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FULL-LENGTH ORIGINAL RESEARCH

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Are we responding effectively to bone mineral density loss and fracture risks in people with epilepsy?

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Abstract

Objective: A 2007 study performed at Montefiore Medical Center (Bronx, NY) identified high prevalence of reduced bone density in an urban population of patients with epilepsy and suggested that bone mineralization screenings should be regularly performed for these patients. We conducted a long-term follow-up study to determine whether bone mineral density (BMD) loss, osteoporosis, and fractures have been successfully treated or prevented.

Methods: In the current study, patients from the 2007 study who had two dual-energy absorptiometry (DXA) scans performed at least 5 years apart were analyzed. The World Health Organization (WHO) criteria to diagnose patients with osteopenia or osteoporosis were used, and each patient's probability of developing fractures was calculated with the Fracture Risk Assessment Tool (FRAX).

Results: The median time between the first and second DXA scans for the 81 patients analyzed was 9.4 years (range 5-14.7). The median age at the first DXA scan was 41 years (range 22-77). Based on WHO criteria, 79.0% of patients did not have worsening of bone density, while 21.0% had new osteopenia or osteoporosis; many patients were prescribed treatment for bone loss. Older age, increased duration of anti-epileptic drug (AED) usage, and low body mass index (BMI) were risk factors for abnormal BMDs. Based on the first DXA scan, the FRAX calculator estimated that none of the patients in this study had a 10-year risk of more than 20% for developing major osteoporotic fracture (hip, spine, wrist, or humeral fracture). However, in this population, 11 patients (13.6%) sustained a major osteoporotic fracture after their first DXA scan.

Significance: Despite being routinely screened and frequently treated for bone mineral density loss and fracture prevention, many patients with epilepsy suffered new major osteoporotic fractures. This observation is especially important as persons with epilepsy are at high risk for falls and traumas.

KEYWORDS

bone mineral density, dual-energy absorptiometry scan, fracture, Fracture Risk Assessment Tool, osteoporosis

1 | INTRODUCTION

Persons with epilepsy are at an increased risk of sustaining fractures.[1–4] A large meta-analysis that compared the fracture risk for persons with and without epilepsy showed that the relative risk of having any fracture for persons with epilepsy is doubled, and it is fivefold and sixfold for hip and spine fractures, respectively.[5] The determination of why persons with epilepsy maintain a higher fracture risk remains inconclusive. Prior studies have revealed that fractures can be directly caused from seizure-related falls and trauma.[6,7] Several studies have shown that duration of anti-epileptic drug (AED) treatment increases fracture risk,[1,8–10] while other studies show that only current and recent AED usage affects fracture risk.[11] It remains unclear whether taking certain types of AEDs, namely enzyme-inducing AEDs, elevates one's fracture risk and to what degree.[5,9,11] It is also unclear how gender-specific and concurrent disease impacts fracture risk.[1,4,9,12] Calcium and vitamin D are common supplements for bone density loss prevention; however, the evidence for their efficacy in the prevention of osteoporotic fractures is limited.[13] There are multiple studies that show the efficacy of bisphosphonates in maintaining bone density loss and in fracture risk reduction.[14]

A 2007 study performed at our institution—Comprehensive Epilepsy Center, Montefiore Medical Center (Bronx, NY), identified high prevalence of reduced bone mineral density (BMD) in an urban population of persons with epilepsy.[15] Out of the 130 patients included in this Montefiore study, 55% presented with T-scores less than or equal to −1. The study showed that certain risk factors, such as specific AED usage, duration of AED treatment, gender, and age, increase the likelihood of having an abnormal BMD. The study suggested that bone mineralization screenings should be regularly performed for these patients.

This long-term follow-up study was conducted to determine whether BMD loss, osteoporosis, and fractures have been successfully treated or prevented in our clinic setting. Another goal of this study was to determine whether certain risk factors and patient characteristics can predict whether a person with epilepsy will develop or maintain an abnormal BMD or suffer a fracture over an extended period of time.

Key Points

- This long-term study assesses whether osteoporosis and fractures have been effectively treated or prevented in persons with epilepsy.
- Based on WHO criteria, 21.0% of subjects developed new osteopenia or osteoporosis.
- Older age, increased duration of anti-epileptic drug usage, and low BMI were risk factors for abnormal bone mineral density.
- The FRAX Calculation Tool underestimated risk of fracture in this patient population.

2 | METHODS

2.1 | Study design

This retrospective study analyzes data obtained from patients involved in the initial 2007 study. In the current study, patients were included if they had a follow-up dual-energy absorptiometry (DXA) scans performed at least 5 year after the initial one. Patients' BMDs at the initial and follow-up scans were compared, and patient charts were reviewed to determine whether they sustained a major osteoporotic fracture since the original study. Major osteoporotic fracture was defined as a fracture at one of these sites: hip, spine, wrist, or humerus. Changes in BMDs were analyzed in relation to various potential risk factors, and the Fracture Risk Assessment Tool (FRAX) was used to calculate the 10-year risk of suffering a major osteoporotic fracture.

2.2 | Data sources

Patient information was collected from the 2007 study database and from follow-up chart review. All the patients were adults who received care at the Comprehensive Epilepsy Center at Montefiore Medical Center, which is an urban hospital that serves a predominantly low-income and demographically diverse population. Data gathered included demographics, T-scores from the two DXA scans performed, type of AEDs, and bone loss treatment (calcium, vitamin D, bisphosphonates, or a combination of these treatments) taken at the initial and follow-up DXA scans.

2.3 | Bone mineral density (BMD)

Each patient's BMD was measured using DXA scans and reported in the form of T-scores and Z-scores. T-score is defined as the standard deviation of an individual's BMD from the mean value for healthy young white women. Z-score represents the number of standard deviations from the normal mean value for age-, race- or ethnicity-, and sex-matched control subjects.[16] According to the World Health Organization (WHO), a T-score ≥ -1 is considered normal, a T-score between −1 and −2.5 is defined as osteopenia or low bone density, and a T-score ≤ -2.5 is defined as osteoporosis.[17] In this study, patients' femoral neck T-scores were used.

2.4 | FRAX calculation tool

The FRAX Calculation Tool was developed by the University of Sheffield to estimate a person's 10-year probability of suffering a major osteoporotic fracture.[18,19] The FRAX incorporates clinical risk factors, such as previous fracture, alcohol consumption, current smoking, and BMD of the femoral neck. The calculator has models that are population-specific to different nationalities and ethnicities all around the world. For the United States, the FRAX differentiates ethnicity into four demographic categories: Caucasian, Black, Hispanic, and Asian. In the United States, postmenopausal women and men aged 50 years or older who have a major osteoporotic fracture risk ≥ 20% in the next 10 years qualify for treatment with antiresorptive or anabolic osteoporotic medication as appropriate.[20,21] In this study, the FRAX Calculation Tool was used to calculate each patient's 10-year risk of suffering a major osteoporotic fracture, and the tool's ability to successfully identify persons with epilepsy who have a high fracture risk and to predict which patients would ultimately sustain a fracture was assessed.

2.5 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 24, IBM Corp. Risk factors for low BMD and fractures were compared using Mann-Whitney *U* test and Kruskal-Wallis test for nonparametric data. Fisher's exact test was used for analysis of distribution of variables.

This study was conducted with the approval of the Montefiore Medical Center Institutional Review Board.

3 | RESULTS

3.1 | Demographic data

Of the 130 patients enrolled in the 2007 Montefiore study, 81 patients (62.3%) had at least one follow-up DXA scan more than 5 years after their first DXA and were included in the current analysis. For the 81 subjects with complete data, the median time between the first and second DXA scans was 9.4 years (range 5-14.7 years). The patients' demographic data are displayed in Table 1. 54.3% of the patients were female. Patient median age at initial DXA scans was 41 years (range 22-77 years) and was 52 years (range 29-88 years) at their follow-up DXA scans. The patients enrolled in this study were racially diverse as indicated.

Of the remaining 49 subjects who were in the initial 2007 cohort and not part of the current study, 31 did not have a repeat DXA scan or had their repeat DXA less than 5 years apart after first. The rest were lost to follow-up or insufficient information was available. For the 31 patients at their initial DXA scan, the average age was 39.6, 54.8% were female, and 3.2% (one patient) had osteoporosis.

TABLE 1 Demographic data (total sample size: 81 patients)

	Value (% of total population)	
Gender	Female (54.3), male (45.7)	
Race	Asian (3.7), Black (35.8), Hispanic (35.8), Caucasian (24.7)	
WHO clinical status (femoral neck)		
Normal at both DXA scans	44.4	
Osteopenia at both DXA scans	19.8	
Osteoporosis at both DXA scans	1.2	
Normal to osteopenia	8.6	
Normal to osteoporosis	1.2	
Osteopenia to normal	8.6	
Osteopenia to osteoporosis	11.1	
Osteoporosis to osteopenia	4.9	
Secondary osteoporosis (at any site)		
Never	70.4	
At both DXA scans	7.4	
Only at first DXA scan	8.6	
Developed after first DXA scan	13.6	
	1st DXA scan	2nd DXA scan
Smoker	11.1	8.6
Taking glucocorticoids	1.2	4.9
Rheumatoid arthritis	1.2	2.5
Alcohol consumption:> 3 units/day	1.2	1.2
	Value	
Median BMI at second DXA Scan (kg/m^2)	27.2	
Median time between DXA scans in years (range)	9.4 (5-14.7)	
FRAX score—major osteoporotic fracture risk (median, range)	1.4% (0.5%-14%)	
	1st DXA Scan	2nd DXA Scan
Median age in years (range)	41 (21-77)	52 (29-88)

3.2 | Osteoporosis/T-scores

Based on WHO criteria, 44 (54.3%) of the 81 patients included in this study had normal BMD, 32 (39.5%) had

osteopenia, and five patients (6.2%) had osteoporosis at their first DXA scan (femoral neck).

Overall, 79.0% of patients had stable or improved WHO status (femoral neck) between the DXA scans. Of the 44 patients who had normal BMDs at their first DXA scans, 36 (81.8% of all normal patients) continued to have normal BMDs at the second DXA scan; seven osteopenic patients (21.8% of all osteopenic patients) improved to normal bone density and 16 patients (50%) remained osteopenic; four patients (80% of all patients with osteoporosis) improved from osteoporosis to osteopenia. At the second DXA scan, three patients (8.8%) out of the 34 who were below the age of 50 had osteoporosis; 14 patients (29.7%) out of the 47 patients who were 50 and older had osteoporosis. Figure 1 shows the change in BMD from the first to their second DXA scan. Overall, 45 patients (55.6%) had a lower T-score at the femoral neck at their second DXA scan than at their initial one.

3.3 | AEDs and bone density loss supplements

At the time of the first DXA, 86.4% of patients were taking AEDs known or suspected to decrease BMD (benzodiazepines, valproic acid, zonisamide, and enzyme-inducing AEDs: carbamazepine, phenytoin, oxcarbazepine, topiramate, and phenobarbital). Although gabapentin does not have liver effects, it appears to also reduce BMD, and it was therefore included with other AEDs known to decrease BMD in the analysis.[2] AEDs that are not considered to influence bone metabolism include lamotrigine, levetiracetam, and lacosamide.[2] 46.9% of patients were only taking calcium and vitamin D, and 11.1% were taking bisphosphonates alone or in combination with calcium and vitamin D (Table 2).

At the time of the second DXA, 80.2% of all patients were taking AEDs known to decrease BMD and 74.1% were

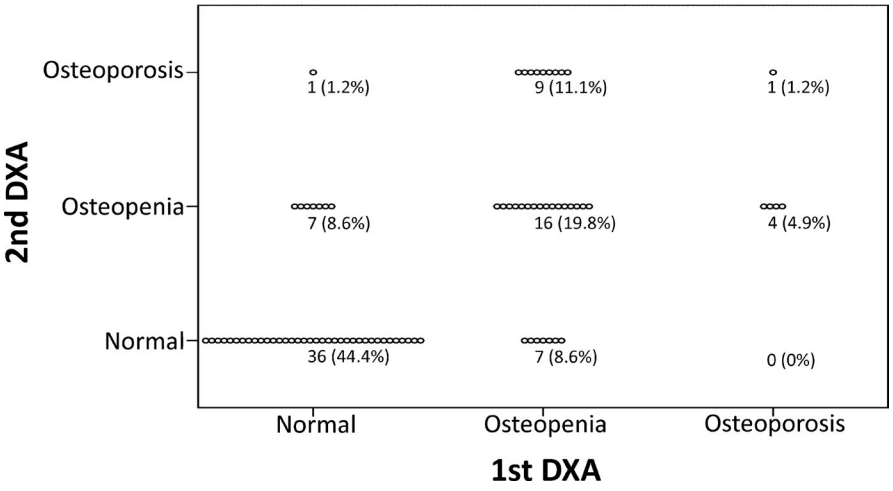

FIGURE 1 Comparison of BMD at both DXA scans: Horizontal axis represents WHO status at DXA 1, and vertical axis represents WHO status at DXA2. In the graph, each circle represents a patient; numbers represent patients in that group (% of total population)

TABLE 2 Comparison of patient medications at both DXA scans

	Value (% of total population)	
	1st DXA scan	2nd DXA scan
Taking AEDs known to decrease BMD[a]	86.4	80.2
Bone loss treatment		
Calcium/vitamin D	46.9	44.4
Bisphosphonates	1.2	2.5
Calcium/vitamin D and bisphosphonates	9.9	27.2
No treatment/cannot obtain results	42.0	25.9
	Value (%)	
	1st DXA scan	**2nd DXA scan**
% of patients taking AEDs known to decrease BMD treated with bone loss treatment	55.7 (39/70 patients)	76.9 (50/65)
% of patients with abnormal BMD treated with medications for bone loss	89.2 (33/37)	84.2 (32/38)
% of patients with abnormal BMD and on AEDs known to decrease BMD treated with medications for bone loss	90.3 (28/31)	87.5 (28/32)

[a]Includes benzodiazepines, carbamazepine, phenytoin, valproic acid, gabapentin, oxcarbazepine, topiramate, phenobarbital, and zonisamide

taking medications to prevent or treat bone loss. The exact duration of treatment for each specific AED could not be definitively assessed from chart review, and only an aggregate total length of time that patients took any AED could be analyzed: The median duration of treatment was 21 years at the first DXA scan and was 32 years at the second DXA scan.

Of the 70 patients who were taking AEDs known to decrease BMD at the first DXA scan, 55.7% were simultaneously being treated for bone loss. Of the 65 patients who were taking AEDs known to decrease BMD at the second DXA scan, 76.9% were also being treated for bone loss, reflecting a 21.2% increase. Of the 37 patients who had abnormal BMD at their first DXA scan, 89.2% were also taking medications to prevent or treat bone loss. At the second DXA scan, out of 32 patients who took both AEDs known to decrease BMD and had abnormal BMD, at least 87.5% were prescribed bone loss treatment.

3.4 | Risk factors for abnormal BMDs and worsening WHO clinic statuses

Patients who had abnormal BMD at baseline or decline in WHO status in their follow-up DXA scans were compared with patients who improved or maintained normal BMD at follow-up. This first group of patients initially had normal BMD and subsequently developed abnormal BMD, had osteopenia and developed osteoporosis, had osteopenia at both DXAs, or had osteoporosis at both examinations. The second group had normal BMD at both scans, had abnormal BMD initially and subsequently developed normal BMD, or had osteoporosis and developed osteopenia. This comparison is displayed in Table 3A.

Older age was associated with either worsening or persistently abnormal BMD: The median age at the second DXA scan of this group was 54 years, whereas the median age of patients who improved or maintained normal BMD was 48 years ($P = .017$). Low body mass index (BMI) was also positively correlated with either worsening or persistently abnormal BMD: The median BMI of patients who had worsening or persistently abnormal BMDs was 25.0 kg/m^2 vs 28.3 kg/m^2 for patients who improved or maintained normal BMD ($P = .003$).

Overall, many patients took AEDs known to decrease BMD (85.3% of patients who had worsening or persistently abnormal BMDs vs 87.2% of patients who improved or maintained normal BMDs). From chart review, duration of treatment for each specific AED could not be established. However, the total time the patients took any AED at first DXA scan could be determined: 29 years for patients who had worsening or persistently abnormal BMDs vs 19 years for those who improved or maintained normal BMDs ($P = .043$). Gender, smoking, and alcohol intake were not found to be associated with worsening or persistently abnormal BMD in this study.

3.5 | Fractures and FRAX-calculated risks

The FRAX Calculation Tool was used to compare the patients' 10-year risk of sustaining a major osteoporotic fracture with the actual incidence of fractures in this population. The median major osteoporotic fracture risk calculated by FRAX at the first DXA scan was 1.4% both in men and in women (range: 0.5%-14%). No patients had a 10-year risk of a major osteoporotic fracture ≥20%, which is the recommended risk threshold for when treatment should be considered. However, in our study population, 11 patients (13.6%) sustained a major osteoporotic fracture after their first DXA scan (Table 3B). Of the 11 patients who sustained a fracture, 3 patients (27.3% of patients in this group) were younger than 50 years old and 8 (72.7% of patients in this group) were 50 years or older. Four patients sustained hip fractures, two patients had vertebral fractures, one patient had a wrist fracture, two patients had humeral fractures, one patient had a hip and a vertebral compression fracture at different times, and one had vertebral, wrist, and humeral fractures. It is unclear from chart reviews whether these fractures could be attributed to seizure-related falls or to other traumas.

Of the patients with new fractures, nine (81.8%) were taking AEDs known to decrease BMD at their first DXA scan. Five (45.4%) of the patients with new fractures were taking calcium or vitamin D alone, and two (18.2%) were taking bisphosphonates at their first DXA scan. Out of the nine patients who were taking bisphosphonates, two (22.2%) sustained major osteoporotic fractures and seven did not. No statistically significant correlations were found between individual risk factors analyzed and incidence of sustaining a fracture.

4 | DISCUSSION

The study objective was to determine the extent to which reduced BMD and major osteoporotic fractures occurred over an extended period of time in persons with epilepsy and to identify any risk factors which may have predicted that outcome. The results demonstrate that 79.0% of the initial population had no significant change in bone mineral density over an approximately 10-year period; of these, 44.4% had normal results in both DEXA scans, 13.5% initially had abnormal BMDs but improved, and nearly 20% showed osteopenia at both time points.

However, 21.0% of our patients did show worsening in bone mineral density over the 10-year time frame. Overall, 12.3% of patients developed osteoporosis (femoral neck), and 13.6% suffered new major osteoporotic fractures. This occurred despite the observation that most of the patients who had low BMDs and were taking AEDs known to decrease BMD were consistently treated with bone mineral density loss treatments. The probability for worsening or

TABLE 3 (A) Correlation between risk factors and change in WHO clinical status (at femoral neck). (B) Correlation between risk factors and occurrence of major osteoporotic fractures between DXA scans (after the first DXA and before the second DXA)

	A		B	
	Abnormal or worsened WHO clinical status (osteopenia/osteoporosis) N = 34 (42.0%)	**Normal or improved WHO clinical status N = 47 (58.0%)**	**Sustained major osteoporotic fracture N = 11 (13.6%)**	**Did not sustain major osteoporotic fracture N = 70 (86.4%)**
	Value (*P* value)		**Value (*P* value)**	
Age at second DXA scan in years (median)	54	48 (.017)	52	50.5 (.121)
Gender: female/male (%)	58.8/41.2	51.1/48.9 (.489)	54.5/45.5	54.3/45.7 (.987)
Race: Asian/Black/Hispanic/White (%)	2.9/20.6/41.2/35.3	4.3/46.8/31.9/17	9.1/27.3/27.3/36.4	2.9/37.1/37.1/22.9
BMI in kg/m^2 (median)	25.0	28.3 (.003)	25.7	27.3 (.174)
Smoking at 1st DXA (%)	14.7	8.5 (.381)	27.3	8.6 (.067)
Time between DXA scans in years (median)	10.1	8.6 (.043)	11.3	9.3 (.123)
Took AEDs known to decrease BMD at 1st DXA (%)	85.3	87.2 (.801)	81.8	87.1 (.632)
Duration of AED treatment at 1st DXA in years (median)	29	19 (.043)	23	21 (1)
FRAX score 1st DXA (median)	1.6	1.1 (.018)	3.1	1.4 (.018)
Bone Loss treatment at 1st DXA (%)				
Calcium/vitamin D	67.7	31.9	45.4	47.1
Bisphosphonates	2.9	0	0	1.4
Calcium/vitamin D and bisphosphonates	11.8	8.5	18.2	8.6
No treatment/cannot obtain results	17.6	59.6	36.4	42.9
Bone Loss treatment at 2nd DXA (%)				
Calcium/vitamin D	41.2	46.8		
Bisphosphonates	5.9	0		
Calcium/vitamin D and Bisphosphonates	35.3	21.3		
No treatment/cannot obtain results	17.6	31.9		

maintaining abnormal BMDs was predicted by various patient characteristics, such as older age, low BMI, and increased time between DXA scans. Prior studies have shown that lower BMIs are correlated with an increased likelihood of developing osteoporosis and maintaining abnormal BMDs.[22] Although the relationship between BMI and a reduced BMD remains inconclusive, some possible explanations are that a higher BMI/body weight imposes a greater mechanical load on the bone which leads to an increase of bone mass to accommodate this load.[22] It is worth noting that the estimated prevalence of osteoporosis in the general population varies between 5.1% (50-59 years old) and 16.4% (70-79 years old).[23] In our population, 8.8% of patients under the age of 50 and 29.7% of patients who were 50 years and older at the second DXA scan had osteoporosis. Furthermore, in our study 8.8% of patients who were younger than 50 years old and 17% of patients who were 50 years and older sustained fractures. Although bisphosphonates have been shown to prevent fractures, it is worth noting that just two (18.2%) of the 11 patients who sustained

major osteoporotic fractures were taking bisphosphonates; it is unclear whether increased usage of bisphosphonates could have decreased the incidence of major osteoporotic fracture in this study population.

In this study, the FRAX scores (median 1.4%, with no 10-year risk ≥20%) suggested that none of the patients were at a major risk of sustaining fracture; thus, no treatment recommendations were derived from these scores. The median FRAX score of 11 patients who ultimately sustained a major osteoporotic fracture was only 3.4%. Thus, the FRAX severely underestimated the 10-year risk of sustaining a major osteoporotic fracture in this group of persons with epilepsy. The FRAX calculator is limited in that it neglects to consider the added risk of fracture for persons who are prone to falling, accidents, or physical injury.[24,25] This observation is particularly relevant to patients in our clinic setting, as persons with epilepsy are at high risk for falls and trauma,[7] and could explain why the FRAX underestimated the number of patients who would suffer a fracture. The major osteoporotic risk threshold of ≥20% for preventative bone loss treatment appears to be too high a bar for persons with epilepsy, and treatment should be considered for persons with epilepsy who present a FRAX major osteoporotic fracture risk less than 20%. Due to the small size of this study, the results should not be used to quantify the exact percent risk at which persons with epilepsy should be preventatively treated. Rather, the results of this study underscore the FRAX's underestimation of fracture risk in persons with epilepsy and should be taken into consideration when making clinical treatment decisions for persons with epilepsy.

Multiple fracture risk assessment tool exists in addition to the FRAX, such as Garvan and Qfracture.[26] Unlike the FRAX, both Garvan and Qfracture include falls as an input risk variable. Out of these three tools, Qfracture is the only one to include epilepsy or taking anticonvulsants as an additional input risk factor. Previous findings have concluded that the FRAX calculator is superior to the Qfracture in the setting of Parkinson's disease[27] or multiple sclerosis.[28] Further research is needed to evaluate which risk assessment tool would be superior at predicting incidence of fractures in the presence of epilepsy.

This study had several limitations. As chart review was the primary method for data gathering, patient information included in the charts may have been incomplete. For example, AED usage and bone loss treatment may have been omitted in the medical records and therefore their prevalence may have been underreported in the analysis. There were no aggregate data which could be compiled regarding the seizure frequency, seizure type, treatment compliance, AED doses, bone density loss treatment length, and dose—and their relation to fractures and other outcomes. Since the time of the study, treatment guidelines for bone density loss prevention have been proposed.[29] Additionally, newer treatments for bone loss, including Denosumab, were not used in our patients at the time of the study.[13] Improved treatment protocols could mitigate bone loss in patients with epilepsy in the future. Additionally, the details regarding the fracture circumstances are limited, and it is unclear whether these could be attributed to seizure-related falls or other traumas. The statistical power was limited due to the relatively small number of patients enrolled in the study, as only 81 met inclusion criteria for the study and several potential risk factors such as diet, menopause, family history, and other medical conditions were unable to be taken into account. Although attrition bias is possible, the demographics and osteoporosis prevalence of the excluded patients are similar to the studied cohort and likely do not skew the results significantly. It is not completely clear whether there were additional reasons for repeat DXA scans other than routine follow-ups; this may be a bias toward those 81 patients who had repeat DXA scans vs those 49 patients not analyzed here.

The usage of the FRAX Calculation Tool was further limited by available patient information. Data about parental fractures were unable to be gathered and therefore assumed "no" for "parent fractured hip." As the FRAX Calculation Tool only calculates 10-year probability risks for persons between 40 and 90 years of age, for patients younger than 40 the tool automatically calculated the fracture risk at the age of 40 years. Some studies suggest that women over 50 years old who have taken bisphosphonates for longer than five years may have an actual fracture lower than estimated by the FRAX Calculation Tool.[30] As mentioned, we were unable to determine the exact duration of bisphosphonate treatment, and therefore, all patients who received bisphosphonates were included in the study. Despite the FRAX Calculation Tool's overestimation of this group's fracture risk, the observed incidence of fracture in this population was still much higher than estimated.

The results of the study showed that the majority of patients with epilepsy had no significant worsening in bone mineral density over an approximately 10-year period. However, there were many patients with epilepsy who presented initially with abnormal BMDs and subsequently sustained fractures. This indicates that overall, the patients with epilepsy maintain an amplified risk of suffering major osteoporotic fractures. We recommend that persons with epilepsy who present any evidence of BMD loss should be closely monitored and considered for treatment to prevent further BMD loss and to prevent fractures. These findings suggest the need for strict treatment algorithms for persons with epilepsy and any evidence of bone loss. Further studies should evaluate how to account for additional risk factors which are specifically pertinent to persons with epilepsy when using the FRAX calculator in clinical practice.

CONFLICTS OF INTEREST

A. Miller, V. Ferastraoaru, V. Tabatabaie, T. Gitlevich, R. Spiegel, and S. Haut have no conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Preliminary results were presented at the 71st Annual American Epilepsy Society Meeting.

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REFERENCES

1. Shiek Ahmad B, Hill KD, O'Brien TJ, Gorelik A, Habib N, Wark JD. Falls and fractures in patients chronically treated with antiepileptic drugs. Neurology. 2012;79:145–51.
2. Meier C, Kraenzlin ME. Antiepileptics and bone health. Ther Adv Musculoskel Dis. 2011;3:235–43.
3. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia. 2004;45:1330–7.
4. Persson HBI, Alberts KA, Farahmand BY, Tomson T. Risk of extremity fractures in adult outpatients with epilepsy. Epilepsia. 2002;43:768–72.
5. Vestergaard P. Epilepsy, osteoporosis and fracture risk - a meta-analysis. Acta Neurol Scand. 2005;112:277–86.
6. Kristiansen B, Christensen S. Fractures of the proximal end of the humerus caused by convulsive seizures. Injury. 1984;16:108–9.
7. Wirrell EC. Epilepsy-related injuries. Epilepsia. 2006;47(Suppl 1):79–86.
8. Pack AM. Falls and fractures in patients with epilepsy Is there an increased risk? If so, why? Neurology. 2012;79:119–20.
9. Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts A. Use of antiepileptic drugs and risk of fractures case-control study among patients with epilepsy. Neurology. 2006;66:1318–24.
10. Souverein PC, Webb DJ, Petri H, Weil J, Staa TPV, Egberts T. Incidence of fractures among epilepsy patients: a population-based retrospective cohort study in the general practice research database. Epilepsia. 2005;46:304–10.
11. Tsiropoulos I, Andersen M, Nymark T, Lauritsen J, Gaist D, Hallas J. Exposure to antiepileptic drugs and the risk of hip fracture: a case-control study. Epilepsia. 2008;49:2092–9.
12. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health.Osteoporosis Int. 2007;18:129–42.
13. Black DM, Rosen CJ. Clinical Practice. Postmenopausal osteoporosis. N Engl J Med. 2016;21(374):254–62.
14. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31:16–35.
15. Lado F, Spiegel R, Masur JH, Boro A, Haut SR. Value of routine screening for bone demineralization in an urban population of patients with epilepsy. Epilepsy Res. 2008;78:155–60.
16. Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American Association of Clinical Endocrinologists and AMERICAN College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis — 2016. Endocr Pract. 2016;22(Supplement 4):1–42.
17. Miller PD. Guidelines for the diagnosis of osteoporosis: T-scores vs fractures. Rev Endocr Metab Disord. 2006;7:75–89.
18. University of Sheffield. Fracture Risk Assessment Tool; 2008. https://wwwsheffieldacuk/FRAX/indexaspx
19. van den Bergh JPW, van Geel TACM, Lems WF, Geusens PP. Assessment of individual fracture risk: FRAX and beyond. Curr Osteoporosis Rep. 2010;8:131–7.
20. Tosteson ANA, Melton LJ, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporos Int. 2008;19:437–47.
21. Conley RB, Adib G, Adler RA, Åkesson KE, Alexander IM, Amenta KC, et al. Secondary fracture prevention: consensus clinical recommendations from a multistakeholder coalition. J Bone Miner Res. 2020;35:36–52.
22. Asomaning K, Bertone-Johnson ER, Nasca PC, Hooven F, Pekow PS. The association between body mass index and osteoporosis in patients referred for a bone mineral density examination. J Women's Health. 2006;15:1028–34.
23. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. 2014;29:2520–6.
24. Masud T, Binkley N, Boonen S, Hannan MT, Members FPDC. Official Positions for FRAX(R) clinical regarding falls and frailty: can falls and frailty be used in FRAX(R)? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom. 2011;14:194–204.
25. Herman ST. Screening bone mineral density in epilepsy: a call to action, but what action? Epilepsy Curr. 2009;9:44–6.
26. Kanis JA, Harvey NC, Johansson H, Oden A, McCloskey EV, Leslie WD. Overview of fracture prediction tools. J Clin Densitom. 2017;20(3):444–50.
27. Shribman S, Torsney KM, Noyce AJ, Giovannoni G, Fearnley J, Dobson R. A service development study of the assessment and management of fracture risk in Parkinson's disease. J Neurol. 2014;261:1153–9.
28. Dobson R, Leddy SG, Gangadharan S, Giovannoni G. Assessing fracture risk in people with MS: a service development study comparing three fracture risk scoring systems. BMJ Open. 2013;11:3.
29. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society* clinical practice guideline. J Clin Endocrinol Metab. 2019;104:1595–622.
30. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Miner Res. 2012;27:1243–51.

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