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Hyponatremia and metabolic bone disease in patients with epilepsy A cross-sectional study

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ABSTRACT

Aim: Patients with epilepsy frequently develop hyponatremia due to the treatment with antiepileptic drugs and have an increased risk of developing metabolic bone disease. Hyponatremia is known to be associated with osteoporosis. The aim of the study was to investigate the association between hyponatremia and osteoporosis in patients with epilepsy.

Method and material: This cross-sectional study included patients with epilepsy from a tertiary epilepsy outpatient clinic in Denmark, who had a Dual Energy X-ray Absorptiometry scan performed and an accompanying plasma sodium (p-Na) measured prior to or a maximum of 14 days after the scan. Information regarding the patients' health and medical conditions were obtained from their medical reports.

Results: A total of 695 patients (females 53.8%, age 49 (34:63) years (median (quartiles)) were included. 10.4% had hyponatremia (p-Na ≤ 135 mmol/L). The hyponatremic patients had significantly lower T-scores in the lumbar spine, femoral neck and total femur (all $p < 0.023$) and the odds ratio of osteoporosis (T-score < −2.5) was significantly increased (2.91 (1.61–5.27) (95% confidence interval) ($p = 0.001$)). When adjusting for potential confounders the patients with moderate and severe hyponatremia (p-Na < 129 mmol/L) had a significantly lower mean T-score in the lumbar spine ($p = 0.030$).

Conclusion: We conclude that hyponatremia is common in patients with epilepsy and that moderate and severe hyponatremia is independently associated with decreased bone mineral density in the lumbar spine. Therefore, hyponatremia in a patient with epilepsy should warrant further examination of the patient for bone loss and osteoporosis.

1. Introduction

Hyponatremia, defined as low plasma concentrations of sodium (p-Na) ≤ 135 mmol/L [1], is a common electrolyte disturbance posing a grave problem for the patients affected. Hyponatremia has been associated with morbidity and mortality in patients with liver disease, postoperative patients, and patients who are involved in strenuous exercise [2–4]. In the past decade accumulating evidence shows an association between low p-Na levels and an increased risk of metabolic bone disease including osteoporosis and an increased risk of fractures [5–8]. In fact, the first presentation of hyponatremia could be a bone fracture [9].

Patients with epilepsy have a higher risk of developing metabolic bone disease and have 2 to 6 times increased fracture risk [10,11]. The

Abbreviations: AEDs, Antiepileptic Drugs; EIAEDs, Enzyme Inducing Antiepileptic Drugs; NEIAEDs, Non-Enzyme Inducing Antiepileptic Drugs; BMD, Bone Mineral Density; DXA-scan, Dual Energy X-ray scan; OR, Odds Ratio; CI, Confidence Interval; SIADH, Syndrome of Inappropriate ADH secretion; SD, Standard Deviation; BMI, Body Mass Index

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incidence of osteoporosis in this population is between 11% and 31% and for osteopenia between 48% and 55% [12–14]. Osteoporosis causes considerable loss in disability-adjusted life years [15] and poses a marked cost for society [16]. Several mechanisms have been suggested as an explanation for the high occurrence of metabolic bone disease including less weight-bearing exercise, inadequate intake of calcium and vitamin D and the use of antiepileptic drugs (AEDs) and especially those that are enzyme-inducing [12,17,18]. A common side-effect to several AEDs is hyponatremia. The mechanism by which AEDs cause hyponatremia is thought to be similar to the Syndrome of Inappropriate ADH Secretion (SIADH) resulting in chronic hyponatremia [19–22]. The incidence of hyponatremia in patients with epilepsy ranges from 7% to 46% and poses a great problem for the patients including increased risk of seizures and also possibly increased bone turnover [23,24]. To our knowledge, there are no studies linking the occurrence of hyponatremia to the increased incidence of osteoporosis in patients with epilepsy.

In the present study, we evaluated the association between hyponatremia and osteoporosis in a cross-sectional study. The aim of the study was to investigate whether the occurrence of osteoporosis is associated with hyponatremia in patients with epilepsy.

2. Materials and method

2.1. Study design and participants

The study was a cross-sectional study including patients attending the tertiary out-patient clinic at the Epilepsy Unit, Department of Neurology, Rigshospitalet Glostrup, Denmark. The study included patients that had results from a Dual Energy X-ray Absorptiometry (DXA) scan and p-Na measurements available as part of the clinic's standard of care within the period 1st of January 2006 to and including 31st of January 2018. The DXA scans were performed using the same Lunar Prodigy™ scanner (GE Healthcare, Chicago, USA). The scanner underwent daily, and weekly calibration and quality control and all scans were performed by trained technicians. Due to technical problems one examination had to be excluded from the study. In the event of duplicate scans, the newest was chosen. The regions of interest were the lumbar spine L_1-L_4, femoral neck and of the total femur. Osteoporosis was defined by the WHO definition of site-specific T-score ≤ -2.5 standard deviation (SD) in any of the sites. Weight and height from the DXA scans were included and used to calculate Body Mass Index (BMI).

Based on The Danish Personal Identification Number (Danish CPR-number) [25] results of the patients' blood samples were linked to the DXA scan. Only patients with a p-Na measured prior to the scan or a maximum of 14 days after the scans were included in the study. Other biochemical parameters taken at the same time as the p-Na were plasma potassium, plasma total calcium and plasma alkaline phosphatase which were also included in the study. Hyponatremia was defined as p-Na $\leq$ 135 mmol/L [26], and moderate and severe hyponatremia was defined as p-Na $\leq$ 129 mmol/L [27]. Patients with p-Na $>$ 135 mmol/L were considered as non-hyponatremic.

Information regarding the patients' health and medical conditions were obtained from their medical reports in closest timely relation to the DXA scan. This information included gender, age, information about epilepsy and other risk factors for osteoporosis. Concerning epilepsy, information about classification (generalized, focal or unspecified epilepsy), the etiology (magnetic resonance imaging verified presence of cerebral epileptogenic pathology), age of onset, and the duration of the disease has been collected. The remission rate of epilepsy was defined as either no remission, remission for 6 months or remission for 12 months or longer. The use of AEDs was classified according to number of users of the specific drugs, the number of drugs used classified as 1, 2 or 3 or more drugs, and as either enzyme-inducing AEDs (EIAEDs) or non-enzyme-inducing AEDs (NEIAEDs). The following drugs were classified as EIAEDs: carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, primidone, phenobarbital, topiramate $>$ 200 mg, zonisamide $>$ 200 mg, perampanel $>$ 12 mg and brivaracetam. Drugs classified as NEIAEDs were lamotrigine, levetiracetam, valproic acid, topiramate $\leq$ 200 mg, zonisamide $\leq$ 200 mg, rufinamide, perampanel $\leq$ 12 mg, lacosamide, gabapentin, pregabalin, ethosuximide, and benzodiazepine.

Information on other risk factors for osteoporosis included alcohol consumption classified as either $<$ 7 or 14 units per week for women and men, respectively, as recommended by the National Danish Board of Health or as current or previous overconsumption. Information about smoking was collected as well and classified as either never having smoked or current or previous smoking. Information achieved about diseases known to cause secondary osteoporosis were as follows: rheumatoid arthritis, type 1 diabetes, hyperthyroidism, hypogonadism, gastro-intestinal disease, chronic liver disease, pulmonary disease, and organ transplantation.

The study was approved by the Danish Data Protection Agency (2012-58-0004), and the Danish Patient Safety Authority (3-3013-1459/1 and 3-3013-2456/1). No experiments and procedures were done that conflict with the Helsinki Declaration of 1975 (revised 2000).

2.2. Statistical analysis

To characterize the population all descriptive variables were tested for normal distribution and expressed as either mean and standard deviation (SD), median and quartiles, or N-value and percentage (N (%)) as appropriate and listed in Table 1. Patients were categorized in two groups according to the p-Na levels, either p-Na $\leq$ 135 mmol/L (hyponatremic) or p-Na $>$ 135 mmol/L (non-hyponatremic). The characteristics of the two groups were compared using an independent-samples *t*-test for parametric data and Mann-Whitney *U* test for non-parametric data. For categorical data Pearson chi-square test or Fisher's exact test were used when appropriate.

To investigate the incidence of osteoporosis in the hyponatremic population Pearson chi-square test with odds ratio (OR) was done and due to the known association between hyponatremia and the use of EIAEDs, the Pearson chi-square test was subsequently repeated but with the use of EIAEDs as predictor rather the hyponatremia.

Difference in incidence of osteoporosis between the hyponatremic and non-hyponatremic group was estimated using a binary logistic regression. The outcome of osteoporosis was defined as a T-scores $<$ -2.5 at any of the three regions of interest. P—Na was included in the model first as a continuous variable and subsequently as a dichotomous with a cut-off point p-Na $\leq$ 135 mmol/L. Both models were adjusted for variables which differed in the descriptives between the groups and that are known to be associated with osteoporosis in patients with epilepsy, which included: BMI, age at scan, number of AEDs used and the use of EIAEDs. The results are expressed as OR (95% CI OR).

Subsequently, the T-scores of the three regions of interest were investigated as continuous variables. For this an ANCOVA for each region was performed and compared across the categorical variable of hyponatremia at the cutoff point of p-Na $\leq$ 135 mmol/L. The models were adjusted for BMI, age at scan and number of AEDs used. The use of EIAEDs was not included as covariate in the analysis as it already correlates with the other variables. The results are expressed as mean (SD).

All data were analyzed using the SPSS software package (version 22.0) (IBM, Armonk, New York). A p-value < 0.05 (two-sided) was considered statistically significant.

3. Results

3.1. Descriptives

Of the 695 patients in the cohort (Table 1) 623 (89.6%) were non-hyponatremic, (p-Na $>$ 135 mmol/L) and 72 (10.4%) were

Table 1
Descriptives of the population.

		All (N = 695 (100%))	Non-hyponatremia (N = 623 (89.6%))	Hyponatremia (N = 72 (10.4%))	Statistical significance non-hyponatremia vs hyponatremia
Descriptive					
Female sex (N (%))		374 (53.8)	331 (53.1)	43 (59.7)	0.319
BMI (kg/m^2) (mean(SD))		26.5 (5.3)	26.6 (5.4)	25.4 (4.3)	0.075
Height (cm) (mean(SD))		169.7 (9.4)	169.8 (9.4)	168 (8.7)	0.266
Weight (kg) (mean(SD))		76.4 (17.1)	76.9 (17.4)	72.2 (13.7)	0.030
Age at DXA scan (years) (median (quartiles))		49 (34:63)	49 (33:63)	54 (44.25:66)	0.010
Age at onset of epilepsy (years) (median (quartiles))		24.0 (12.5:50)	23 (12:49.50)	35 (14:58.75)	0.235
Duration of epilepsy from debut to DXA (years) (median (quartiles))		12 (5:27.50)	12 (5:27)	12.5 (5:34.75)	0.634
Epilepsy classification (N (%))					
Focal		384 (55.3)	336 (53.9)	48 (66.7)	
Generalized		285 (41.0)	261 (41.9)	24 (33.3)	
Unspecified		26 (3.7)	26 (4.2)	–	0.048
Presence of cerebral pathology (N (%))					
No		380 (54.7)	345 (55.4)	35 (48.6)	
Yes		311 (44.7)	274 (44.0)	37 (51.4)	
Missing		4 (0.6)	4 (0.6)	–	0.262
Remission rates (N (%))					
No remission		199 (28.6)	175 (28.1)	24 (33.3)	
Remission for 6 months		74 (10.6)	68 (10.9)	6 (8.3)	
Remission for 12 months or longer		421 (60.6)	379 (60.8)	42 (58.3)	
Missing		1 (0.1)	1 (0.2)	–	0.580
Number of AEDs (N (%))					
1		457 (65.8)	423 (67.9)	34 (47.2)	
2		164 (23.6)	142 (22.8)	22 (30.6)	
3 or more		72 (10.4)	56 (9.0)	16 (22.2)	
Missing		2 (0.3)	2 (0.3)	–	< 0.001
Using EIAED (N (%))					
No		496 (71.4)	468 (75.1)	28 (38.9)	
Yes		197 (28.3)	153 (24.6)	44 (61.1)	
Missing		2 (0.3)	2 (0.3)	–	< 0.001
Smoking (N (%))					
No		498 (71.7)	443 (71.1)	55 (76.4)	
Currently smoking		185 (26.6)	169 (27.1)	16 (22.2)	
Missing		12 (1.7)	11 (1.8)	1 (1.4)	0.400
Alcohol (N (%))					
No excess use		598 (86.0)	537 (86.2)	61 (84.7)	
Current or previous excess use		89 (12.8)	78 (12.5)	11 (15.3)	
Missing		8 (1.1)	8 (1.3)	–	0.577
Other disease relevant for osteoporosis (N (%))					
No		525 (75.5)	472 (75.8)	53 (73.6)	
Yes		168 (24.2)	149 (23.9)	19 (26.4)	
Missing		2 (0.3)	2 (0.3)	–	0.664
Biochemical parameters	Reference interval				
Sodium (mmol/L) (mean(SD)) (N)	136–145	140 (4.2) (695)	141 (2.5) (623)	130 (3.8) (72)	< 0.001
Potassium (mmol/L) (mean(SD)) (N)	3.5–4.6	4.1 (0.3) (635)	4.1 (0.3) (571)	4.1 (0.4) (64)	0.425
Calcium (total) (mmol/L) (mean(SD)) (N)	2.15–2.51	2.34 (0.12) (386)	2.34 (0.12) (353)	2.32 (0.12) (33)	0.511
Alkaline phosphatase (U/L) (median (quartiles)) (N)	35–105	71 (59:85) (560)	70 (58:85) (517)	75 (62:107) (43)	0.035

Descriptive data for all patients, the non-hyponatremic and the hyponatremic group. All data is shown as number and percentage (N (%), mean and standard deviation (mean (SD)) or median and quartiles, when appropriate. No excess alcohol use was defined as < 7 or 14 units per week for women and men, respectively. Other disease relevant for osteoporosis was defined as rheumatoid arthritis, type 1 diabetes, hyperthyroidism, hypogonadism, gastro-intestinal disease, chronic liver disease, pulmonary disease, and organ transplantation. Statistical differences between the non-hyponatremic and the hyponatremic patients were for normally distributed data evaluated by Independent Samples t-test, for continuous but not normally distributed variables the Mann-Whitney U test was applied. For categorical data the Pearson chi-square test or Fisher's exact test was used, when appropriate.

hyponatremic (p-Na ≤ 135 mmol/L). Table 1 shows the characteristics of the total population, the non-hyponatremic and the hyponatremic group. The hyponatremic group weighed less, were older at the time of the scan, had significantly more frequent focal epilepsy, more frequently use 2, 3 or more AEDs and were also more frequently treated with EIAEDs. For biochemical parameters, alkaline phosphatase was significantly increased for the hyponatremic group, however still within the normal reference range. All biochemical parameters were taken 78 (−14:4024) (median (minimum:maximum)) days prior to the scan.

The use of AEDs was classified according to enzyme-inducing properties for the entire population, the non-hyponatremic and the hyponatremic groups (Figs. 1 and 2). The hyponatremic patients significantly more often used EIAEDS as carbamazepine, oxcarbazepine and eslicarbazepine, and less often the NEIAED lamotrigine and benzodiazepine compared to non-hyponatremic patients.

3.2. Bone mineral density and hyponatremia

When looking at differences in bone mineral density (BMD) between the non-hyponatremic and hyponatremic group the hyponatremic patients had significantly lower T-scores in the lumbar spine L_1-L_4 region (p = 0.019), femoral neck (p = 0.023) and total femur (p = 0.001) (Fig. 3).

Osteoporosis was significantly more frequent in the hyponatremic patients (25.0%) than in the non-hyponatremic patients (10.3%) (p = 0.001), and the OR for having osteoporosis at any site when

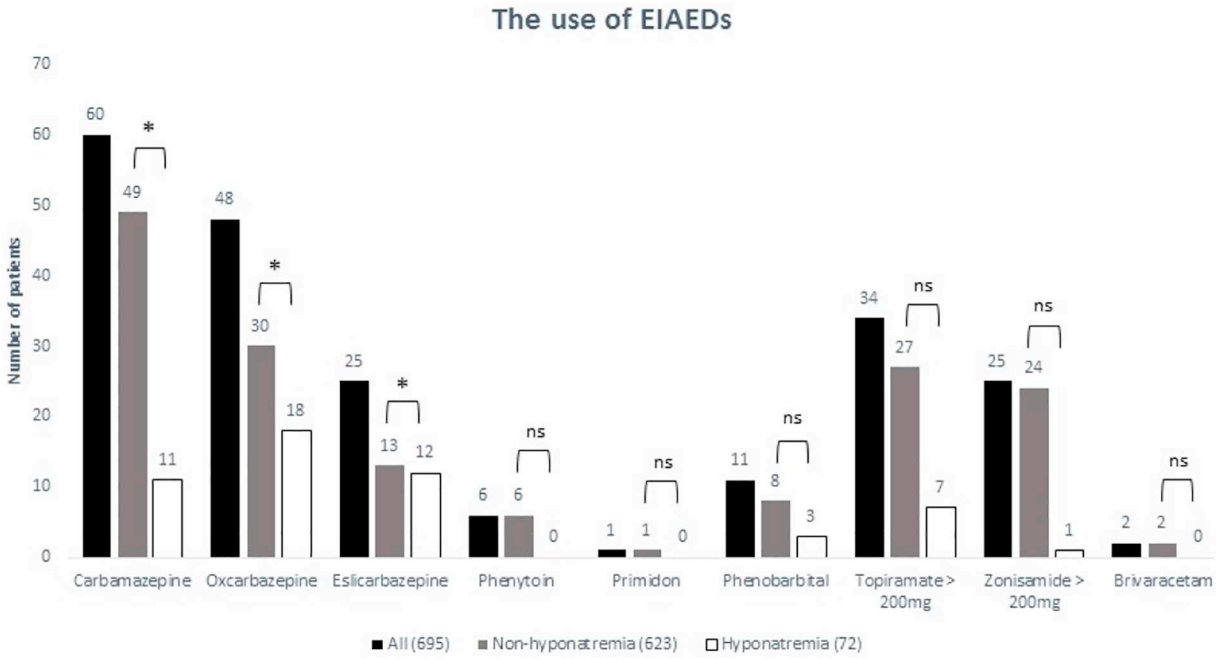

Fig. 1. Graphical display of the use of EIAEDs in the total population (black bar) and for the non-hyponatremic (grey bar) and hyponatremic (white bar) groups. Numbers above the bars represent the number of patients of the AEDs (N-value). The statistical difference between the non-hyponatremic and the hyponatremic groups were tested with Pearson chi-square test or Fisher's exact test, when appropriate. The hyponatremic patients more often use carbamazepine, oxcarbazepine and eslicarbazepine.

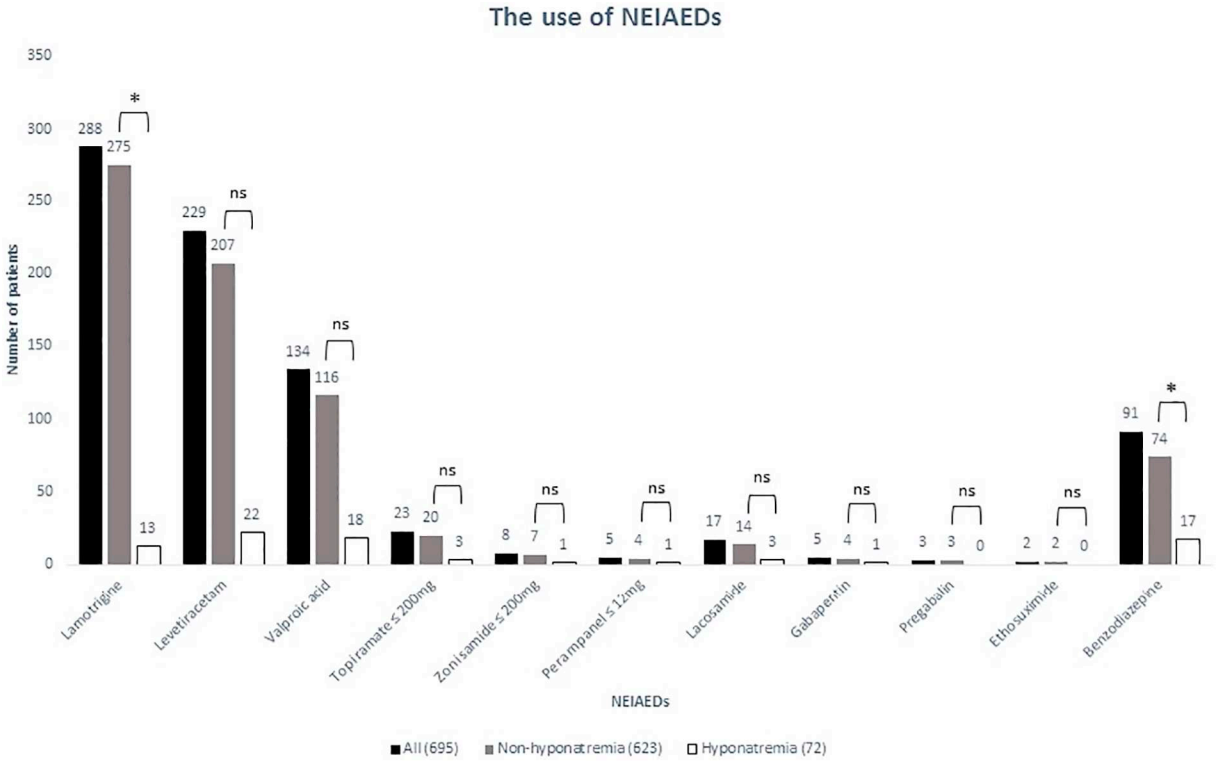

Fig. 2. Graphical display of the use of NEIAEDs in the total population (black bar) and for the non-hyponatremic (grey bar) and hyponatremic (white bar) groups. Numbers above the bars represent the number of patients of the AEDs (N-value). The statistical difference between the non-hyponatremic and the hyponatremic groups were tested with Pearson chi-square test or Fisher's exact test, when appropriate. The hyponatremic patients less often use lamotrigine and benzodiazepine.

hyponatremic was 2.91 (1.61–5.27) (95% CI) (p = 0.001) (Table 2). Likewise, the OR of having osteoporosis when treated with an EIAED was 4.81 (2.89–7.99) (95% CI) ($p < 0.001$) (Table 3).

To investigate whether hyponatremia was an independent risk factor for osteoporosis and not just a surrogate marker for the use of the EIAEDs, we used a logistic regression with p-Na as a continuous variable and osteoporosis defined categorically as a T-score < -2.5 at any of the three regions of interest. When only including p-Na in the analysis we found a significant association between the risk of osteoporosis and decreasing p-Na, OR 1.09 per mmol/L p-Na (95% CI 1.04, 1.15),

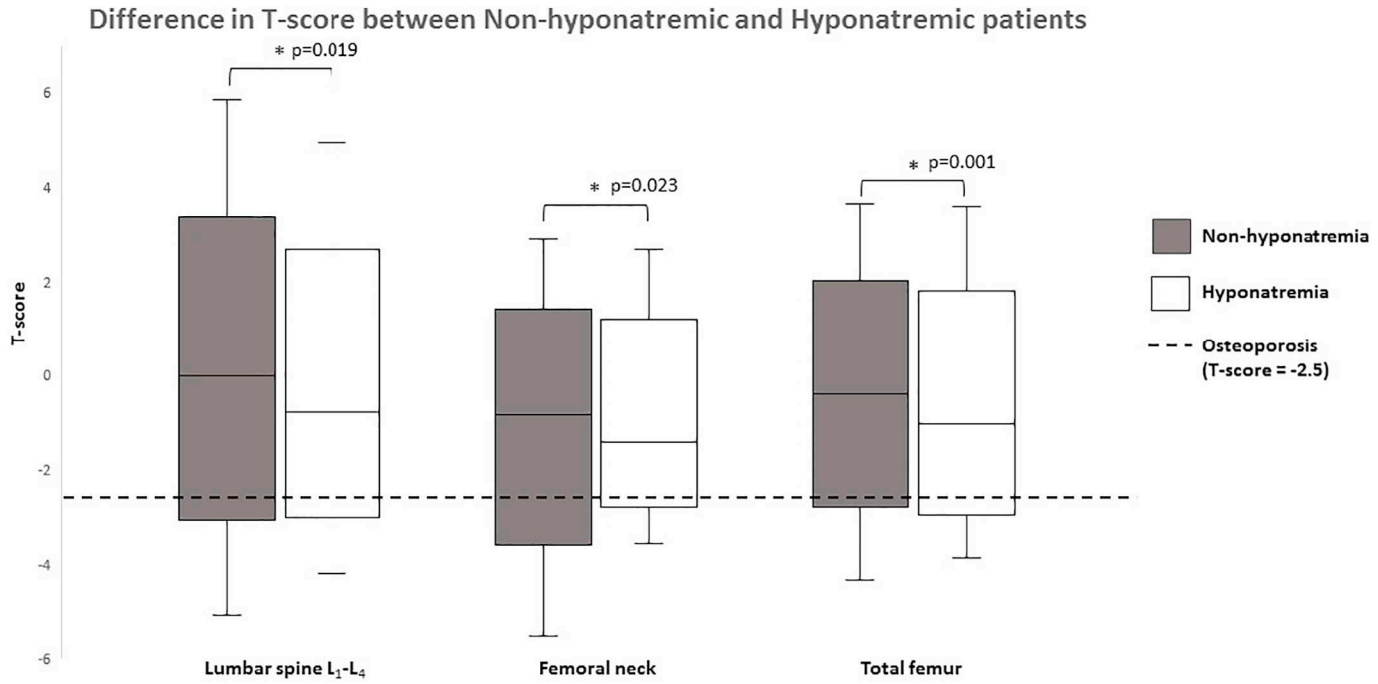

Fig. 3. Graphical display of the T-scores for the non-hyponatremic (grey box) and hyponatremic (white box) patient populations at the three sites of interest: The lumbar spine, the femoral neck and the total femur. Boxes represent the interquartile range, the line across the boxes represents the median and the whisker represents the minimum and maximum values, respectively. The dotted line represents the definition of osteoporosis (T-score = −2.5). The hyponatremic groups had significantly lower T-scores in all regions tested using an Independent samples *t*-test.

Table 2
Chi-square test for hyponatremia and osteoporosis.

	No osteoporosis (N (%))	Osteoporosis (N (%))	Total (N (%))	Statistical significance
Non-hyponatremia (N (%))	559 (89.7)	64 (10.3)	623 (100)	
Hyponatremia (N (%))	54 (75.0)	18 (25.0)	72 (100)	
Total (N (%))	613 (88.2)	82 (11.8)	695 (100)	**0.001**
OR for osteoporosis when hyponatremic		2.91 (1.61–5.27) (95% CI)		**0.001**

Patients with hyponatremia have an increased OR of osteoporosis at the lumbar spine, femoral neck or total femur. Tested with Pearson chi-square test.

Table 3
Chi-square test for the use of EIAEDs and osteoporosis.

	No osteoporosis (N (%))	Osteoporosis (N (%))	Total (N (%))	Statistical significance
NEIAED (N (%))	468 (75.4)	153 (24.6)	621 (100)	
EIAED (N (%))	28 (38.9)	44 (61.1)	72 (100)	
Total (N (%))	496 (71.6)	197 (28.4)	693 (100)	< **0.001**
OR for osteoporosis when using EIAEDs		4.81 (2.89–7.99) (95% CI)		< **0.001**

Patients treated with EIAEDs have an increased OR of osteoporosis at the lumbar spine, femoral neck or total femur. Tested with Pearson chi-square test.

Table 4
Results of the binary logistic regression with sodium levels as a continuous variable.

	B (95% CI B)	OR	95% CI OR		Statistical significance
			Lower	Upper	
Sodium levels [Na^+]	−0.05 (−0.10, 0.01)	0.95	0.91	1.00	0.069
BMI	−0.14 (−0.23, −0.08)	0.87	0.81	0.92	< **0.001**
Age at scan	0.05 (0.03, 0.07)	1.05	1.03	1.07	< **0.001**
1 AED	–	–	–	–	–
2 AEDs	0.69 (0.12, 1.30)	2.00	1.12	3.56	**0.019**
3 or more AEDs	0.12 (−0.82, 0.90)	1.13	0.48	2.67	0.787
EIAEDs	0.90 (0.38, 1.51)	2.45	1.35	4.43	**0.003**
Constant	5.27 (−2.25, 12.97)	–	–	–	–

Results of the binary logistic regression. OR of osteoporosis at any of the three regions of interest (lumbar spine, femoral neck or total femur) is significantly association with BMI, age at scan, the use of 2 AEDs and the use of EIAEDs. Hyponatremia is borderline significantly associated with OR of osteoporosis.

($p < 0.001$). When adjusting for known risk factors for osteoporosis in patients with epilepsy, including BMI, age at scan, number of AEDs used and the use of EIAEDs, the association was no longer significant, OR 0.95 per mmol/L [Na^+] (95% CI 0.91, 1.00), ($p = 0.069$). Instead a significant association was found between the risk of osteoporosis and decreases in BMI (OR 0.87 (95% CI: 0.81, 0.92) ($p < 0.001$)), age at scan (OR 1.05 (95% CI: 1.03, 1.07) ($p < 0.001$)), use of 2 AEDs (OR 2.00 (95% CI: 1.12, 3.56) ($p = 0.019$)) and the use of EIAEDs (OR 2.45 (95% CI: 1.35, 4.43) ($p = 0.003$)) (Table 4) in the adjusted analysis. The same logistic regression was performed with hyponatremia as a categorical variable at p-Na ≤ 135 mmol/L, and likewise, a significant association between the risk of osteoporosis and hyponatremia was found, OR 2.83 (95% CI 1.55, 5.17), ($p = 0.001$) in the simple analysis. When adjusting for the above-mentioned risk factors, the association with hyponatremia was no longer significant, OR 1.64 (95% CI 0.84, 3.18), ($p = 0.147$) but just like before there was a significant association between the risk of osteoporosis and decreased BMI (OR 0.87 (95% CI: 0.81, 0.92) ($p < 0.001$)), age at scan (OR 1.05 (95% CI: 1.03, 1.06) ($p < 0.001$)), the use of 2 AEDs (OR 1.94 (95% CI: 1.09, 3.46) ($p = 0.025$)) and the use of EIAEDs (OR 2.57 (95% CI: 1.43, 4.61) ($p = 0.002$)) (data not shown).

Furthermore, we wanted to look at BMD as a continuous variable, the T-score, for each of the three regions of interest, the lumbar spine L1-L4, femoral neck and total femur. Therefore, an ANCOVA was performed to investigate differences in mean T-score between the hyponatremic (p-Na ≤ 135 mmol/L) and non-hyponatremic patients (p-Na > 135 mmol/L). As in the binary logistic regression the analyses were adjusted for covariates associated with increased risk of osteoporosis in patients with epilepsy as BMI, age at scan, and a number of AEDs were used. The use of EIAEDs was omitted from the analysis to avoid correlation with the covariates hyponatremia and number of AEDs used, since the variables are correlated. In this analysis, a borderline significant lower mean T-score was found in the lumbar spine L_1-L_4 region ($p = 0.063$) but not in the femoral neck ($p = 0.834$) or total femur ($p = 0.133$) (Table 5).

Next, we wanted to investigate whether patients with the most severe hyponatremia had a higher risk of osteoporosis than less severe cases. Therefore, we repeated the binary logistic regression and the ANCOVA comparing BMD across the categorical variable of moderate and severe hyponatremia, p-Na ≤ 129 mmol/L. In the binary logistic regression, with osteoporosis defined categorically as a T-score < −2.5 at either the lumbar spine L_1-L_4, femoral neck or total femur the simple analysis showed a significant association between the risk of osteoporosis and moderate and severe hyponatremia, OR 3.34 (95% CI 1.15, 9.74), ($p = 0.027$). However, in the adjusted analysis when adjusting for BMI, age at scan, number of AEDs used and the use of EIAEDs the significant association disappears, OR 1.87 (95% CI 0.58, 6.04), ($p = 0.298$) (Table 6). As previous an ANCOVA was performed to look for differences in mean T-score between the moderate and severe hyponatremic patients and the rest of the population. The analyses were performed for the T-score for the three regions of interest, lumbar spine L_1-L_4, femoral neck and total femur, respectively and adjusted for the same covariates as previously: BMI, age at scan, and number of AEDs used. Here a significantly lower mean T-score in the lumbar spine L_1-L_4 region was found for the patients with moderate and severe hyponatremia ($p = 0.030$), a borderline significant difference in mean T-score was also found for the total femur ($p = 0.061$), whereas no significant difference in mean T-score was found for the femoral neck ($p = 0.251$) (Table 7).

Table 5
Results of the ANCOVA with hyponatremia defined as values p-Na ≤ 135 mmol/L.

	Non-hyponatremic	Hyponatremic	Mean difference	P-value
L_1-L_4				
N (%)	611 (89.5)	71 (10.5)		
T-score (mean (SD))	−0.054 (1.46)	−0.607 (1.88)	−0.553	0.063
Femur Neck				
N (%)	606 (89.4)	72 (10.6)		
T-score (mean (SD))	−0.783 (1.20)	−1.136 (1.30)	−0.353	0.834
Femur Total				
N (%)	608 (89.4)	72 (10.6)		
T-score (mean (SD))	−0.390 (1.25)	−0.932 (1.47)	−0.542	0.133

T-scores (mean(SD)) for the three regions of interest (lumbar spine, femoral neck or total femur) when corrected for BMI, age at scan and number of AEDs used. A borderline significant difference in found for the lumbar spine L_1-L_4 region. No significant difference is found in the other regions on interest between non-hyponatremic and hyponatremic.

4. Discussion

4.1. Hyponatremia-induced osteoporosis in patients with epilepsy

To our knowledge, this is the first study linking hyponatremia-induced osteoporosis to the increased risk of metabolic bone disease in patients with epilepsy and demonstrating that moderate to severe hyponatremia could be an independent risk factor for osteoporosis in patients with epilepsy.

In the current study we found a significant association between moderate and severe hyponatremia and osteoporosis in patients with epilepsy. This is in accordance with the accumulating evidence of hyponatremia-induced osteoporosis as has been shown in large cross-sectional studies, animal models and in cell culture studies of osteoclasts [5,28–30]. Likewise, hyponatremia has been shown to be associated with increased risk of fractures, especially at the hip [30,31]. However, in contrast to other studies we found the association at lumbar spine L_1-L_4 which is not consistently seen in studies of hyponatremia-induced osteoporosis where effects are seen primarily at the hip and less consistently at the lumbar spine [28,32]. Cortical bone seems more vulnerable to changes in sodium than trabecular bone. Our finding of a difference in BMD the lumbar spine might reflect an interplay between various risk factors for osteoporosis in patients with *epi*lepsy. However, hyponatremia should lead to further investigations of the patient's bone health.

In the initial investigations of the T-scores (Fig. 3) the hyponatremia patients have significantly lower T-scores in all regions of interest than the non-hyponatremic patients. However, in adjusted models (Table 4) this finding is no longer present, but BMI, age at scan, the use of 2 AEDs and the use of EIAEDs are all significantly associated with increased risk of osteoporosis. All variables are known to be explanatory factors when it comes to bone health and could be confounding the effects of hyponatremia.

Hyponatremia-induced osteoporosis is caused by chronic hyponatremia and in the general population the most common cause of chronic hyponatremia is SIADH [33]. Hyponatremia in patients with epilepsy is very common, with an prevalence of AED induced hyponatremia ranging from 7 to 46% [23]. Although, hyponatremia in patients with epilepsy can be caused by various reasons, including the use of concomitant medication (e.g. diuretics), hepatic cirrhosis, renal disease and congestive heart failure [34–36], the occurrence of hyponatremia comprises 10.4% of our study population. This is higher than similar studies in the general population with various medication use, where the occurrence of hyponatremia has been found to be ranging from 2.4 to 8.7% [8,37]. This indicates that the common denominator in our population, the use of AEDs, is a considerable contributor to the occurrence of hyponatremia. Hyponatremia associated with AED's shares many of the clinical characteristics found in patients with SIADH; however, it is not accompanied by a rise in ADH levels. Clinical and in vitro data suggest that AED's, especially those that are EIAEDs, such as carbamazepine and oxcarbazepine, enhance the sensitivity of the

Table 6
Results of the binary logistic regression with moderate and severe hyponatremia, p-Na ≤ 129 mmol/L.

	B (95% CI B)	OR	95% CI OR		Statistical significance
			Lower	Upper	
Moderate and severe hyponatremia, [Na^+] ≤ 129 mmol/L	0.62 (−1.06, 1.94)	1.87	0.58	6.04	0.298
BMI	−0.15 (−0.22, −0.08)	0.86	0.81	0.92	< **0.001**
Age at scan	0.05 (0.03, 0.07)	1.05	1.03	1.07	< **0.001**
1 AED	–	–	–	–	–
2 AEDs	0.69 (0.13, 1.26)	2.00	1.12	3.54	**0.019**
3 or more AEDs	0.15 (−0.81, 0.95)	1.16	0.49	2.74	0.733
EIAEDs	0.97 (0.42, 1.57)	2.65	1.48	4.74	**0.001**
Constant	−1.51 (−3.41, 0.31)	–	–	–	–

Results of the binary logistic regression. OR of osteoporosis at any of the three regions of interest (lumbar spine, femoral neck or total femur) is significantly association with BMI, age at scan, the use of 2 AEDs and the use of EIAEDs. Moderate and severe hyponatremia is not significantly associated with increased risk of osteoporosis.

Table 7
Results of the ANCOVA with moderate and severe hyponatremia, p-Na ≤ 129 mmol/L.

	Mild- to non-hyponatremic	Moderate and Severe Hyponatremic	Mean difference	P-value
L_1-L_4				
N (%)	665 (97.5)	17 (2.5)		
T-score (mean (SD))	−0.087 (1.51)	−1.055 (1.24)	−0.968	**0.030**
Femur Neck				
N (%)	661 (97.5)	17 (2.5)		
T-score (mean (SD))	−0.809 (1.22)	−1.251 (1.25)	−0.442	0.251
Femur Total				
N (%)	663 (97.5)	17 (2.5)		
T-score (mean (SD))	−0.429 (1.28)	−1.157 (1.43)	−0.728	0.061

T-scores (mean (SD)) for the three regions of interest (lumbar spine, femoral neck or total femur) when corrected for BMI, age at scan and number of AEDs used. A significant difference is found for the lumbar spine L_1-L_4 region between mild- to non-hyponatremic patients and the moderate to severe hyponatremic patients.

kidney to ADH and may actually increase the permeability of the collecting duct to water in the absence of ADH [38–41]. It has been suggested that ADH levels also play a role in hyponatremia-induced osteoporosis since an animal model has shown a negative effect of ADH on bone metabolism [42]. If this is a contributing factor to hyponatremia-induced osteoporosis in humans, this is not an effect which we expect to see in our study.

A relevant issue to consider is whether the hyponatremic epilepsy patients represent a more vulnerable subgroup of patients with additional comorbidities not captured in the study. A recent study from 2016 showed that all levels of hyponatremia is associated with all-cause mortality, increased risk of being diagnosed with any form of cancer and especially pulmonary and head and neck cancers, suggesting that hyponatremia might be used as a marker for underlying disease [37]. It is possible that the difference in weight seen between non-hyponatremic and hyponatremic patients could represent underlying disease or worse general health condition.

4.2. Epilepsy and bone health

Investigating hyponatremia-induced osteoporosis in patients with epilepsy is complicated due to simultaneous risk factors of osteoporosis as long-term use of AEDs, cumulative AED drug load, generalized seizures, increased intake of alcohol, higher occurrence of smoking, less weight bearing exercise, false low exposure to sunlight and inadequate intake of calcium and vitamin D [13,43–45]. Furthermore use of EIAEDs led to the term ‘Anticonvulsant osteomalacia’ where their induction of the livers cytochrome P450 enzyme-system is believed to increase the catabolism of vitamin D leading to a form of secondary hyperparathyroidism and increased bone turnover [17,46,47]. Adverse effects on bone health is also seen in relation to treatment with enzyme-inhibiting drugs such as valproic acid and newer drugs with no known enzyme effect such as levetiracetam [48–50]. In our population, patients with hyponatremia more often uses 2 and 3 or more drugs than non-hyponatremic patients which indicates a greater cumulative drug load and they are more likely to use EIAEDs which we also show is significantly associated with increased risk of osteoporosis. The increased use of EIAEDs and the hypothesized secondary hyperparathyroidism is difficult to evaluate since neither PTH levels nor vitamin D measurements were available. The total calcium levels were normal, but interpretations made difficult due to the lack of above mentioned biochemical parameters. The only biochemical parameter that differs between the non-hyponatremic and hyponatremic groups is alkaline phosphatase, which is higher in patients with hyponatremia, however still within the normal reference range. Furthermore, this is not a bone-specific alkaline phosphatase and could be elevated for various reasons not related to the bones. Otherwise, the two groups do not differ in any other variables associated with increased risk of osteoporosis in patients with epilepsy. The hyponatremic patients do not have more seizures or other diseases leading to secondary osteoporosis.

4.3. Strengths and limitation

The study's primary strength is the large number of DXA scans offering a unique insight into a large population of patients with epilepsy. Likewise, does the use of the Danish CPR number allow for specific matching of DXA scan and biochemical parameters with high validity. Information from the patients' medical report allows to correct for variables that we know influence bone health in patients with epilepsy. As the populations greatly resemble other patient populations with epilepsy it is likely that a certain degree of generalizability to other patient populations with epilepsy exists.

However, there are also certain limitations to the study. Despite our effort to collect information from the patients' medical reports we lack

information about family history of osteoporosis, prior fractures, ethnicity, nutrition and exercise when adjusting for potential confounders. Another limitation is the definition of hyponatremia, which when associated with osteoporosis is a chronic condition and not as in the present study a single p-Na value taken prior to the scan or a maximum of 14 days after. However, we cannot know if the hyponatremia is acute or chronic nor how p-Na changes in the time span between the blood sample is drawn and the DXA scan performed. Although we assume, that the most likely cause of hyponatremia in patients with epilepsy is chronic SIADH hyponatremia caused by AEDs we cannot confirm it. We have no information about parameters such as ADH levels, plasma or urinary osmolality, or about other diseases and drugs known to cause hyponatremia. Hyponatremia and osteoporosis should be considered as two chronic conditions with a causal link, which was sought illustrated when choosing a p-Na value prior to the scan or a maximum of 14 days after. Furthermore, a limitation is the lack of information about fracture incidence which is the ultimate consequence of osteoporosis.

To be included in the study, the DXA scan had to be performed at Rigshospitalet Glostrup. If the patient had a scan at another hospital, they would not be included in the study and therefore the occurrence of osteoporosis in the present study population is underestimated. Moreover, institutionalized patients in the clinic, who may be more likely to have osteoporosis due to increased drug load, less sun-exposure, less weight bearing exercise or being wheel-chair bound, are also less likely to have a DXA scan performed due to high occurrence of comorbidities such as mental retardation, cerebral palsy and spasticity, all of which poses cognitive- and physical-barriers in cooperating and completing the scan.

Lastly, our observational cross-sectional design offers no explanation on mechanisms underlying hyponatremia and osteoporosis in patients with epilepsy.

5. Conclusion

We conclude that hyponatremia is common in patients with epilepsy and that moderate and severe hyponatremia is independently associated with decreased BMD in the lumbar spine. Thus, a finding of hyponatremia in patients with epilepsy should therefore warrant further examination of the patient's bone health to exclude or treat existing osteoporosis. Further studies are needed to increase our knowledge on this association as well as prospective studies looking into the underlying mechanisms behind hyponatremia-induced osteoporosis in patients with epilepsy.

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Conflicts of interest

SSD has received unrestricted research grants from Eisai Co, Ltd. ASS has since the initiation of the work has been employed by Novo Nordisk A/S. NRJ and CS have no conflicts of interest to disclose. PE is an advisory board member for Amgen Inc. and Eli Lilly A/S, and on the speakers' bureau for Amgen Inc. and Eli Lilly A/S, and own shares in Novo Nordisk A/S. NBA is a lecturer at scientific meetings organized by Eisai Co, Ltd., and has received unrestricted research grants from Eisai Co, Ltd.

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