded. The study group (n=27) received risedronate and the control group (n=26) a matching placebo. During two years of follow-up there had been six MOFs in the placebo group and none in the study group (p=.023). Despite the

importance of this research, the results may not be generalizable to other patients with epilepsy, due to the specific in- and exclusion criteria. A less restricted sample was described in the clinical setting of Miller *et al*.[32]. They retrospectively reviewed an urban population of patients with epilepsy. All participants (n=81) had had two DXA scans at least five years apart (median 9.4 years, range 5-14.7). Eleven patients (13.6%) had sustained at least one MOF during follow-up, of whom two patients (18.2%) were prescribed bisphosphonates at their initial DXA scan. Lacking a control group, it is unclear whether anti-osteoporosis treatment influenced the incidence of MOFs. Whitney[33] adjusted for anti-osteoporosis treatment, by comparing five matched groups (n=828 per group) by epilepsy status (with or without) and use of osteoporosis medication (no user, consistent user, or new user). His study showed a twelve-month (non-traumatic) fracture risk attenuation in adults with epilepsy who were treated with anti-osteoporosis medication, especially in those who just started treatment.

In our study, we cannot draw conclusions about the efficacy of bisphosphonates on fractures, as it was ethically not justified to form a control group within our cohort. With regards to safety; two reported adverse effects of long-term bisphosphonate therapy are osteonecrosis of the jaw and atypical subtrochanteric femoral fractures[34]. To our knowledge, none of our study participants had suffered from these side effects.

Limitations

Although all our patients live in a sheltered and relatively safe environment, we observed a total of 156 fractures in 82 patients. Overall, this number might be underestimated for several reasons. Patients who were lost to follow-up were significantly older than patients who completed follow-up, which may probably have resulted in underestimation.

In addition, it can be difficult to diagnose fractures in patients with severe physical deformities or in patients who are unable to lie still for diagnostics. Patients are not always referred to the hospital when suspecting a fracture. For example, when there are no treatment options (e.g. a well-positioned nose fracture without obstruction of the airway) or when the fracture is considered as minor and does not affect physical outcome (e.g. a fractured toe or metatarsal bone in a patient who is not able to stand or walk). In those cases, a visit to the hospital results in a high burden and a lot of stress and does not lead to any benefit for the patient itself. Since we have only included radiographically verified fractures, these fractures are not accounted for in this study.

Also, patients may not be able to indicate pain or discomfort caused by a fracture due to poor intellectual and/or verbal capacities. In these (more disabled) patients, minor fractures may not have been recognized. All the above-mentioned reasons could have

led to an underestimation of the real fracture incidence. Due to the severity and the impact, we do believe that no major osteoporotic fractures had been missed during follow-up of the patients in our study.

Information regarding the circumstances and/or cause of the fracture was missing in some patients. In those cases, we were not able to differentiate between fractures caused by trauma or seizures. Fractures of unknown causes in our study, may have been the result of an unwitnessed trauma or seizure.

CONCLUSION

This study demonstrated that 40% of institutionalized adults with epilepsy and intellectual disability had at least one clinical fracture during seven years of follow-up, despite anti-osteoporosis treatment according to the Dutch guidelines. The use of (multiple) antiseizure drugs is known to decrease bone mineral density and increase fracture risk. In our study, at least 70% of the fractures had been caused by a fall and/or seizure. In addition to seizure reduction, it is essential to have a focus on fall prevention. Physical disabilities, comorbidity, behavioral issues and drug side effects might increase the risk of falling, especially in patients who are able to walk. This study emphasizes the complex and multifactorial nature of fractures in patients with epilepsy and intellectual disability. These patients already suffer from multiple physical disabilities and are mainly dependent on others for their daily living. Fractures have a high impact on their quality of life. Even unrecognized, fractures may cause pain, discomfort and further limit daily activities. In order to prevent fractures in this specific group, more research is needed to establish optimal treatment options.

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Prevalence and incidence of vertebral fractures: a 7-year follow-up study in institutionalized adults with refractory epilepsy and intellectual disability

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SUMMARY

Objective

The main objective of this cohort study is to determine the prevalence and incidence of morphometric vertebral fractures (VFs) over 7 years follow-up, in institutionalized adults with refractory epilepsy and intellectual disability (ID).

Methods

Dual-energy X-ray Absorptiometry (DXA) and Vertebral Fracture Assessment (VFA) were performed in 2009 and 2016. Vertebrae T4-L4 were assessed using quantitative morphometry. Severity of VFs was graded as 1 (mild; 20-25% reduction in height), 2 (moderate; 25-40% reduction) or 3 (severe; >40% reduction) according to the method described by Genant. Prevalent VFs were analyzed at baseline. VFs (grade 1, 2 or 3) present at follow-up, but not at baseline, were considered new VFs. Worsening VFs were defined as VFs with at least one grade deterioration at follow-up, compared to baseline (grade 1 to 2 or 3, or grade 2 to 3). Patients were treated with anti-osteoporosis treatment according to the Dutch guideline.

Results

Baseline and follow-up DXA and VFA could be obtained in 141 patients (87 male) aged between 18-79 years old (mean 44.8±15.7). At baseline, 56 patients had at least one prevalent VF. Patients with a prevalent VF were significantly older than patients without (49.2±13.7 vs 41.9±16.4, $p<.01$). After 7 years follow-up, 38 new VFs occurred in 27 patients and 15 patients had a worsening VF, leading to an overall cumulative incidence of 27.0%. VF incidence was significantly higher in patients with at least one prevalent VF at baseline (48.2% vs 12.9%, respectively, $p<.01$) compared to no VF.

Conclusion

In adults with refractory epilepsy VFA is challenging, due to physical and behavioral aspects, resulting in a substantial proportion of unevaluable vertebrae and scans. Nevertheless, 40% of the patients had a VF at baseline and after 7 years follow-up, 27% had at least one new and/or worsening VF despite adequate anti-osteoporosis treatment.

INTRODUCTION

Worldwide, approximately 50 million people are affected by epilepsy. About 70% of those affected can be successfully treated with antiseizure drugs[1]. Unfortunately, antiseizure drugs may have a negative impact on bone metabolism. The combination of bone mineral disorders (such as osteopenia and osteoporosis) and the use of antiseizure drugs has first been described around 1970 and focused on strong enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin and primidone[2-4]. In the intervening years, multiple studies have indicated the association between a decreased bone mineral density (BMD) and long-term use of antiseizure drugs[5-8], including antiseizure drugs with minimal to no enzyme-inducing effects[9-11].

Besides the use of antiseizure drugs, patients with epilepsy are at a higher risk for fractures, due to seizures[8,12] or (seizure-related) falls[13]. In addition, neurological disorders and drug side effects can cause dizziness, incoordination, ataxia, clumsiness and weakness. In patients with epilepsy, fracture rates are found to be two to six times higher than in the general population[6-8].

The most frequently occurring osteoporotic fractures are vertebral fractures (VFs)[14-16] and those are often underdiagnosed, because only one third of patients with VFs present with an acute symptomatic episode[17-19]. In patients with epilepsy, it has also been reported that VFs might occur with minor to no (seizure-related) trauma[20,21]. The presence, number and severity of VFs are strong predictors of future fracture risk, independent of age and BMD[22,23] and VFs are associated with an increased mortality rate[24-26].

The Dutch guideline on osteoporosis and fracture prevention recommends systematic evaluation of VFs in high risk patients with osteopenia and osteoporosis[27].

There is a lack of knowledge concerning the prevalence and incidence of VFs in institutionalized adult patients with refractory epilepsy and studies using standardized protocols for identifying VFs in this specific group are scarce. Therefore, the main objective of this study is to determine the prevalence and incidence of VFs in adults with refractory epilepsy and intellectual disability (ID), residing at a long-stay care facility between 2009 and 2016.

MATERIAL AND METHODS

Study population and design

This prospective cohort study included adult patients from Epilepsy Center Kempenhaeghe, a long-stay care facility for people with epilepsy and ID in the Netherlands. All patients have a diagnosis of epilepsy, caused by a variety of factors (i.e. structural, genetic, infectious, metabolic, immune or unknown) and almost all patients (99%) have some degree of intellectual disability, ranging from mild to profound.

In 2009, all patients aged 18 years or older (n=261), were invited for a fracture risk assessment, including dual-energy X-ray absorptiometry (DXA) measurements and a vertebral fracture assessment (VFA). Of these, 205 patients (or their legal representatives) agreed to participate (78.5%). In 2016, DXA and VFA were repeated. Patients with a missing VFA at baseline and/or follow-up, were excluded from analyses.

Patient characteristics (age, sex, length, weight, ID, Barthel scale, ambulatory status, use of cigars/cigarettes and alcohol, number and types of seizures) and medication use (antiseizure drugs, calcium, vitamin D, bisphosphonates) were collected through the medical records of the patients. In general, patients were recommended oral bisphosphonates according to the Dutch guidelines. At the care facility, all prescribed medications (including bisphosphonates and supplementation of vitamin D and calcium) are administered by nurses and/or taken under direct supervision.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local medical ethical committee of Epilepsy Center Kempenhaeghe, Heeze (NL26095.068.09). In 2009, informed consent was obtained from all individual participants and/or their legal representatives. During DXA and VFA procedures, all patients were accompanied by a familiar nurse and/or family member. Measurements were stopped when a patient refused to cooperate or showed significant signs of resistance.

DXA and VFA

Initial DXA and VFA measurements were performed between August 31st and September 29th 2009, and follow-up measurements between October 5th and November 30th 2016, using a Hologic densitometer (Discovery W and A, respectively).

BMD of lumbar spine (L1-L4), femoral neck and total hip was expressed as the amount of mineral (g) divided by the area scanned (cm^2) and in T-scores. T-scores compare data with sex-matched peak bone mass, which is attained at the age of 20-30 years. The

criteria of the World Health Organization (WHO) were used to classify bone mineral disorders, based on the lowest reported T-score. A T-score of -1.0 and above was considered as normal bone mass, a T-score between -1.0 and -2.5 as osteopenia and a T-score of -2.5 and below as osteoporosis[28].

For VFA, all scans of 2009 and 2016 were evaluated in a random order by one trained staff member, who was blinded for previous VF and DXA outcomes. First, the evaluable vertebrae were determined for each individual, starting with the identification of L4. Vertebrae with deformities were excluded from the vertebral fracture analyses. In case of doubt, images were discussed with two experienced researchers to reach consensus. Subsequently, vertebral height at the anterior, middle and posterior part of the vertebral body was measured and the percent reduction in height was used to grade VFs as grade 0 (<20% reduction in height), 1 (mild; 20-25% reduction in height), 2 (moderate; 25-40% reduction) or 3 (severe; >40% reduction) according to the method described by Genant[29].

Incident VFs were defined as new or worsening VFs. A new VF was defined as a VF (grade 1, 2 or 3) that was present at the follow-up scan, but not at baseline (grade 0). A worsening VF was defined as a VF with at least one grade deterioration at follow-up, compared to baseline (i.e. from grade 1 to 2 or 3, or from grade 2 to 3).

Statistical analysis

The primary outcome of this study is VF incidence after seven years follow-up. Data are presented as means (±SD) or as percentages. Cumulative incidences were calculated as the number of patients with incident VFs divided by the total number of patients. Differences between groups were compared using Student's *t*-test for continuous variables and Pearson's Chi-Square or Fisher's exact test for categorical variables. All outcomes were analyzed using SPSS version 25 (IBM Corporation, UK). Statistical tests were two-tailed with a level of significance of $p<.05$.

RESULTS

From a total of 205 patients who gave informed consent, a DXA including VFA was obtained in 184 patients at baseline (Figure 1). At follow-up (mean follow-up duration of 7.1±0.04 years), DXA and VFA could be obtained in 141 patients. In total, 64 patients (31.2%) were lost to follow-up or had a missing VFA in 2016. Patients without follow-up measurements were older (51.2±17.7 vs 44.8±15.7 years, p=.011), scored worse on the Barthel scale (8.9±7.3 vs 12.8±5.9, p<.01) and were less often able to walk (57.8% vs 78.0%, p<.01) than patients with complete follow-up.

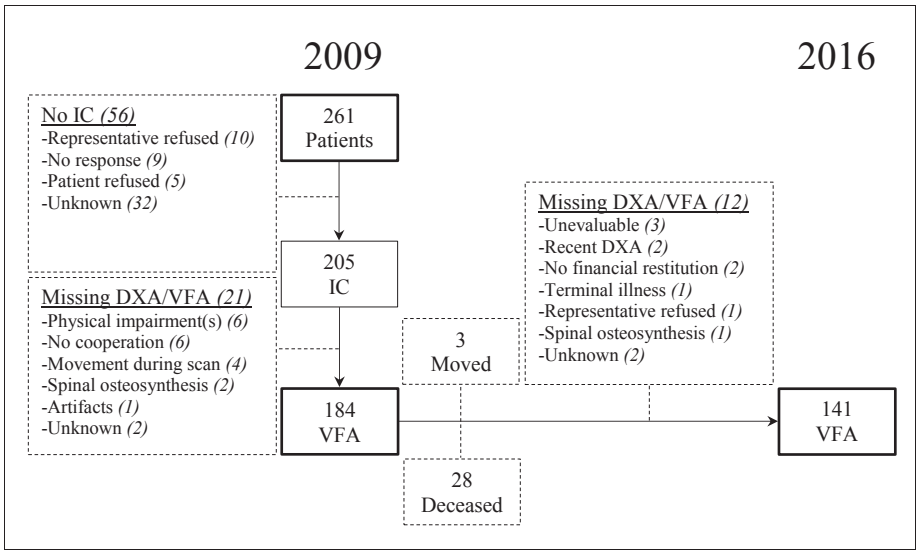

Figure 1. Flowchart of included and evaluable patients

DXA=Dual-Energy X-Ray Absorptiometry, IC=Informed consent, VFA=Vertebral Fracture Assessment

Baseline characteristics of the 141 fully evaluable patients (87 male, 61.7%) aged between 18-79 years (mean 44.8±15.7) are summarized in Table 1. The average number of prescribed antiseizure drugs at baseline was 2.5 (SD±1.0). Most prescribed were carbamazepine (61.0%), valproic acid (44.7%) and lamotrigine (36.9%). A total of 76 patients (53.9%) had no changes in types of antiseizure drugs that were prescribed during follow-up. Forty-eight patients (34.0%) stopped at least one antiseizure drug and 51 patients (36.2%) started at least one other antiseizure drug. Between baseline and follow-up, a total of 117,510 seizures were reported (Table 2). The median number of seizures per patient was 344 (IQR 64-1193) over seven years. Twelve patients (8.5%)

were reported to be seizure-free. Half of the patients (49.6%) had more than one seizure a week. Of all seizures, a focal onset was reported in 36.6% and a generalized onset in 18.5%. The onset of the remaining seizures (45.0%) was unknown.

Table 1. Baseline (2009) and follow-up (2016) characteristics of 141 patients with refractory epilepsy and intellectual disability

		2009			2016	
Characteristics	**n**	**Mean±SD**	**%**	**n**	**Mean±SD**	**%**
Age (years)	141	44.8±15.7		141	52.0±15.7	
Sex						
Male	87		61.7			
Female	54		38.3			
Body Mass Index (in kg/m^2)	141	25.4±4.0		141	25.5±3.8	
Underweight (<18.5)	2		1.4	1		0.7
Normal weight (18.5-25)	67		47.5	69		48.9
Overweight (25-30)	52		36.9	49		34.8
Obese (≥30)	20		14.2	22		15.6
Intellectual disability (IQ score)						
None (≥70)	2		1.4			
Mild (55-70)	43		30.5			
Moderate (40-55)	52		36.9			
Severe (25-40)	38		27.0			
Profound (<25)	6		4.3			
Barthel scale (0-20)	141	12.8±5.9		141	11.8±6.3	
Ambulatory status						
Immobile	16		11.3	21		14.9
Independent in wheelchair	15		10.6	19		13.5
Walk with aid	11		7.8	21		14.9
Walk without aid	99		70.2	80		56.7
Smoking (cigars/cigarettes a day)						
None	123		87.2			
1-5	5		3.5			
6-10	1		0.7			
11-15	3		2.1			

Table 1. Continued

		2009			2016	
Characteristics	**n**	**Mean±SD**	**%**	**n**	**Mean±SD**	**%**
16-20	5		3.5			
>20	4		2.8			
Alcohol (units a week)						
None	110		78.0			
1-2	16		11.3			
3-5	8		5.7			
6-10	6		4.3			
>10	1		0.7			
Number of antiseizure drugs	141	2.5±1.0		141	2.6±1.1	
None	5		3.5	4		2.8
1	14		9.9	14		9.9
2	47		33.3	51		36.2
3	53		37.6	48		34.0
4	19		13.5	18		12.8
5	3		2.1	6		4.3
≥1 Enzyme-inducing drug*	120		85.1	117		83.0
Strong Carbamazepine	86		61.0	79		56.0
Phenobarbital	15		10.6	13		9.2
Phenytoin	32		22.7	26		18.4
Primidone	-		-	1		0.7
Weak Oxcarbazepine	21		14.9	19		13.5
Topiramate	22		15.6	22		15.6
≥1 Non-enzyme-inducing drug*	108		76.6	110		78.0
Acetazolamide	1		0.7	3		2.1
Clonazepam	24		17.0	23		16.3
Ethosuximide	3		2.1	3		2.1
Felbamate	1		0.7	1		0.7
Gabapentin	6		4.3	3		2.1
Lacosamide	1		0.7	11		7.8
Lamotrigine	52		36.9	51		36.2
Levetiracetam	22		15.6	22		15.6

Table 1. Continued

	2009			2016	
Characteristics	**n**	**Mean±SD**	**%**	**n**	**Mean±SD**	**%**
Perampanel	-		-	3		2.1
Pregabalin	6		4.3	7		5.0
Valproic acid	63		44.7	69		48.9
Vigabatrin	1		0.7	1		0.7
Zonisamide	2		1.4	5		3.5
≥1 enzyme-inducing and ≥1 non-enzyme-inducing drug	92		65.2	90		63.8

IQ=Intelligence quotient, SD=Standard deviation
*Due to polytherapy and/or the use of both enzyme- and non-enzyme-inducing antiseizure drugs, total numbers add up to more than 100%.

At baseline, 32 patients (22.7%) were classified as having a normal BMD, 70 (49.6%) as having osteopenia and 39 (27.7%) as having osteoporosis. At follow-up, 26 patients (18.4%) had a normal BMD, 64 (45.4%) had osteopenia and 50 (35.5%) osteoporosis. In one patient (0.7%) the BMD result was missing. At baseline, 24 patients (17.0%) were prescribed calcium and 19 (13.5%) vitamin D.

VFA

Vertebrae were excluded for VFA because of projection of arms or hands (n=29), intestinal gas (n=25), movement errors (n=18), the presence of osteosynthetic material (n=12) and projection of jewelry or clothing (n=2). Within the range of T4 to L4, 80.1% of the vertebrae were considered evaluable at baseline versus 76.1% at follow-up. Consequently, a total of 23 prevalent VFs (in 19 patients) were not evaluable at follow-up, and 5 fractured vertebrae (in 4 patients) at follow-up were not evaluable at baseline.

Prevalent VFs at baseline

At baseline, 56 of 141 patients (39.7%) had at least one prevalent VF (Table 3) of whom 40 patients (28.4%) had ≥1 mild VF, 34 (24.1%) had ≥1 moderate VF and 3 patients (2.1%) had a severe VF. Twenty of these patients (14.2%) had multiple VFs with different grades. About half of the prevalent VFs (52.5%) were located in the thoracolumbar region (T11-L1). When comparing patients with and without a prevalent VF, those with a VF were significantly older (49.2±13.7 vs 41.9±16.4, $p<.01$). No significant differences were found regarding Barthel score ($p=.294$) and ambulatory status ($p=.264$). The proportion of men and women with at least one VF was not different (46.0% vs 29.6%, $p=.054$).

Table 2. Seizure frequency and types of seizures between baseline (2009) and follow-up (2016) of 141 patients with refractory epilepsy and intellectual disability

Seizure frequency			**n of patients**	**%**		
None			12	8.5		
Less than 1 a year			9	6.4		
1 a month to 1 a year			21	14.9		
1 a week to 1 a month			29	20.6		
1 a day to 1 a week			60	42.6		
More than 1 a day			10	7.1		
Type of seizure			**n of patients**	**%**	**n of seizures**	**%**
Focal onset	Motor	Automatisms	62	66.0	13,205	11.2
		Atonic	11		2,887	2.5
		Clonic	22		1,599	1.4
		Hyperkinetic	15		5,202	4.4
		Myoclonic	5		2,300	2.0
		Tonic	20		10,251	8.7
	Non-motor	Autonomic	9	32.6	1,196	1.0
		Behavior arrest	27		4,276	3.6
		Sensory	12		1,537	1.3
	Focal to bilateral tonic clonic		5	3.5	505	0.4
Generalized onset	Motor	Atonic	6	29.1	203	0.2
		Clonic	6		210	0.2
		Myoclonic	8		1,113	0.9
		Tonic	37		20,168	17.2
	Non-motor	Atypical	1	1.4	2	0.0
		Typical	1		6	0.0
Unknown onset	Motor	Myoclonic	23	71.6	3,109	2.6
		Tonic	40		17,757	15.1
		Tonic Clonic*	86		13,806	11.7
	Non-motor	Behavior arrest	2	1.4	104	0.1
	Unclassified		122	86.5	18,074	15.4
		Total			**117,510**	**100.0**

*Incomplete information to differentiate between 'generalized tonic clonic' and 'focal to bilateral tonic-clonic' seizures

Table 3. Prevalence and cumulative incidence of VFs, stratified by presence and severity of VFs at baseline (n=141)

	n patients (prevalence %)		n patients (cumulative incidence %)		
	Baseline*	**Follow-up***	**New VFs**	**Worsening VFs**	**Incident VFs**
No VF	85 (60.3)	80 (56.7)	11 (12.9)	-	11 (12.9)
VF	56 (39.7)	61 (43.3)	16 (28.6)	15 (26.8)	27** (48.2)
Grade 1	21 (14.9)	17 (12.1)	5 (23.8)	7 (33.3)	9** (42.9)
Grade 2	32 (22.7)	37 (26.2)	10 (31.2)	6 (18.8)	15** (46.9)
Grade 3	3 (2.1)	7 (5.0)	1 (33.3)	2 (66.7)	3 (100.0)
		Total	27 (19.1)	15 (10.6)	38* (27.0)

VFs=Vertebral fractures

* In 19 patients prevalent VFs were not evaluable at follow-up and in 4 patients VFs at follow-up were not evaluable at baseline.

**Four patients had both new and worsening VFs.

Incident VFs after seven years follow-up

After seven years follow-up, 38 new VFs occurred in 27 patients (19.1%) and 15 patients (10.6%) had a worsening VF (Table 3). Four patients (2.8%) had both new and worsening VFs, leading to an overall cumulative incidence of 27.0% over seven years. Of all patients with a new morphometric VF, only two (7.4%) were diagnosed as having a clinical (symptomatic) VF.

The cumulative VF incidence was significantly higher in patients with at least one prevalent VF at baseline (48.2% vs 12.9%, respectively, $p<.01$) compared to no VF at baseline (Figure 2). No significant differences regarding age ($p=.125$), sex ($p=.544$), Barthel scale ($p=.752$), ambulatory status ($p=.451$), number of seizures ($p=.561$) and severity of prevalent VFs at baseline ($p=.534$) were found between patients with and without an incident VF. No significant differences in VF incidence were found between patients who were seizure-free (25.0%) and those who were not (27.1%, $p>.999$). In patients with osteoporosis at baseline, VF incidence was significantly higher (41.0%) than in patients with a normal BMD (18.8%, $p=.043$) or osteopenia (22.9%, $p=.046$).

Bisphosphonates use

A total of 82 patients (58.2%) had never used bisphosphonates at the end of follow-up. Thirty-one patients (22.0%) started treatment with bisphosphonates during the follow-up period, for a duration of at least 1 year. Of those, 23 (16.3%) started within 1 year after baseline. In this particular group, the incidence of VFs was 39.1%, compared to 19.5% ($p=.051$) in the group of patients who have never used bisphosphonates.

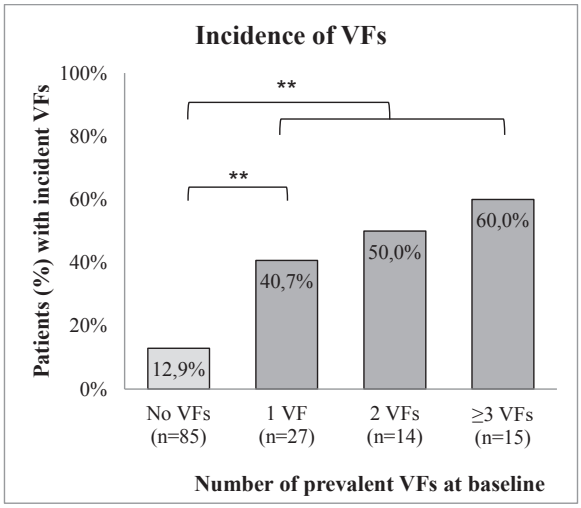

Figure 2. Incidence of VFs after seven years follow-up, stratified by the presence and number of prevalent VFs at baseline

**p<.01

DISCUSSION

The prevalence (39.7%) and 7-year cumulative incidence (27.0%) of morphometric VFs in institutionalized adult patients with refractory epilepsy is found to be high, even though the study population is relatively young (mean age 44.8±15.7 years) with a predominance of male patients. In a population-based study in the Netherlands, the prevalence of VFs in men and women aged 55 and over, was found to be 6.9% and 7.6%, respectively[30]. Studies reporting on VFs in patients with epilepsy are scarce. To our knowledge, our study is among the first in this population to address VFs longitudinally and in a systematic way.

VF prevalence at baseline in our study is higher (39.7% overall, 46.0% in males) than reported by Lazzari *et al*.[31] in male veterans with epilepsy and chronic use of antiseizure drugs (30%). Noteworthy, they attributed the high prevalence to the use of tobacco (71%) and alcohol (35%) in their study participants. In our study population, though, only 18 patients (12.8%) smoked at baseline and 31 patients (22.0%) occasionally drank alcohol. The difference might be explained by the inclusion of study participants, as Lazzari *et al*.[31] included ambulatory outpatients who were not osteoporotic at baseline. In addition, only 10% of their study participants was on polytherapy[31], vs 86.5% of our patients.

The incidence of VFs in patients without a prevalent VF in our study was twice as high (7-year incidence of 12.9%) compared to the annual VF incidence of 0.9% reported by Nevitt *et al*.[32] in postmenopausal women, aged 65 or older, without a prevalent VF. The risk of (vertebral and non-vertebral) fractures is shown to be higher as the number and severity of VFs is greater[33-36]. We observed that the incidence of VFs increased with the presence, but not with the number or severity of prevalent VFs.

Annegers *et al*.[20] assessed the incidence of clinical fractures (both vertebral as non-vertebral) among patients with unprovoked seizures without using a standardized protocol for detection of VFs. As a result, only symptomatic VFs were analyzed, probably leading to an underestimation of the total number of VFs. Based on their findings, Annegers *et al*.[20] concluded that the incidence of VFs in patients with epilepsy decreased with duration of epilepsy (11.1/1000 p-y at the first years of follow-up to 4.4/1000 p-y at ≥10 years after diagnosis) and with duration of treatment with antiseizure drugs (10.6/1000 p-y during the first 5 years to 6.1/1000 p-y at ≥10 years of treatment with antiseizure drugs). Similarly, Vasconcelos[21] concluded that in his study, many VFs occurred during the first, second or third seizure the patient had ever experienced. As for all fractures, Vestergaard *et al*.[37] found an increased risk within the first year after diagnosis of epilepsy. They provided

two possible explanations: 1) fractures may be the first presentation of epilepsy, or 2) seizure control has not been achieved in the initial period following diagnosis[37]. The first possibility is not likely to explain the high incidence of VFs in our study group, since most of the patients have been diagnosed in childhood. The second explanation might be more relevant for our study group. In most of our patients, seizure control remains difficult, as shown by the high seizure frequency and the number of patients (46.1%) who had changes in types of prescribed antiseizure drugs during the study.

In our study, a total of 117,510 seizures were reported, including many seizures with a generalized and/or motor onset. In a systematic review of Grzonka *et al.*[12] thoracic and lumbar vertebral compression fractures were found to be among the most frequently reported fractures (14 of 48 in detail described fractures) as a direct consequence of generalized convulsive seizures and/or status epilepticus. Since we performed a systematic assessment of morphometric VFs, independent of the moment of seizures or trauma, no conclusions can be drawn regarding preceding factors, like seizures or (seizure-related) falls. However, of the twelve patients who were seizure-free, three (25.0%) patients had incident VFs, eliminating seizures as a cause in those cases. Desai *et al.*[38] and Vestergaard *et al.*[37] suggested that antiseizure treatment contributes to the increased fracture risk, independent of the influence of seizures.

Retrospectively, of the patients who were diagnosed with a new morphometric VF, only two (7.4%) presented themselves at the hospital for back pain. The rest of the patients either experienced no pain, or more likely, they were not able to express it. Increased awareness among professionals for the presence of subclinical VFs in these patients is therefore essential.

Early reports about bone mineral disorders and antiseizure drugs focused on strong enzyme-inducing drugs which induce the liver's cytochrome P450 enzyme-system, resulting in an increased vitamin D metabolism and bone loss. However, antiseizure drugs with minimal to no enzyme-inducing effects are shown to decrease BMD as well, even though the multiple pathophysiological mechanisms are far from clear[9-11], In our study, 65.2% of the patients used both enzyme- and non-enzyme-inducing antiseizure drugs at baseline. As for enzyme-inducers, oxcarbazepine and topiramate are weaker inducers than carbamazepine, phenobarbital, phenytoin and primidone. The majority (82.5%; 99 of 120) of the patients on enzyme-inducers were prescribed strong inducing antiseizure drugs at baseline. Six patients went from using enzyme-inducing drugs to using no enzyme-inducing drugs during the study. Due to the many changes in prescriptions and the use of multiple types of antiseizure drugs, no conclusions can be drawn regarding the effects of (strong) enzyme- versus non-enzyme-inducing drugs.

Strengths and limitations

This study has limitations. Follow-up results could only be obtained in half (54.0%) of all invited patients (n=261). Our results, may therefore represent the better part of our total group of institutionalized patients with refractory epilepsy and ID. Of the patients who had a VFA at baseline, 15.2% (n=28) died during follow-up, highlighting the frailty of the participants.

In this specific study population, VFA appeared to be complicated. Both physical and behavioral issues led to challenges and failed scans in multiple patients. In addition, image artifacts and disrupting factors were frequently present, resulting in a substantial number of baseline vertebrae with and without prevalent VFs not evaluable at follow-up, and in vertebrae with VFs at follow-up which could not be evaluated at baseline. All images were analyzed by the same researcher and discussed with two other researchers for consensus in case of doubt. However, some technical issues may have led to an underestimation of the total number of VFs and the proportion of patients diagnosed with VFs.

Also, the exact timing of incident VFs is unknown, since we only had one follow-up moment seven years after baseline assessment. In our study population all patients suffered from epilepsy since childhood, so no conclusions can be drawn regarding the influence of duration of epilepsy or antiseizure treatment on VF incidence.

We followed a large group of patients over seven years and started treatment with bisphosphonates according to the Dutch guidelines. In patients who started treatment after baseline, the incidence of VFs was found to be higher than in patients who had never used bisphosphonates. This confirms that patients who are osteoporotic and in need of therapy have a higher risk of VFs than those who have a normal BMD. This study was not designed as an intervention study and it was ethically not justified to define a control group within our cohort. Hence, no conclusions can be drawn regarding the effects of bisphosphonate therapy in our study group.

CONCLUSION

In adults with refractory epilepsy VFA is challenging, due to physical and behavioral aspects, resulting in a substantial proportion of unevaluable vertebrae and scans. Nevertheless, 40% of the evaluable patients had a VF at baseline and after seven years follow-up, 27% had at least one new and/or worsening VF despite anti-osteoporosis treatment according to the Dutch guidelines. This high prevalence and incidence of VFs emphasizes the importance of routine screening with DXA and VFA in institutionalized adult patients with refractory epilepsy. Early recognition may improve prevention and treatment of VFs.

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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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SUMMARY

Objective

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.

INTRODUCTION

Worldwide, approximately 50 million people suffer from epilepsy[1]. Although most patients benefit from treatment with antiseizure drugs, a minority of patients does not respond to antiseizure drugs even with adequate dosage in either mono- or polytherapy[2]. Long-term exposure to (particularly enzyme-inducing) antiseizure drugs 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 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 antiseizure drug 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 antiseizure drug 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.

MATERIAL AND METHODS

Study population and design

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 antiseizure drug 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.

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].

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 ≤-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 ≥-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).

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.

Statistical analysis

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

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.

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.

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 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.

RESULTS

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

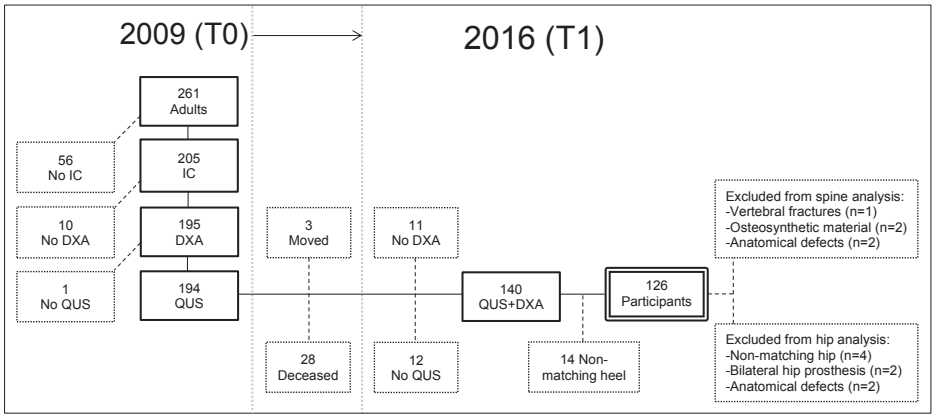

Figure 1. Flowchart of participants

IC=Informed Consent, DXA=Dual-energy X-ray Absorptiometry, QUS=Quantitative Ultrasound

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 antiseizure drugs 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 Figure 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).

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

	Total (n=126)	
	n	**Mean±SD or %**
Age (in years)		44.6±15.4
Sex		
Male	78	61.9
Female	48	38.1
Body Mass Index (kg/m^2)		25.6±4.16
Underweight (<18.5)	2	1.6
Normal weight (18.5-25)	57	45.2
Overweight (25-30)	45	35.7
Obese (≥30)	22	17.5
Intellectual disability		
Normal (IQ ≥70)	2	1.6
Mild (IQ 55-70)	36	28.6
Moderate (IQ 40-55)	49	38.9
Severe (IQ 25-40)	32	25.4
Profound (IQ <25)	7	5.6
Barthel scale		
20	16	12.7
15-19	45	35.7
10-14	32	25.4
5-9	17	13.5
0-4	16	12.7
Ambulatory status		
Immobile	13	10.3
Independent in wheelchair	15	11.9
Walk with aid	8	6.3
Walk without aid	90	71.4
Epilepsy duration (in years)		38.9±13.8
Cholecalciferol and/or calcium use		
Yes	86	68.3
No	40	31.7

	Group A (n=53)		Group B (n=73)		*p*
	n	**Mean±SD or %**	**n**	**Mean±SD or %**	
		50.7±14.5		40.3±14.7	<.001**
					.658
	34	64.2	44	60.3	
	19	35.8	29	39.7	
		25.0±3.42		26.1±4.59	.129
	1	1.9	1	1.4	
	27	50.9	30	41.1	
	19	35.8	26	35.6	
	6	11.3	16	21.9	
					.751
	2	3.8	0	0	
	15	28.3	21	28.8	
	20	37.7	29	39.7	
	12	22.6	20	27.4	
	4	7.5	3	4.1	
					.096
	5	9.4	11	15.1	
	18	34.0	27	37	
	10	18.9	22	30.1	
	9	17.0	8	11.0	
	11	20.8	5	6.8	
					.003*
	10	18.9	3	4.1	
	9	17.0	6	8.2	
	3	5.7	5	6.8	
	31	58.5	59	80.8	
		43.1±12.5		35.9±14.0	.004*
					<.001**
	46	86.8	40	54.8	
	7	13.2	33	45.2	

Table 1. Continued.

	Total (n=126)	
	n	**Mean±SD or %**
Number of antiseizure drugs		
None	6	4.8
1	11	8.7
2	40	31.7
3	49	38.9
4	18	14.3
5	2	1.6
SOS (m/s)		1519.6±27.3
BUA (dB/MHz)		50.3±19.5
Est. heel BMD (g/cm^2)		0.382±0.117
LS BMD (g/cm^2)		0.966±0.158
FN BMD (g/cm^2)		0.710±0.136
TH BMD (g/cm^2)		0.842±0.156

*p<.05, **p<.001. SD=Standard deviation, 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

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.

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.

Group A (n=53)		Group B (n=73)		*p*
n	**Mean±SD or %**	**n**	**Mean±SD or %**	
				.613
4	7.5	2	2.7	
6	11.3	5	6.8	
13	24.5	27	37.0	
23	43.4	26	35.6	
7	13.2	11	15.1	
0	0	2	2.7	
	1506.0±22.2		1529.3±26.5	<.001**
	41.1±17.2		56.9±18.4	<.001**
	0.323±0.096		0.425±0.112	<.001**
	0.875±0.149		1.031±0.131	<.001**
	0.621±0.100		0.770±0.124	<.001**
	0.735±0.126		0.914±0.132	<.001**

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.

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

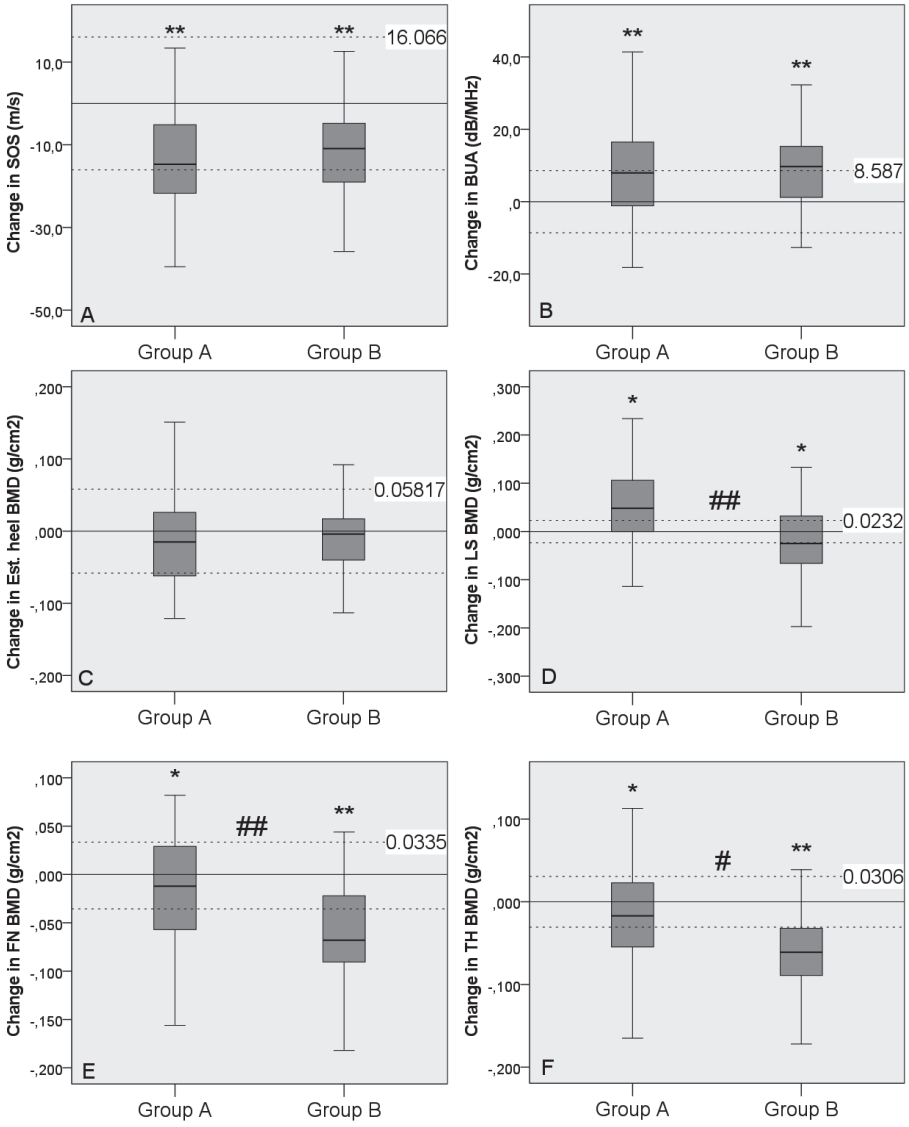

Figure 2. Absolute changes of bone data measured in patients treated (group A) and patients not treated with bisphosphonates (group B) for A.) Speed of sound, B.) Broadband ultrasound attenuation, C.) Estimated heel BMD, D.) Lumbar spine BMD, E.) Femoral neck BMD and F.) Total hip BMD.

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

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)	
	LSC	**Mean change±SE**	**n (%) exceeding pLSC**
SOS (m/s)	(-)16.066	-13.581±2.691	5 (9.6)
BUA (dB/MHz)	(-)8.587	7.325±1.801	24 (46.2)
Est.heel BMD (g/cm^2)	(-)0.05817	-0.015±0.010	8 (15.1)
LS BMD (g/cm^2)	(-)0.0232	0.043±0.012**	31 (62.0)**
FN BMD (g/cm^2)	(-)0.0335	-0.020±0.010**	10 (21.3)*
TH BMD (g/cm^2)	(-)0.0306	-0.021±0.010*	8 (17.0)

*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**
ΔLS BMD$_A$	.37* (.009)	.38* (.008)	.43* (.002)
ΔFN BMD$_A$	.15 (.333)	.47* (.001)	.31* (.033)
ΔTH BMD$_A$	.22 (.148)	.59** (<.001)	.42* (.003)
	ΔSOS	**ΔBUA**	**ΔEst. heel BMD**
ΔLS BMD$_B$	.13 (.290)	.14 (.243)	.15 (.213)
ΔFN BMD$_B$	.22 (.065)	.40* (.001)	.34* (.004)
ΔTH 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

Group A (n=53)		Group B (n=73)	
n (%) exceeding nLSC	Mean change±SE	n (%) exceeding pLSC	n (%) exceeding nLSC
22 (42.3)	-10.863±1.913	5 (6.8)	29 (39.7)
7 (13.5)	8.968±1.327	40 (54.8)	6 (8.2)
14 (26.4)	-0.005±0.007	11 (15.1)	15 (20.5)
11 (22.0)*	-0.029±0.009	21 (29.6)	36 (50.7)
14 (29.8)**	-0.063±0.007	3 (4.2)	45 (63.4)
19 (40.4)**	-0.064±0.008	5 (7.0)	54 (76.1)

DISCUSSION

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

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].

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 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 antiseizure drug use, limited mobility and little sun exposure. Why 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].

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.

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. antiseizure drugs, 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.

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 antiseizure drug therapy, such as polytherapy, treatment duration and type of antiseizure drugs 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.

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 antiseizure drug 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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Assessment of Trabecular Bone Score: a 7-year follow-up study in institutionalized adults with refractory epilepsy and intellectual disability

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SUMMARY

Objective

The aim of this longitudinal study was to assess trabecular bone scores (TBS) in institutionalized adults with refractory epilepsy and intellectual disability and to study the association of TBS and incident fractures during seven years of follow-up.

Methods

In 2009 and 2016, all institutionalized adult patients of a long-stay care facility in the Netherlands (n=261) were invited to undergo a dual-energy X-ray absorptiometry (DXA) including vertebral fracture assessment (VFA) and assessment of TBS. Vertebrae T4-L4 were analyzed using quantitative morphometry. New and worsening vertebral fractures (VFs) were considered as incident VFs. Data regarding clinical fractures were extracted from the medical files. Patients were treated with anti-osteoporosis medication according to the Dutch guideline.

Results

Baseline and follow-up DXA, VFA and TBS could be obtained in 136 patients (83 male) aged between 18 and 79 years old (44.7±15.5). At baseline, 36 patients (26.5%) were diagnosed with osteoporosis, 68 (50.0%) with osteopenia and 32 patients (23.5%) had a normal bone mineral density (BMD). As for TBS, 26 patients (19.1%) had a partially degraded microarchitecture and 26 patients (19.1%) a degraded microarchitecture. During seven years of follow-up, 80 patients (59%) sustained at least one fracture, of which 28 patients (35%) had one or more major osteoporotic fractures. Thirty-four patients (25.0%) had at least one new or worsening morphometric VF. Compared to baseline, TBS significantly decreased over seven years of follow-up in non-treated patients (-0.039±0.064, $p<.001$). In patients who were treated with bisphosphonates for more than one year during follow-up, TBS did not change significantly ($p=.093$). In multivariate analyses, no significant associations were found between TBS at baseline and incident fractures during follow-up.

Conclusion

In this study, we found a high incidence of fractures and TBS decreased significantly over seven years of follow-up in non-treated institutionalized adult patients with refractory epilepsy and intellectual disability, but TBS was not associated with incident fractures.

INTRODUCTION

Osteoporosis is defined as "a systemic skeletal disorder characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture"[1]. The current gold standard for diagnosing osteoporosis is the assessment of bone mineral density (BMD) by using a dual-energy x-ray absorptiometry scan (DXA).

In 2019, the prevalence of osteoporosis in Europe was estimated at 32.0 million people; 5.6% of the total population[2]. A high prevalence of osteopenia, osteoporosis (48% and 32%, respectively) and a high fracture risk has been reported in patients with refractory epilepsy and intellectual disability (ID) residing in a long-term care facility[3,4]. In these patients, the long-term exposure to multiple antiseizure drugs may attribute to decreased BMD[5-7]. Although BMD is a key determinant of bone strength and therefore fracture risk, the proportion of non-osteoporotic patients with fractures, is substantial[8].

Another determinant of bone strength is microarchitecture of the bone. With the development of the trabecular bone score (TBS), a non-invasive, gray-level textural measurement of bone microarchitecture, derived from lumbar spine DXA images[9], it is feasible to study trabecular architecture on previously obtained DXA images. Measurement of TBS enables physicians to differentiate between patients who have similar BMDs, but different microarchitectures of the bone[10,11]. Lumbar spine TBS, in combination with BMD measurement, has been shown to improve fracture risk prediction as compared to the measurement of BMD alone[12-14].

In several patient groups, the use of TBS has been well established; it has been shown to be associated with fractures in patients with primary osteoporosis and secondary osteoporosis caused by diabetes, rheumatoid arthritis, chronic kidney disease, adrenal incidentaloma, HIV, primary hyperparathyroidism and in patients on long-term glucocorticoid therapy[15,16]. To our knowledge, TBS has not been studied (longitudinally) in patients with epilepsy, who are on chronic antiseizure drug treatment and have an estimated 2- to 6-fold increased risk of fractures[7].

We therefore aimed to study the bone microarchitecture obtained from lumbar spine DXA images by TBS in institutionalized adults with refractory epilepsy and intellectual disability, as well as the association of TBS with incident fractures during seven years of follow-up.

MATERIAL AND METHODS

Study population

This retrospective cohort study was conducted at the long-stay care department of a tertiary care facility for patients with epilepsy in the Netherlands. All patients had a diagnosis of epilepsy and the majority (99%) had a mild to profound ID.

In 2009 and 2016, all adult patients of 18 years or older (n=261) were invited to participate in a study regarding bone status, including DXA measurements and a Vertebral Fracture Assessment (VFA). The study was conducted in accordance with the Declaration of Helsinki and was approved by the local medical ethical committee of Epilepsy Center Kempenhaeghe, Heeze (NL26095.068.09). A total of 205 patients and/or their legal representatives (78.5%) provided informed consent (47 declined and 9 did not respond). All patients were accompanied by a familiar nurse and/or family member during measurements and procedures were stopped when a patient refused or showed significant signs of resistance. For this study, patients were excluded if lumbar spine DXA or VFA was missing at baseline or follow-up.

Patients were prescribed treatment with oral bisphosphonates in accordance with the national guidelines[17,18]; in case of a diagnosis of osteoporosis or osteopenia in combination with a vertebral fracture grade two or three. Additionally, patients were prescribed supplementation of calcium and vitamin D, if indicated. None of the study participants were treated with denosumab, strontium ranelate, raloxifene, teriparatide or recombinant parathyroid hormone during follow-up.

Study design and data collection

DXA

BMD measurements of lumbar spine (L1-L4), femoral neck and total hip were performed by DXA (Hologic Discovery W/A). BMD values were expressed as the amount of mineral (in gram) divided by the area that was scanned (in cm^2). An individual's BMD was compared to a sex-matched reference database (as provided by the manufacturer), containing peak bone mass values of a healthy population. The T-score is the number of standard deviations (SD) below or above the mean of this reference population. In accordance with the classification of the World Health Organization (WHO), a T-score of -1.0 or above at one of the three locations was considered as normal BMD, a T-score between -1.0 and -2.5 as osteopenia and a T-score of -2.5 or below as osteoporosis[19].

VFA

All scans were evaluated in a random order by one trained staff member, who was blinded for previous scan outcomes. VFA started with the identification of the evaluable vertebrae between T4 and L4 on lateral DXA images. Vertebrae with deformities or artifacts were excluded from analysis. A vertebra was considered evaluable if the posterior and anterior cortices and both endplates were fully and clearly visible. If this was not the case, the vertebra was not evaluated. Subsequently, vertebrae with deformities, e.g. degenerative changes or Scheuermann's disease, were excluded. All evaluable vertebrae were morphometrically assessed with measurement of the anterior, middle and posterior height. Following the method as described by Genant *et al.*[20], vertebrae were classified as no VF (less than 20% height reduction), mild VF (grade 1; 20-24% height reduction), moderate VF (grade 2; 25-39% height reduction) or severe VF (grade 3; ≥40% height reduction). New VFs were defined as VFs (grade 1, 2 or 3) present at follow-up, but not at baseline. Worsening VFs were defined as VFs with at least one grade deterioration at follow-up, compared to baseline (from grade 1 to 2 or 3, or from grade 2 to 3). Both new and worsening VFs during follow-up, were considered as incident VFs.

TBS

All DXA spine images were reanalyzed to obtain TBS data, using TBS iNsight software version V3.03 (Medimaps Group, Geneva, Switzerland). Each vertebra between L1 and L4 was assessed and mean TBS was calculated. Vertebrae that were excluded from BMD or VFA analysis (due to the presence of a VF or artifacts), were also excluded from TBS analysis. For the analysis, the trabecular microstructure is projected onto a plane, generating a 2D image with pixel-to-pixel gray-level variations. A variogram (calculated as the sum of the squared gray-level differences between pixels at a specific distance) can estimate a 3D structure. TBS (unitless) is then calculated as the slope of the log-log transform of the variogram, where the slope characterizes the rate of gray-level amplitude variations[21]. A TBS value of 1.310 or above was considered as normal microarchitecture, a TBS value between 1.230 and 1.310 as partially degraded microarchitecture and values below 1.230 as degraded microarchitecture[22].

Clinical fractures

The patients' medical records were screened for clinical fractures. Major osteoporotic fractures (MOF) were defined as fractures of hip, clinical spine, forearm and proximal humerus[23].

Statistical analysis

The primary outcome of this study is the assessment of TBS. Baseline and follow-up measurements of TBS and BMD and changes over seven years are given. A subgroup analysis for bisphosphonate use (no use vs more than one year during follow-up) was performed using Student's *t*-tests. Odds ratios were calculated to study the association between TBS and fractures, with adjustment for age, BMD of femoral neck, prevalent VF and body mass index (BMI) at baseline.

Data are presented as means (±SD), medians (interquartile range, IQR) or as frequencies (percentages). All outcomes were analyzed using SPSS version 27 (IBM Corporation, UK). Statistical tests were two-tailed with a level of significance of .05.

RESULTS

A total of 136 patients (83 male, 61%) aged between 18-79 years (mean 44.7±15.5) were eligible for analysis. Baseline characteristics of the study participants are summarized in Table 1. The majority (88.2%) of the patients was on polytherapy with antiseizure drugs. Most prescribed were carbamazepine (62.5%), valproic acid (44.9%) and clobazam (40.4%). At baseline, 14 patients (10.3%) were prescribed calcium supplements, 9 patients (6.6%) vitamin D supplements and 9 patients (6.6%) were prescribed both. Eighty patients (58.8%) had not been treated with bisphosphonates before or during follow-up. Twenty-six patients (19.1%) were on bisphosphonate therapy at the start of the study and in 22 patients (16.2%) treatment was initiated within one year. Fifty-five patients (40.4%) had been treated with bisphosphonates for more than one year during follow-up. Median duration of bisphosphonate treatment during the study was 6.6 years (IQR 5.2-7.1).

DXA and TBS

Within the range of L1 to L4, 93.0% of the vertebrae were included in the analyses. At baseline, 36 patients (26.5%) were diagnosed with osteoporosis, 68 patients (50.0%) were diagnosed with osteopenia and 32 patients (23.5%) had a normal BMD. Twenty-six patients (19.1%) had a partially degraded microarchitecture and 26 patients (19.1%) a degraded microarchitecture. Sixteen patients (11.8%) had both a densitometric diagnosis of osteoporosis and a TBS-value below 1.230 (Figure 1).

Values for BMD and TBS at baseline and follow-up are shown in Table 2. In patients who were treated with bisphosphonates (more than one year during follow-up), TBS and BMD of total hip did not change significantly over seven years of follow-up (p=.093 and p=.055, respectively). BMD of lumbar spine (0.056±0.110, p<.001) increased significantly and BMD of femoral neck decreased significantly (-0.024±0.069, p<.016). In non-treated patients, TBS decreased significantly (-0.039±0.064, p<.001), as well as BMD of lumbar spine (-0.034±0.082, p<.001), femoral neck (-0.061±0.066, p<.001) and total hip (-0.062±0.075, p<.001).

VFA and clinical fractures

For VFA, 80.1% of the vertebrae between T4 to L4 were considered evaluable at baseline and 76.6% at follow-up. Vertebrae were excluded due to projection of arms, hands, clothing, jewelry or intestinal gas, movement errors or the presence of osteosynthetic material. During a median follow-up of 85.4 months (IQR 85.0-85.8), 80 patients (58.8%) had been diagnosed with at least one incident clinical fracture or morphometric vertebral fracture; 34 patients (25.0%) had at least one new or worsening morphometric VF, 67 patients (49.3%) had at least one clinical fracture and 21 patients (15.4%) had both. Of the 67 patients with clinical fractures, 28 (41.8%) had at least one MOF.

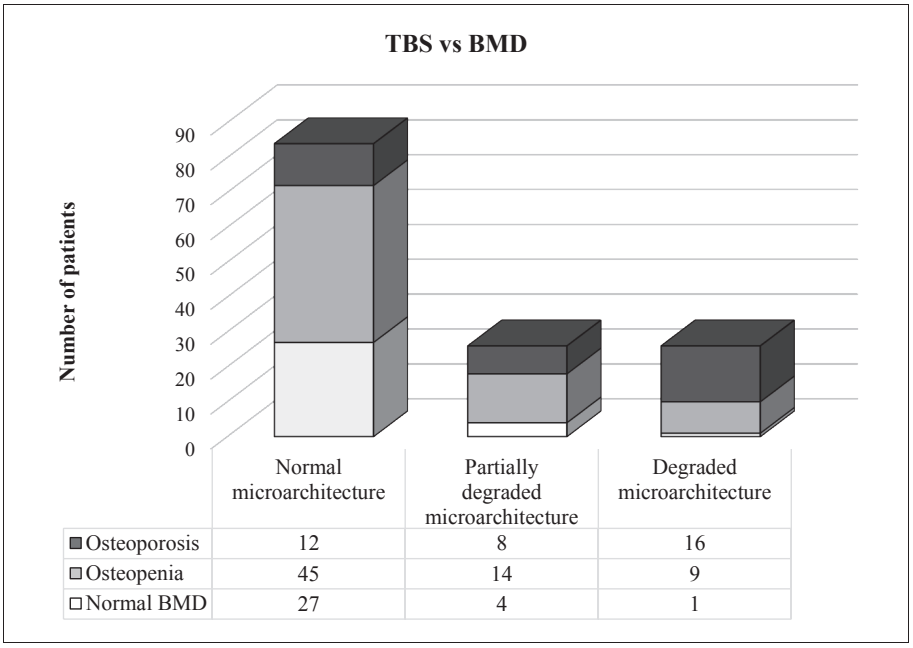

Figure 1. Baseline (2009) classifications of TBS vs BMD in 136 patients with refractory epilepsy and intellectual disability

Of the patients with a normal TBS at baseline, 39 (46.4%) had a clinical fracture during follow-up and 14 patients (16.7%) had an incident morphometric VF (Figure 2). Of the patients with a partially degraded TBS at baseline, 15 patients (57.7%) had a clinical fracture during follow-up and 10 patients (38.5%) had an incident morphometric VF. Of the patients with a degraded TBS at baseline, 13 patients (50.0%) had a clinical fracture during follow-up and 10 patients (38.5%) had an incident morphometric VF.

In univariate analyses, TBS at baseline was significantly associated with incident morphometric VFs. BMD at baseline was not associated with incident clinical fractures and/or VFs. In multivariate analyses (adjusting for age, BMD of femoral neck, prevalent VF and body mass index (BMI) at baseline), TBS was not associated with incident clinical fractures and/or morphometric VFs. Crude and adjusted odds ratios are shown in Table 3.

Table 1. Baseline (2009) characteristics of 136 patients with refractory epilepsy and intellectual disability

Characteristics	**n**	**Mean±SD**
Age (years)	136	44.7±15.5
Sex		
Male	83 (61.0%)	
Female	53 (39.0%)	
Body Mass Index (in kg/m^2)		
Underweight (<18.5)	2 (1.5%)	
Normal weight (18.5-25)	64 (47.1%)	
Overweight (25-30)	51 (37.5%)	
Obese (≥30)	19 (14.0%)	
Intellectual disability (IQ score)		
None (≥70)	1 (0.7%)	
Mild (55-70)	41 (30.1%)	
Moderate (40-55)	51 (37.5%)	
Severe (25-40)	38 (27.9%)	
Profound (<25)	5 (3.7%)	
Ambulatory status		
Immobile	16 (11.8%)	
Independent in wheelchair	13 (9.6%)	
Walk with aid	10 (7.4%)	
Walk without aid	97 (71.3%)	
Number of antiseizure drugs		
None	4 (2.9%)	
1	12 (8.8%)	
2	23 (16.9%)	
3	52 (38.2%)	
4	39 (28.7%)	
5	3 (2.2%)	
6	3 (2.2%)	

IQ=Intelligence quotient, SD=Standard deviation

Table 2. Bone mineral density (in g/cm^2) and trabecular bone scores at baseline (2009) and follow-up (2016) of 136 patients with refractory epilepsy and intellectual disability, stratified by the use of bisphosphonates

	Total (n=136)			
	2009	**2016**	**Δ**	**Δ% per year**
TBS L1-L4	1.328 (±0.111)	1.312 (±0.105)	-0.017 (±0.070)**	-0.15 (±0.75)
BMD L1-L4	0.977 (±0.180)	0.980 (±0.194)	0.003 (±0.104)	+0.09 (±1.50)
BMD FN	0.715 (±0.134)	0.668 (±0.137)	-0.047 (±0.069)**	-0.90 (±1.40)
BMD TH	0.845 (±0.159)	0.798 (±0.168)	-0.047 (±0.080)**	-0.77 (±1.40)

BMD=Bone mineral density, BP=Bisphosphonates, FN=Femoral neck, TBS=Trabecular bone score, TH=Total hip
*p<.05 **p<.01

Table 3. Odds ratios for fractures during seven years of follow-up in patients with refractory epilepsy and intellectual disability (n=136)

Fracture	**Baseline**	**Crude OR (95% CI)**
All (clinical and/or VF)	**TBS**	1.784 (0.868-3.669)
	BMD	2.233 (0.999-4.992)
Clinical[c]	**TBS**	1.346 (0.673-2.694)
	BMD	1.578 (0.707-3.525)
VF[d]	**TBS**	3.125 (1.403-6.961)**
	BMD	1.596 (0.595-4.287)
MOF[c]	**TBS**	1.533 (0.662-3.552)
	BMD	1.533 (0.531-4.429)

CI=Confidence interval, MOF=Major osteoporotic fracture, OR=Odds ratio, TBS=Trabecular Bone Score, VF=Vertebral fracture
*p<.05 **p<.01
[a]Adjusted for age

No BP (n=80)				BP >1 year during follow-up (n=55)				*p*
2009	**2016**	**Δ**	**Δ% per year**	**2009**	**2016**	**Δ**	**Δ% per year**	
1.378 (±0.085)	1.338 (±0.095)	-0.039 (±0.064)**	-0.39 (±0.67)	1.261 (±0.106)	1.276 (±0.106)	0.016 (±0.067)	+0.19 (±0.75)	<.001**
1.049 (±0.157)	1.015 (±0.180)	-0.034 (±0.082)**	-0.46 (±1.12)	0.874 (±0.162)	0.930 (±0.206)	0.056 (±0.110)**	+0.91 (±1.64)	<.001**
0.772 (±0.125)	0.711 (±0.136)	-0.061 (±0.066)**	-1.12 (±1.22)	0.625 (±0.094)	0.600 (±0.112)	-0.024 (±0.069)*	-0.54 (±1.60)	.004**
0.917 (±0.132)	0.856 (±0.157)	-0.062 (±0.075)**	-0.98 (±1.25)	0.732 (±0.130)	0.709 (±0.145)	-0.024 (±0.084)	-0.43 (±1.58)	.009**

Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]	*p*
1.651 (0.775-5.518)	1.339 (0.583-3.078)	.492
1.386 (0.666-2.881)	1.229 (0.556-2.716)	.610
3.018 (1.298-7.018)*	2.403 (0.937-6.164)	.068
1.446 (0.596-3.511)	1.239 (0.473-3.250)	.663

[b]Adjusted for age, bone mineral density (BMD) of femoral neck, prevalent VF and body mass index (BMI) at baseline

[c] Excluding asymptomatic morphometrically assessed VFs

[d]Morphometrically assessed VFs

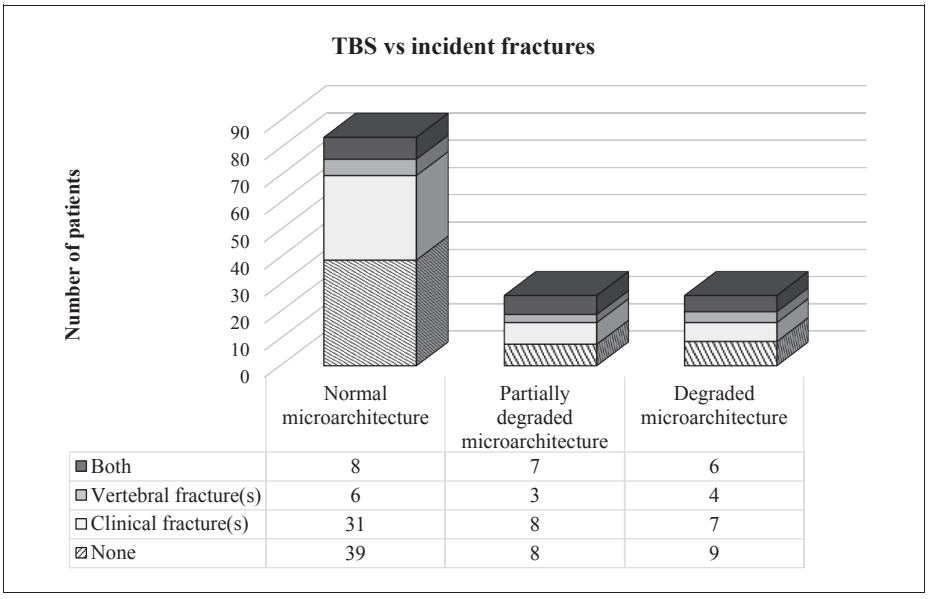

Figure 2. Baseline (2009) classifications of TBS vs incident fractures over seven years of follow-up in 136 patients with refractory epilepsy and intellectual disability

DISCUSSION

In the present study, we studied bone microarchitecture by TBS and incident fractures over seven years of follow-up. At baseline, 27% of institutionalized adult patients with epilepsy and intellectual disability were diagnosed with osteoporosis, 38% had a partially degraded or degraded microarchitecture based on TBS and 12% had osteoporosis in combination with degraded microarchitecture. Over seven years of follow-up, 59% of the patients had sustained at least one incident (non-) vertebral fracture. In patients who were treated with bisphosphonates for more than one year during follow-up, TBS did not change significantly as compared to baseline. In non-treated patients, TBS decreased significantly over seven years of follow-up.

Several longitudinal studies investigated the effects of antiresorptive treatment on TBS and BMD. In the study of Di Gregorio *et al.*[24], different osteoporosis treatments were evaluated (including therapy with bisphosphonates, denosumab or teriparatide) over a follow-up of 24 months. Compared to naïve treatment, all treatments significantly improved TBS and BMD.

In our study, significant differences in both TBS and BMD were found between treated and non-treated patients. However, we found no significant improvement of BMD of femoral neck and total hip in those who were prescribed bisphosphonates for more than one year during the study. Krieg *et al.*[25] found a lower increase in TBS than in BMD in women over the age of 50 on antiresorptive treatment (+0.20% per year vs +1.86% per year). Leslie *et al.*[26] consistently reported larger gains in both BMD and TBS in women with greater adherence to antiresorptive drug treatment. However, the increases were greater for BMD than for TBS. Similarly, in our study patients who were treated with bisphosphonates for more than one year during follow-up, we found a significant increase in lumbar spine BMD (+0.91% per year), but not in TBS. Leslie *et al.*[26] suggest that a relatively larger increase in BMD might be due to (confounding) degenerative changes, leading to an overestimation of BMD. A similar conclusion had been made by Shin *et al.*[27], as they reported a more degraded TBS than BMD in 10.6% of their study participants. In line with these results, we found a (partially) degraded microarchitecture in 5 patients (3.7%) with a normal BMD and a degraded microarchitecture in 9 patients (6.6%) with osteopenia.

In our non-treated patients, values of TBS and BMD tended to decrease over time, as expected with increasing age. Relative decreases (TBS -0.39%, LS BMD -0.46%, FN BMD -1.12% and TH BMD -0.98%) were found to be higher in our study than in the large community-based study of Park *et al*.[28] (TBS -0.27%, LS BMD +0.27%, FN BMD -0.67% and TH BMD -0.66%), despite a lower mean age of our study participants (44.7±15.5 vs 61.4±8.7 in males and 62.4±8.4 in females).

To our knowledge, this is the first study regarding TBS in patients with epilepsy on chronic antiseizure drugs. Patients with refractory epilepsy and intellectual disability are at high risk for fractures due to the effects of antiseizure drugs on BMD[5-7], the presence of seizures[29] and (seizure-related) falls[30]. Our patients received individual bisphosphonate treatment according to the national guidelines[17,18]. Despite treatment in those who, supposedly, needed it, fracture incidences were found to be at least five times higher[4] than in healthy participants of a population-based study in the Netherlands[31]. In combination with already existent physical disabilities, fractures may (further) limit daily activities in this specifically vulnerable population. In our study, we found no significant association between TBS at baseline and fractures during follow-up. Despite promising results regarding the assessment of TBS in other patient groups[15,16], there seems to be a need for (more) accurate fracture prediction tools in institutionalized adult patients with epilepsy and intellectual disability, in order to assess who will get fractures and who will benefit from treatment.

Limitations

There are several limitations of our study that we would like to address. First of all, in our study, patients had been prescribed treatment as part of standard care. Consequently, dates of starting or stopping bisphosphonates varied widely. Due to ethical reasons, no control group had been used within our cohort. Therefore, caution is warranted when interpreting the outcomes regarding the use of bisphosphonates.

Secondly, our study population represents a complex, heterogeneous group with differences regarding sex, age, nutritional status, mobility, types and number of antiseizure drugs and other medication. These differences and variety in background and medical history, may limit the generalizability of our results.

Additionally, in patients with severe neurological impairment and intellectual disability, diagnosing bone mineral problems may be complicated by several factors. In a study of Mergler *et al*.[32] in children with intellectual disability and

severe motor disabilities, the mean number of distorting factors and artefacts was 5.3 (range 1-8). In our study population, BMD and VFA measurements appeared to be challenging. Of the patients who gave informed consent, 19% had a missing or completely failed scan, due to physical or behavioral issues. In patients who did have a VFA, about 20% of the vertebrae between T4 and L4 were unevaluable[33]. Movement errors and projection of arms, hands, jewelry, clothing, intestinal gas or osteosynthetic material, complicated the assessments. Five VFs at follow-up that were unevaluable at baseline, were left out of the analysis, as we were not able to verify these VFs as incident VFs.

As for clinical fractures, we have only included radiographically verified fractures. Difficulties in diagnosing fractures (physical and behavioral) were further complicated by the intellectual and verbal capacities of our study population. Therefore, the actual number of fractures might have been underestimated.

Regardless of these limitations, our study is the first to provide insight in the (non-invasive) measurement of TBS in institutionalized adult patients with epilepsy and intellectual disability.

CONCLUSION

Over seven years of follow-up, 59% of institutionalized adult patients with refractory epilepsy and intellectual disability had suffered from at least one incident fracture, despite anti-osteoporosis treatment according to the Dutch guidelines in those who needed it. No association was found between TBS at baseline and incident fractures, demonstrating its limited use for fracture risk assessment in this group. In order to adequately identify and treat those patients who are at high risk of fractures, more research is needed towards diagnostic and preventive measures in patients with refractory epilepsy and intellectual disability.

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General discussion

GENERAL DISCUSSION

The aim of this thesis was to study fracture incidences in a group of patients with refractory epilepsy and intellectual disability residing at a long-stay care facility in the Netherlands, and to examine the skeletal status using dual-energy X-ray absorptiometry (DXA), vertebral fracture assessment (VFA), quantitative ultrasound of the heel (QUS) and Trabecular Bone Score (TBS).

This chapter provides an overview of the main findings, evaluates the methodology of the studies and discusses the implications for clinical practice. Directions for future research and recommendations are summarized in textboxes.

Main findings

Children

In Chapter 2, we found a high prevalence (67%) of low bone mineral density (BMD Z-score ≤-2.0) in children with refractory epilepsy and intellectual disability between the age of 5 and 17 years old. Forty-two percent had at least one clinical fracture in their medical history, of which half had sustained a major osteoporotic fracture (MOF; fracture of proximal humerus, forearm, hip or vertebrae[1]). Based on their fracture history (two or more long bone fractures under the age of 10 years, or three or more long bone fractures under the age of 19 years[2]), 12.5% of the children was diagnosed with osteoporosis.

In the study of Fong *et al.*[3], 21.8% of the children with epilepsy were classified as having low BMD (Z-score ≤-2.0), but none as osteoporotic. However, they included pediatric outpatients in their study and only 12.6% were prescribed more than two antiseizure medications. Using different classification methods (T-score and Z-score >-2.5) and excluding fracture history in diagnostics, Coppola *et al.*[4] and Gniatkowska-Nowakowska[5] classified 14.6% and 7.1%, of children on antiseizure medication as osteoporotic, respectively. In these studies, however, larger proportions of the children were on monotherapy; 37.5%[4] and 47%[5] vs 16.7% of the patients in Chapter 2. In the study of Coppola *et al.*[4], only two third of the children had an intellectual disability and 40% was seizure free. Mobility status was similar to the children in Chapter 2. In contrast, Gniatkowska-Nowakowska[5] reported normal activity levels in the children.

Almost half of the children in Chapter 2, had been diagnosed with at least one fracture during their lifetime, including MOFs. In the Netherlands, fracture incidences in children between 6 and 16 years old are estimated at 40% for boys and 28% for girls[6]. In Chapter 2, percentages were somewhat comparable (50% in boys and 30% in girls).

However, as three-quarter of the study participants had not yet reached the age of 16 and half of the children was below the peak age of fractures (15 years in boys and 12 years in girls[7]), the proportion of children with a fracture before the age of 16 will most certainly even increase during follow-up.

To conclude, in Chapter 2, prevalence of osteoporosis in institutionalized children with epilepsy and intellectual disability, was found to be high as compared to pediatric outpatients with epilepsy in other studies and fracture incidence was higher as compared to children in the general population.

Adults

In Chapter 3, 77% of the adult population with refractory epilepsy and intellectual disability had a low BMD and 31.7% was diagnosed with osteoporosis, using DXA. In a large population-based study in the Netherlands osteoporosis was diagnosed in 9.2% of the participants (mean age 64.7±9.4 years in men and 66.5±10.9 years in women)[8]. In adult patients on antiseizure medication, percentages of osteoporosis range from zero to 25.5%[9-14]. However, these studies only included outpatients who were normally active[9,10,12] and were not on anti-osteoporosis medication[9,12,13]. Monotherapy ranged from 55-64%[9,10,14] to 100%[12,13]. The highest prevalence was found in the study of Pack *et al.*[11] (25.5%). Age ranges within their study were similar to the patients in Chapter 3 (19 to 81 years of age) and all patients had refractory epilepsy. However, patients on non-enzyme-inducing medication had been excluded from this study.

Overall, in Chapter 3, prevalence of low BMD in institutionalized adults with epilepsy and intellectual disability, was higher than in the general population and in outpatients on antiseizure medication.

> Prevalence of low bone mineral density in institutionalized children and adults with refractory epilepsy and intellectual disability is found to be high. Therefore, screening and prevention of low bone mineral density should be part of each patients' care plan.

Clinical fractures

In Chapter 3, 40% of the total adult population (n=205) had sustained at least one clinical fracture and 8.5% at least one MOF, during seven years of follow-up. The incidence rate of 11.6 clinical fractures per 100 person-years, was found to be at least five times higher than the fracture incidence that was reported in a large population-based study in the

Netherlands (2.1 per 100 person-years)[8]. Noteworthy, the patients in the study of Chapter 3 were much younger (46.8±16.6 years vs 64.7±9.4 years in men and 66.5±10.9 years in women). In institutionalized patients with epilepsy, reported fracture incidences ranged from 7.1 to 14.2 per 100 person-years[15-18]. However, in these (non-recent) studies, the degree of mobility, and severity of physical disabilities were underreported and the majority of the study participants were on phenobarbital and phenytoin, while in Chapter 3, only 10.2% of the adult patients were prescribed phenobarbital and 22.0% phenytoin.

Annegers *et al.*[19] found a decrease in incidence rates with duration of follow-up and duration of antiseizure medication use. In line with these findings, Vasconcelos[20] reported vertebral fractures (VFs) occurred during the first, second or third seizure that the patient had ever experienced. Vestergaard *et al.*[21] provided two possible explanations for an increased fracture risk within the first year after diagnosis of epilepsy: 1) fractures may be the first presentation of epilepsy, or 2) seizure control has not been achieved in the initial period following diagnosis. In Chapter 3, most of the patients had been diagnosed with epilepsy during childhood, eliminating the first option to explain the high fracture incidences. The second possibility seems more likely to explain the high (vertebral) fracture incidences in Chapter 3, given the fact that the seizures were extremely drug resistant in most of the patients.

In patients with epilepsy, it may be hard to distinguish between fractures that occurred as a result of a seizure, or as a result of a fall, especially in patients with (severe) intellectual and verbal disabilities. In Chapter 3, 25% of the fractures had been preceded by a seizure. In studies of Vestergaard *et al.*[21] and Shiek Ahmad *et al.*[22], 31%-34% of the fractures were reported to be seizure-related. Furthermore, 49% of the falls in the latter study had been caused by a seizure[22]. In addition to seizures, physical disabilities, comorbid diseases, behavioral issues and drug side effects may lead to an unsteady gait and an impaired balance function[23,24], increasing the risk of falling and fracture. Almost half of the clinical fractures in Chapter 3 (46%) had been reported after a fall. Accordingly, a lower incidence of fractures was found in patients who were wheelchair dependent as compared to those who were able to walk.

In summary, in Chapter 3, fracture incidence in institutionalized adults with epilepsy and intellectual disability, was high, as compared to the general population. A schematic overview of interactions between epilepsy, intellectual disability and fractures is shown in Figure 1. Seizures, (seizure-related) falls, the lack of seizure control and comorbidity might lead to fractures, in addition to a decreased BMD.

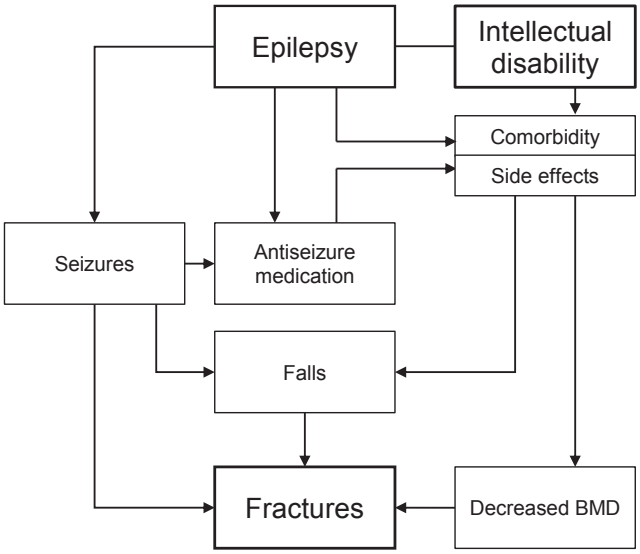

Figure 1. Schematic overview of interactions between epilepsy, intellectual disability and fractures

Vertebral fractures

In Chapter 4, 40% of the adult patients had at least one prevalent VF at baseline and 27% of the patients with baseline and follow-up VFA sustained at least one (asymptomatic) vertebral fracture, over seven years of follow-up. In our opinion, this is an important finding since VFs are associated with an increased mortality rate[25-27] and the presence, number and severity of VFs are strong predictors for future fracture risk[28,29].

To our knowledge, only few studies have addressed vertebral fractures in patients on antiseizure medication[19,20,30,31]. Lazzari *et al.*[30] studied male veterans with epilepsy (using phenytoin, carbamazepine, phenobarbital or sodium divalproex) and excluded patients who were osteoporotic at baseline. Yet, they found at least one prevalent VF in 30% of their participants and one incident VF in 9% over two years of follow-up. In the study of Dussault *et al.*[31], 56% of male veterans who were referred to an Osteoporosis Clinic, had a prevalent VF. Mean age of their participants was 63 years (vs 45 years in our study).

Vasconcelos[20] and Annegers *et al.*[19], focused only on clinical (symptomatic) VFs; compression fractures had been diagnosed in 47 patients after signs of backache. In their studies, 40.4% of the VFs occurred during a seizure, 31.9% of the VFs were related to trauma, 6.4% of the VFs occurred with metastatic cancer and in 21.3%

of the VFs the cause was unknown[19,20]. Since VFAs were only performed at baseline and follow-up in our study, the exact timing of the VFs is unknown and therefore the preceding factors, like seizures or (seizure-related) falls.

VFs are the most commonly occurring osteoporotic fractures[32-34], but they often go unrecognized and underdiagnosed. It is estimated that only one third of the patients with a VF experience acute pain[35-37]. In a systemic review of the literature, 34 case reports were identified that described patients with seizure-induced spinal fractures[38]. In all cases, continuous pain was the indication for further, radiological, examination. A quarter of the patients also showed some type of neurological deficit, such as sensory problems, cauda equina syndrome, paraparesis, quadriparesis, paraplegia or quadriplegia[38]. Only two of the participants of the study in Chapter 4 had been sent to the hospital as they had shown clear signs of back pain. In the rest of the patients with an incident VF, there had either been no signs of pain or discomfort, or (behavioral) expressions had not been recognized or understood by their caregivers and might have been attributed to other factors.

In conclusion, Chapter 4 showed a very high prevalence and incidence of (unrecognized) VFs in institutionalized adult patients with epilepsy and intellectual disability, as compared to outpatients on antiseizure medication.

Prevalence and incidence of morphometric vertebral fractures in institutionalized adults with refractory epilepsy and intellectual disability is found to be high. Therefore, screening and prevention of (subclinical) vertebral fractures should be part of each patients' care plan.

Quantitative Ultrasound of the heel

In Chapter 5, we evaluated the use of QUS in monitoring changes in bone status over follow-up in adults with refractory epilepsy and intellectual disability. Overall, correlations between changes in QUS and DXA parameters were found to be weak to moderate. These results were similar to the findings of Trimpou *et al*.[39] and Frost *et al*.[40] who studied changes in postmenopausal women on antiresorptive treatment over seven years and two years follow-up, respectively. In patients with physical disabilities, the use of QUS has several advantages over DXA regarding portability and ease of use in particular. Strong and positive correlations had been reported between DXA and QUS T-scores in adult patients with epilepsy and intellectual disability in a cross-sectional study[41].

Although BMD is one of the strongest predictors of fragility fractures[42], it has been shown that all QUS parameters can be used for fracture risk assessment[43,44]. For each standard deviation decrease in calcaneal QUS measurements, the estimated relative risk of fractures ranged between 1.55 and 1.74[45], similar to DXA (1.5-2.6[1,46]). Therefore, QUS is a valuable tool for identifying patients at high risk of osteoporotic fractures, especially when DXA is not available[47,48]. In general, QUS measurements are considered as an acceptable alternative to DXA measurements to estimate fracture risk and/or to distinguish individuals at high or low risk[48]. For monitoring response to therapy, however, there is insufficient evidence to use QUS[49].

In Chapter 5, longitudinal change of QUS parameters only showed weak to moderate correlations with BMD change (by DXA) and is considered as inadequate in measuring treatment response in patients with epilepsy and intellectual disability.

> Correlations between changes in QUS parameters and changes in BMD (by DXA) were found to be weak to moderate in institutionalized adult patients with refractory epilepsy and intellectual disability. Despite advantages of QUS regarding portability and feasibility in this specific patient group, the use of DXA remains warranted in monitoring treatment effects.

Trabecular Bone Score

Important determinants in assessing bone strength are bone mineral density and microarchitectural quality. As DXA only gives an indication of bone density, TBS was developed as a novel tool around 2008. TBS is a measure of the microarchitecture of the trabecular bone that evaluates the pixel gray-level variations in lumbar spine DXA images. It is a software application that can be installed on a DXA computer. No additional scan time or radiation exposure is needed.

In Chapter 6, a (partially) degraded microarchitecture (TBS value below 1.310[50]) of lumbar spine was found in 38% of the institutionalized adults with refractory epilepsy an intellectual disability. During seven years of follow-up, 80 patients (59%) sustained at least one fracture, of which 28 patients (35%) had one or more MOFs. Over seven years of follow-up, TBS decreased significantly in patients who were not treated with bisphosphonates. In patients who were treated with bisphosphonates for more than one year during follow-up, lumbar spine BMD significantly increased, whereas TBS did not, as compared to baseline. In line with these results, Krieg *et al.*[51] and Leslie *et al.*[52] focused

on women on antiresorptive treatment and found larger increases in BMD than in TBS. It was suggested that the relatively larger increases in BMD might be an overestimation of BMD due to (confounding) degenerative changes[52]. Similarly, Shin *et al.*[53] reported a more degraded TBS than BMD in 10.6% of the patients (women of 40 years and older); in Chapter 6, a more degraded TBS than BMD was found in 10.3% of the patients.

Lumbar spine TBS, in combination with BMD measurement has been shown to improve fracture risk prediction in several patient groups with secondary osteoporosis[54,55] such as patients on glucocorticoids. In this patient group, fractures occur before bone loss can be measured by DXA[56], which could be related to changes in bone micro-architecture[57]. In a meta-analysis, TBS was consistently shown to be an independent contributor to the assessment of fracture risk[50]. It was concluded that TBS could be used as a standalone assessment of fracture risk. In Chapter 6, however, no significant association was found between TBS at baseline and incident fractures during follow-up.

To conclude, in Chapter 6, we found a high incidence of fractures and TBS decreased significantly over seven years of follow-up in non-treated institutionalized adult patients with refractory epilepsy and intellectual disability, but TBS was not associated with incident fractures.

In institutionalized adults with refractory epilepsy and intellectual disability, no association was found between TBS and incident fractures, despite promising results regarding the use of TBS for fracture risk assessment in other patient groups.

Feasibility and methodological evaluation

The study population described in this thesis was recruited from a long stay care facility and the results may not be generalizable to the population of adult patients with epilepsy and intellectual disability in general:

- All patients of the Department of Residential Care were invited to participate in the study, but sixty-two (21.3%) of the children and adults (and/or their legal representatives) in the care facility, did not provide informed consent. Patients were not required to provide reasons for refusal, but anxiety, agitation, the high burden of a DXA scan and frailty were some of the reasons that were mentioned spontaneously;

- In order to decrease the burden for participants, DXA equipment was transported to the care facility. Still, complete follow-up measurements could only be obtained in about half (52.1%) of the adult patients. Physical and behavioral challenges led to failed or unevaluable scans, even though all participants were guided by a familiar caregiver and/or a family member and special attention was given to signs of resistance and uncooperative behavior;
- Thirty patients deceased during the time of follow-up. They were significantly older (mean age 57.8±18.2) and had significant lower BMD of femoral neck and total hip than patients who completed follow-up;
- The participants represent a complex population (Figure 1) with heterogeneity regarding sex, age, mobility, activities of daily living (ADL), nutritional status and prescribed antiseizure medication. All patients had various backgrounds and medical histories, including the presence of comorbid diseases and genetic syndromes.

Therefore, the results may represent the 'better' part of a very specific and complex group of institutionalized patients. Diagnosing fractures is further complicated by physical, behavioral, intellectual and communicative factors of the individual patient in residential care. In the analyses, fractures only have been included when radiographically verified, which may have led to an underestimation of the actual number of fractures.

Considering the limited number of studies that focus on patients with epilepsy, intellectual disability and bone parameters, this thesis included a relatively large group of a specific patient population and provides new information. It is one of the first studies to evaluate (non-)vertebral fractures in a methodological and systematic way and to assess QUS and TBS over seven years of follow-up in institutionalized patients with refractory epilepsy and intellectual disability.

GENERAL CONCLUSION

In institutionalized patients with refractory epilepsy and intellectual disability, prevalence of osteoporosis is high as compared to the general population and outpatients with epilepsy (without intellectual disability). BMD might be decreased due to side effects of antiseizure medication, as well as comorbidity (neurological impairments, immobility, feeding difficulties, malnutrition, etc.) Side effects of medication and comorbidity also lead to a higher risk of falls. Consequently, the risk of vertebral and non-vertebral fractures in institutionalized patients is severely increased. Furthermore, the nature of fractures in these patients is complex and multifactorial. Considering the overall high risk of (non-)vertebral fractures in institutionalized patients with refractory epilepsy and intellectual disability, it is essential to implement the assessment of bone health, preventive measures concerning bone quality and fall risk, and treatment of high-risk patients, as part of the care plan.

Recommendations

Bone health assessments

Despite substantial numbers of patients on antiseizure medication who have a low BMD, awareness amongst neurologists remains alarmingly low (as studied in high-income countries)[58-61]. In clinical practice, only 10% to 41% of pediatric neurologists frequently evaluate children on long-term antiseizure medication for bone disease[58,59]. Two-third of pediatric neurologists estimated that they only evaluate bone health in less than a quarter of the children they treat[61]. Of the adult neurologists, less than one third reported to routinely evaluate bone health in patients on antiseizure medication[58]. One in eight neurologists never addresses bone health[60].

The guideline of the Dutch Society of Neurology on Epilepsy currently provides little assistance for neurologists in how to handle patients on chronic antiseizure therapy[62]. The guideline provides two recommendations, which are limited to patients of 50 years and older, who are treated with (the older antiseizure medication) carbamazepine, phenobarbital, phenytoin, primidone or valproate. According to the guideline, neurologists should:

1. “Advise sufficient physical activity and intake of calcium and vitamin D
2. Determine levels of vitamin D and supplement if necessary”

Additionally, it is recommended to follow the most recent Dutch guideline ‘Osteoporosis and Fracture Prevention’. In September 2022, there is a newly updated guideline available, mainly focusing on case-finding, and assessment and treatment of patients

at high risk of fractures. In this guideline, antiseizure medication is recognized as a risk factor for secondary osteoporosis, however, there is a predominant focus on patients of 50 years and older as well. In Chapters 2 and 3, 56% of the participants was under the age of 50 and 25% of these patients was already diagnosed with osteoporosis. In general, between the age of 20 and 30 years, the peak bone mass is reached. Consequently, childhood is a critical period for bone mass development. Exposure to antiseizure medication during this period might lead to a lower peak bone mass, resulting in an increased fracture risk later in life[63].

Furthermore, most of the participants in this thesis were on polytherapy, including both enzyme-inducing and non-enzyme-inducing antiseizure medication. An increasing number of studies indicate an association between non-enzyme-inducing antiseizure medication and a decreased BMD, not strictly the older antiseizure drugs carbamazepine, phenobarbital, phenytoin, primidone and valproate[14,64-68]. In addition, polytherapy of antiseizure medication is shown to be a significant risk factor for low BMD[3,9,69], as well as cumulative drug load (the total duration of epilepsy multiplied by the number of antiseizure medication)[70].

To conclude, established guidelines in the field of both endocrinology and neurology, do not meet the need in how to handle bone health in; 1) a younger patient on chronic antiseizure medication and 2) patients on polytherapy and/or non-enzyme-inducing antiseizure medication.

In residential care, we recommend bone health assessments according to the current guideline 'Osteoporosis and Fracture Prevention', including DXA and VFA measurements, laboratory tests (albumin, calcium, creatinine, 25-hydroxyvitamin D, thyroid stimulating hormone) and a nutritional intake analysis, as part of each patients' care plan and to initiate anti-osteoporosis medication and calcium and vitamin D supplementation if needed.

However, bone health of *all* patients on chronic antiseizure medication should be assessed, regardless of *age* and *type of antiseizure drug(s)*. Additionally, it is advised to regularly (re-)evaluate the prescribed antiseizure medication and consider reducing polytherapy.

Future research

Treatment options

In the study population, patients were supplemented with calcium and vitamin D (serum concentration of albumin-corrected calcium below 2.20 mmol/L or blood serum concentration of 25-hydroxyvitamin D below 50 nmol/L) and received bisphosphonates if needed, as part of standard care.

While the use of bisphosphonates is well established in post-menopausal women[71], there has been relatively little attention for the efficacy of bisphosphonates in patients with chronic epilepsy. Some studies reported positive results regarding increases of BMD or fracture incidences / risks[30,72,73]. However, several methodological issues had been present, such as small sample sizes, strict in- and exclusion criteria and/or a lack of control group. Examining the efficacy of medications in institutionalized children and adults, would raise logistical and ethical concerns, as well as a multidisciplinary approach.

To date, no research has focused on osteoanabolic medication like teriparatide or romosozumab in patients on chronic antiseizure medication, although it may be considered to start treatment with osteoanabolic medication, especially in patients having a low BMD in combination with one or more vertebral fractures.

More research is needed towards optimal treatment options and preventive measures for improving bone quality in children and adults on chronic antiseizure drug therapy.

Fracture risk prediction

In the study, we faced many physical and behavioral challenges in positioning patients on the DXA equipment, performing the scans and assessing the images. In patients with intellectual disabilities and severe neurological impairment, a mean number of 5.3 distorting factors had been found by Mergler *et al.*[74]. In our study, besides physical limitations (scoliosis, contractures) and movement errors (caused by epileptic activity, tremors, shaking, anxiety, agitation, et cetera.) there were projections of arms, hands, jewelry, clothing, gastrostomy catheters / feeding tubes, intestinal gas and presence of osteosynthetic material on the images. The more feasible option QUS, was shown to be of limited use in assessing longitudinal changes of BMD in patients with epilepsy and intellectual disability in Chapter 5. There is considerably room for improvement in assessing fracture risk and determining who to treat. The newer, promising, application TBS, however, was shown to be inadequate in determining fracture risk in the study population of Chapter 6.

In children and adults with physical and intellectual disabilities, future research should focus on feasible alternatives regarding monitoring bone health and/or assessing fracture risk.

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Summary

SUMMARY

The aim of this thesis was to study fracture incidence in a group of patients with refractory epilepsy and intellectual disability (ID), residing at a long-stay care facility in the Netherlands and to examine the skeletal status using Dual-energy X-ray Absorptiometry (DXA), Vertebral Fracture Assessment (VFA), Quantitative Ultrasound (QUS) and Trabecular Bone Scores (TBS).

In **Chapter 2** we evaluated the prevalence of low bone mineral density (BMD) and the history of fractures in institutionalized children with refractory epilepsy and ID.

A DXA was performed in 24 children between the age of 5 and 17 years. BMD of the lumbar spine and hip were measured using DXA and serum concentrations of albumin, calcium and 25-hydroxyvitamin D were determined. Eight children (33%) had a normal BMD (Z-score >-2.0). Of the 16 children with a low BMD (Z-score ≤-2.0), three were diagnosed as osteoporotic, based on their fracture history. Ten children (42%) were reported to have at least one fracture in their medical history. Serum concentrations of albumin-corrected calcium (2.28-2.50 mmol/L) and (supplemented) vitamin D (16-137 nmol/L) were within the normal range.

This study demonstrated that 67% of institutionalized children with epilepsy and ID had low BMD and 42% had a history of fractures, despite supplementation of calcium and vitamin D according to the Dutch guidelines.

In **Chapter 3** we determined the incidence of clinical fractures over seven years of follow-up, in institutionalized adults with refractory epilepsy and ID.

Medical records of 205 patients between the age of 18 and 88 years were screened for fractures. During follow-up, 156 clinical fractures were reported in 82 patients (40%). Thirty-eight patients (19%) had at least one major osteoporotic fracture. Overall, the Incidence Rate (IR) was 11.6 fractures per 100 person-years. Fracture incidence was significantly lower in patients who were wheelchair dependent than in patients who were able to walk.

This study demonstrated that 40% of institutionalized adults with epilepsy and ID had at least one clinical fracture during seven years of follow-up, despite adequate anti-osteoporosis treatment.

In **Chapter 4** we determined the prevalence and incidence of morphometric vertebral fractures (VFs) over seven years of follow-up, in institutionalized adults with refractory epilepsy and ID.

DXA and VFA were performed in 2009 and 2016 in 141 patients between the age of 18 and 79 years. Vertebrae T4-L4 were assessed using quantitative morphometry. At baseline, 56 patients (40%) had at least one prevalent VF. After seven years follow-up, 38 new VFs occurred in 27 patients and 15 patients had a worsening VF, leading to an overall cumulative incidence of 27%. VF incidence was significantly higher in patients with at least one prevalent VF at baseline, as compared to no VF (48% vs 13%, respectively).

This study demonstrated that 40% of institutionalized adults with epilepsy and ID had a VF at baseline and 27% had at least one incident VF after seven years of follow-up, despite adequate anti-osteoporosis treatment.

In **Chapter 5** we explored changes in bone status over seven years of follow-up, using QUS and DXA in institutionalized adults with refractory epilepsy and ID.

DXA, VFA and QUS were performed in 2009 and 2016 in 126 patients between the age of 18 and 79 years. Overall, weak to moderate correlations between changes in DXA and QUS parameters were found. For the group on bisphosphonate therapy (group A), correlations (r) varied between .31-.59, whereas correlations did not exceed .40 in patients who were not on bisphosphonate therapy (group B). Patients in group A showed a significantly larger increase or a smaller decrease in BMD for all DXA regions during follow-up. For change in QUS parameters, no significant difference between groups was found.

This study demonstrated limited use of QUS in monitoring bone status in institutionalized adults with epilepsy and ID. Despite positive and mostly significant correlations between changes in QUS and DXA parameters, QUS only explains little of the variability in DXA values and is inadequate for measuring treatment response.

In **Chapter 6** we assessed TBS in institutionalized adults with refractory epilepsy and ID and studied the association of TBS and incident fractures during seven years of follow-up.

DXA, VFA and assessment of TBS were performed in 2009 and 2016 in 136 patients between the age of 18 and 79 years. At baseline, 26 patients (19%) had a partially degraded and 26 patients (19%) a degraded microarchitecture. During follow-up, 80

patients (59%) sustained at least one fracture, of which 28 patients (35%) had one or more major osteoporotic fracture. Thirty-four patients (25%) had at least one incident morphometric VF. No significant associations were found between TBS at baseline and incident fractures during follow-up.

This study demonstrated a high incidence of fractures over seven years of follow-up in institutionalized adults with refractory epilepsy and ID, but TBS was not associated with incident fractures.

In **Chapter 7** the main results of this thesis were discussed, as well as the conclusions and recommendations for future research.

Samenvatting

SAMENVATTING

Het doel van deze thesis was het onderzoeken van fractuurincidentie in een groep patiënten met onbehandelbare epilepsie en een verstandelijke beperking, die in een instelling in Nederland op een woonafdeling verblijven en het onderzoeken van de botstatus gebruikmakend van botdichtheidsmeting (DXA), wervelanalyse (VFA), hielecho (QUS) en trabeculaire botscores (TBS).

In **Hoofdstuk 2** evalueerden we de prevalentie van lage botmineraaldichtheid (BMD) en fractuurgeschiedenis in kinderen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg.

Een DXA werd gemaakt bij 24 kinderen in de leeftijd tussen 5 en 17 jaar oud. BMD van wervelkolom en heup werden gemeten met behulp van DXA en bloedspiegels van albumine, calcium en 25-hydroxyvitamine D werden bepaald. Acht kinderen (33%) hadden een normale BMD (Z-score >-2.0). Van de 16 kinderen met een lage BMD (Z-score ≤-2.0), werden er drie gediagnosticeerd met osteoporose, op basis van hun fractuurgeschiedenis. Tien kinderen (42%) hadden minsten één fractuur in de medische voorgeschiedenis. Bloedspiegels van gecorrigeerde calcium (2.28-2.50 mmol/L) en (gesuppleerde) vitamine D (16-137 nmol/L) vielen binnen de normaalwaarden.

Deze studie toonde dat, ondanks suppletie met calcium en vitamine D volgens de Nederlandse richtlijnen, 67% van de kinderen met epilepsie en een verstandelijke beperking binnen de woonzorg een verlaagde BMD had en 42% een fractuur in de medische voorgeschiedenis.

In **Hoofdstuk 3** bepaalden we de incidentie van klinische fracturen over zeven jaar follow-up bij volwassenen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg.

Medische dossiers van 205 patiënten in de leeftijd tussen 18 en 88 jaar oud werden gescreend op fracturen. Tijdens follow-up, werden er 156 klinische fracturen gerapporteerd bij 82 patiënten (40%). Achtendertig (19%) patiënten hadden minstens één osteoporotische fractuur. In totaal werd een incidentieratio (IR) van 11.6 fracturen per 100 persoonsjaren gevonden. Het fractuurrisico was significant lager bij patiënten die rolstoel gebonden waren, dan bij patiënten die konden lopen.

Deze studie toonde dat, ondanks adequate anti-osteoporose behandeling, 40% van de volwassenen met epilepsie en een verstandelijke beperking binnen de woonzorg, minstens één klinische fractuur had tijdens zeven jaar follow-up.

In **Hoofdstuk 4** bepaalden we de prevalentie en incidentie van morfometrische wervelfracturen over zeven jaar follow-up bij volwassenen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg.

DXA en VFA werden gemaakt in 2009 en 2016 bij 141 patiënten in de leeftijd tussen 18 en 79 jaar oud.

Wervels T4-L4 werden beoordeeld door middel van kwantitatieve morfometrie. Bij de beginmeting hadden 56 patiënten (40%) minstens één prevalente wervelfractuur. Na zeven jaar follow-up waren er 38 nieuwe wervelfracturen bij 27 patiënten en 15 patiënten hadden een verergerde wervelfractuur, wat leidt tot een totale cumulatieve incidentie van 27%. De incidentie van wervelfracturen was significant hoger bij patiënten met minstens één prevalente wervelfractuur, in vergelijking met patiënten zonder een wervelfractuur bij de beginmeting (48% vs 13%, respectievelijk)

Deze studie toonde dat, ondanks adequate anti-osteoporose behandeling, 40% van de volwassenen met epilepsie en een verstandelijke beperking binnen de woonzorg, een wervelfractuur had bij de beginmeting en 27% minstens één incidente wervelfractuur na zeven jaar follow-up.

In **Hoofdstuk 5** onderzochten we veranderingen in botstatus over zeven jaar follow-up bij volwassenen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg, door middel van hielecho en DXA.

DXA, VFA en hielecho werden gemaakt in 2009 en 2016 bij 126 patiënten in de leeftijd tussen 18 en 79 jaar oud. Over het geheel werden zwakke tot matige correlaties gevonden tussen veranderingen in DXA en hielecho. Bij de groep die bisfosfonaten gebruikte (groep A), varieerden correlaties tussen .31-.59, waar correlaties niet boven .40 uitkwamen bij patiënten die geen bisfosfonaten gebruikten (groep B). Gedurende follow-up, lieten patiënten in groep A een significant grotere stijging of kleinere daling zien in BMD op alle plaatsen. Met betrekking tot veranderingen in hielecho, werden er geen significante verschillen tussen de groepen gevonden.

Deze studie toonde een beperkt nut van de hielecho in het monitoren van botstatus bij volwassenen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg. Ondanks positieve en overwegend significante correlaties tussen veranderingen in hielecho en DXA-parameters, verklaart de hielecho weinig van de variabiliteit in DXA-waarden en is het ontoereikend voor het meten van behandeleffecten.

In **Hoofdstuk 6** beoordeelden we TBS bij volwassenen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg en bestudeerden we de associatie tussen TBS en incidente fracturen over zeven jaar follow-up.

DXA, VFA en een beoordeling van TBS werden gemaakt in 2009 en 2016 bij 136 patiënten in de leeftijd tussen 18 en 79 jaar oud. Bij de beginmeting hadden 26 patiënten (19%) een gedeeltelijk gedegradeerde en 26 patiënten (19%) een gedegradeerde microarchitectuur. Tijdens follow-up hadden 80 patiënten (59%) minstens één fractuur, van wie 28 patiënten (35%) één of meer grote osteoporotische fracturen. Vierendertig patiënten (25%) hadden minstens één incidente, morfometrische wervelfractuur. Geen significante associaties werden gevonden tussen TBS bij de beginmeting en incidente fracturen tijdens follow-up.

Deze studie toonde een hoge incidentie van fracturen over zeven jaar follow-up bij volwassenen met onbehandelbare epilepsie en een verstandelijke beperking, binnen de woonzorg, maar TBS was niet geassocieerd met incidente fracturen.

In **Hoofdstuk 7** worden de belangrijkste resultaten van dit proefschrift besproken, net als de conclusies en aanbevelingen voor toekomstig onderzoek.

Impact

IMPACT

Thesis

In this thesis we focused on bone mineral density and fractures in a group of patients with epilepsy and intellectual disability, residing at a long-stay care facility in the Netherlands. In 2009 and 2016, patients underwent dual-energy X-ray absorptiometry scans to assess their bone mineral density. About 67% of the children and 80% of the adults, were revealed to have a low bone mineral density. Forty-two percent of the children, had a history of fractures, of which half had suffered a major osteoporotic fracture. Over seven years of follow-up, 59% of the adults sustained one or more (non-) vertebral fractures, of which 35% had at least one major osteoporotic fracture.

Target groups

The care for institutionalized patients with epilepsy and intellectual disability is complex. General practitioners, intellectual disability physicians, neurologists, internist-endocrinologists, physiotherapists, occupational therapists, nurse specialists, nurses, nurse assistants, caregivers (parents/family) etcetera; all play a major role in the multidisciplinary care for these patients. The results and implications of this thesis may be of interest for all of them, but mostly for the patients themselves. In Table 1 we summarize groups involved in the care for patients with epilepsy and intellectual disability, topics they should pay special attention to and (realized) related activities.

Relevance

Current guidelines for diagnosing and treating osteoporosis (Dutch Society of Neurology on Epilepsy and the Dutch protocol Osteoporosis and Fracture Prevention) are limited to patients over the age of 50.

In our study, 56% of the participants were under the age of 50 and, therefore, falling outside the scope. In addition, the guideline of the Dutch Society of Neurology on Epilepsy is limited to the use of carbamazepine, phenobarbital, phenytoin, primidone and valproate. In our study, a wider variety of antiseizure medication had been prescribed. The current guidelines are therefore not completely relevant to the majority of our patients.

Based on the results of this thesis, we recommend (regular) bone health assessments in residential care according to the most recent protocol ‘Osteoporosis and Fracture Prevention’ and to initiate anti-osteoporosis medication if needed.

Table 1. Target groups and (realized) related activities

	In patients with refractory epilepsy and intellectual disability, special attention is needed towards:	Realized	Activities
Patients	· Lifestyle intervention analysis including physical activity, nutritional intake, sunlight exposure (yearly, as part of the care plan)	+	· (Inter)national presentations · Thesis
	· Fall prevention	-	
	· Assessment of medication use (regularly, as part of the care plan)	+	
Healthcare professionals	· Lifestyle intervention analysis including physical activity, nutritional intake, sunlight exposure (yearly, as part of the care plan)	+	· Development of flowchart · Peer-reviewed articles · (Inter)national presentations · Thesis
	· Fall prevention	-	
	· Assessment of medication use (regularly, as part of the care plan)	+	
	· Screening for BMD and VFs (regardless of age and type of antiseizure drug(s))	+	
	· Diagnosing of low BMD and (subclinical) VFs	+	
	· Laboratory testing (concentrations of albumin, calcium, creatinine, 25-hydroxyvitamin D, thyroid stimulating hormone) (yearly, as part of the care plan)	+	
Policymakers	· Development of guidelines for screening and treatment of low BMD and/or fractures	+	· Development of flowchart · Peer-reviewed articles · Thesis
Healthcare financers	· Financial resources for the prevention and treatment of fractures, including BMD, VFA and the prescription of calcium, vitamin D and anti-osteoporosis medication	-	· Peer-reviewed articles
Pharmaceutical industry	· Side effects of both antiseizure and anti-osteoporosis medication	+	· Peer-reviewed articles · Thesis
	· Effectiveness of anti-osteoporosis medication in combination with antiseizure medication	-	

Table 1. Continued

	In patients with refractory epilepsy and intellectual disability, special attention is needed towards:	Realized	Activities
Researchers	· (Feasible) Alternatives regarding screening and monitoring BMD	+/-	· Development of flowchart · Peer-reviewed articles · (Inter)national presentations · Thesis
	· (Feasible) Alternatives regarding assessing fracture risk	+/-	
	· Optimal treatment options and preventive measures in both children and adults	-	

*BMD=Bone mineral density, ID=Intellectual disability, VFs=Vertebral fractures

Unlike the abovementioned protocols/guidelines, we propose not to apply restrictions regarding age or types of antiseizure medication. Bone health assessments are recommended as part of each patients' care plan and would include DXA/VFA measurements, laboratory testing (blood serum concentrations of albumin, calcium, creatinine, 25-hydroxyvitamin D, thyroid stimulating hormone) and a nutritional intake analysis.

One of the current treatment options for osteoporosis is treatment with oral bisphosphonates; drugs that inhibit bone resorption. These medications are typically prescribed for three to five years. Based on the findings in this thesis and no reports of serious side effects in the study group, the use of bisphosphonates in the individual patient might be reconsidered to extend to a period of ten years. To date, no research has focused on osteoanabolic medication like teriparatide or romosozumab in patients on chronic antiseizure medication. Especially in patients with a low BMD in combination with one or more vertebral fractures, osteoanabolic medication may be considered. Further research should focus on optimal treatment options.

Activities

Our recommendations are put together in a flowchart and implemented in the residential care department of Epilepsy Center Kempenhaeghe. Due to an update of the Dutch protocol 'Osteoporosis and Fracture Prevention' and expected changes (regarding the treatment of vertebral fractures), the flowchart is currently under revision and therefore not included in this thesis. The internist-endocrinologist, general practitioners, intellectual disability physicians and nurse specialists are informed and trained to apply the most recent, designed flowchart. In case of doubt, treatment is discussed with experts from the specialized Center of Metabolic Disorders of VieCuri Medical Center. Future plans include the development of educational materials on fracture prevention for health care professionals within our institution.

All studies in this thesis are published or submitted to peer-reviewed international journals and several extended abstracts appeared in a national peer-reviewed journal as well. Many of the findings were presented and discussed during oral and poster presentations at national and international congresses in the fields of epilepsy, intellectual disabilities, neurology and/or endocrinology. Among those congresses were the yearly congresses of Epilepsy Center Kempenhaeghe (2018, 2019), the European (2018) and International (2021) Congress on Epileptology, the World Congress on Osteoporosis (2019) and the European Congress of the Tissue Society (2020).

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DANKWOORD

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En iemand met wie ik beroepsmatig niks te maken had, maar toch een groot deel van mijn promotie-traject een kantoor deelde. Eefje, dat had ik niet willen missen! Werken met foute muziek aan, tussendoor even een gezellig praatje en natuurlijk iedere ochtend om 11 uur samen een soepje. Bedankt ook voor de ontelbare kopjes thee die je voor me haalde, wanneer ik zo druk bezig was dat ik weer eens vergat te drinken!

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je van dat ene nog iets gehoord? Ben je al bijna klaar? En dan? Wat moeten we aan bij zo'n ceremonie? Moeten wij iets doen, of iets zeggen?" En Sandra, een paranimf, wat is dat? "Ik wil best een feestje organiseren, maar als ik iets in het Engels moet zeggen, dan moet iemand anders dat maar doen".

En welke paranimf kan dat nu beter dan jij, Ron? Mijn eigen Amerikanistieker. Lest best! Jij weet als geen ander waar ik doorheen ben gegaan. De ene dag flink balend van een revisie en de volgende dag een publicatie vieren met Bossche bollen. Enorm bedankt voor al je steun, maar ook je bijdrage, want je werd tijdelijk niet alleen mijn thuiswerk-collega, maar ook mijn nieuwe sparringpartner. "Hoe kan ik dit het beste verwoorden? Klopt het als ik dit zo zeg? Wil je dit even lezen?" Waarop jouw standaardreactie kwam: "Hier moet nog een komma" en "Die komma daar had juist niet gehoeven". Dus bij deze; geen komma, maar een punt achter dit proefschrift.

About the author

ABOUT THE AUTHOR

Jessica Johanna Leonarda Berkvens werd op 1 december 1989 geboren in Geldrop. In 2008 behaalde zij haar VWO-diploma aan het Varendonck College in Asten. Zij werd uitgeloot voor de studies Geneeskunde en Biomedische Wetenschappen waardoor ze begon aan een studie Verpleegkunde aan de Fontys Hogeschool in Eindhoven. Ze liep stages in de psychiatrie (de Grote Beek, Eindhoven), in de psychogeriatrie (Engelsbergen en de Landrijt, Eindhoven), op de afdeling orthopedie (St. Anna Ziekenhuis, Geldrop) en binnen de Epilepsie Monitoring Unit (Epilepsiecentrum Kempenhaeghe, Heeze). In 2012 behaalde Jessica haar bachelordiploma Verpleegkunde en begon ze als woonbegeleider op de afdeling Klaver binnen Epilepsiecentrum Kempenhaeghe. Tegelijkertijd begon ze aan de deeltijd master Verplegingswetenschappen aan de Universiteit Utrecht, waar ze in 2015 haar diploma behaalde. Haar onderzoeksstage 'Autisme en gedrag bij volwassen patiënten met het syndroom van Dravet' vond plaats binnen Epilepsiecentrum Kempenhaeghe en resulteerde in een wetenschappelijke publicatie. In 2016 werkte Jessica een jaar als studiecoördinator en researchverpleegkundige op de afdeling Hoofd-Hals Oncologie van het Radboud UMC in Nijmegen. Deze functie combineerde ze met haar werk als oproepkracht (op de afdelingen Reigerlaan en Berkenlaan) en een parttimefunctie als onderzoeksverpleegkundige binnen de onderzoekslijn 'Osteoporose' van Epilepsiecentrum Kempenhaeghe. Dit laatste werd omgezet in een fulltime promotietraject, waardoor ze stopte met haar werkzaamheden in het Radboud UMC. In 2021 is Jessica gestart als docent Verpleegkunde aan de Fontys Hogeschool in Eindhoven. Een jaar later werd ze aangesteld als Lecturer Practitioner binnen het Zorginnovatienetwerk (ZIN) van Epilepsiecentrum Kempenhaeghe.

In 2019 ontving Jessica de ESCEO-AgNovos Healthcare Young Investigator Award op het World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases in Parijs.

Jessica Johanna Leonarda Berkvens was born on December 1st 1989 in Geldrop. In 2008, she graduated her secondary school education at Varendonck College in Asten. She applied for the studies Medicine and Biomedical Science, but did not get in. She started the study Nursing at Fontys Hogeschool Eindhoven. She did her internships in psychiatry (de Grote Beek, Eindhoven), psychogeriatry (Engelsbergen and de Landrijt, Eindhoven), at an orthopedic ward (St. Anna Ziekenhuis, Geldrop) and at an Epilepsy Monitoring Unit (Epilepsiecentrum Kempenhaeghe, Heeze). In 2012, Jessica received her bachelor's degree in nursing and started working at Klaver at Epilepsy

Center Kempenhaeghe. At the same time, she followed the part-time master Nursing Science at Utrecht University, which she finished in 2015. She completed her research internship 'Autism and behavior in adult patients with Dravet syndrome' at Epilepsy Center Kempenhaeghe, which resulted in a scientific publication. In 2016, Jessica took a job as study coordinator and research nurse at the Head and Neck Oncology ward of the Radboud UMC in Nijmegen. She combined the job with her on-call work (at the wards Reigerlaan and Berkenlaan) and a part-time job as research nurse at the 'Osteoporosis' study at Epilepsy Center Kempenhaeghe. The latter turned into a fulltime PhD track, which made her quit her job at the Radboud UMC. In 2021, Jessica became a teacher of Nursing at Fontys Hogeschool Eindhoven. A year later she was appointed as Lecturer Practitioner at Epilepsy Center Kempenhaeghe.

In 2019, Jessica received the ESCEO-AgNovos Healthcare Young Investigator Award at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases in Paris.

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