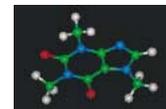


Antiepileptic Drug–Induced Bone Loss in Young Male Patients Who Have Seizures



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Background: Long-term antiepileptic drug (AED) therapy is a known risk factor for bone loss and fractures. Vitamin D deficiency is frequently cited as a cause for bone loss in patients who have seizures.

Objective: To determine whether men who have seizures, but who are otherwise healthy, suffer substantial bone loss in the hip while taking AEDs.

Patients and Methods: We prospectively examined femoral neck bone mineral density (BMD) by dual-energy x-ray absorptiometry in 81 consecutive men, aged between 25 and 54 years old (mean age, 45 years), who were attending an outpatient seizure clinic. Low BMD values were analyzed for known risk factors for bone loss. Dual-energy x-ray absorptiometry scans were repeated in 54 patients, 12 to 29 months later (mean, 19 months), to assess the rate of change in BMD over time.

Results: Multivariate linear regression analysis revealed that age ($P < .001$) and time receiving AEDs ($P < .003$) were the 2 important risk factors associated with low

femoral neck BMD. Neither vitamin D deficiency, hypogonadism, cigarette smoking, nor excess alcohol intake were associated with low BMD after correcting for age and time on AEDs. Longitudinal analysis of femoral neck BMD revealed that only those in the youngest age group (25-44 years) showed significant declines in femoral neck BMD (1.8% annualized loss; 95% confidence interval, -3.1 to -0.9 ; $P < .003$) while receiving AED therapy. There was no evidence that a specific type of AED was more causally related to bone loss in this group although most patients were taking phenytoin sodium or carbamazepine during the longitudinal assessment.

Conclusions: Long-term AED therapy in young male patients who have seizures causes significant bone loss at the hip in the absence of vitamin D deficiency. Dual-energy x-ray absorptiometry scanning of the hip is useful in identifying patients who are particularly susceptible to rapid bone loss while taking AEDs.

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THE LONG-TERM use of antiepileptic drugs (AEDs) in patients who have seizures has been associated with alterations in the levels of circulating calcium and calcitropic hormones.¹⁻³ These findings have led to the belief that susceptible patients who develop bone disease have osteomalacia as the predominant histologic lesion.^{1,4-7} In particular, children and institutionalized patients^{8,9} seem to be at an increased risk for developing hypocalcemia in association with low vitamin D levels, and bone biopsy evidence of osteomalacia has corroborated the deleterious effects of inadequate vitamin D replacement therapy in these patients.¹⁰

Recent studies, however, have shown that vitamin D deficiency and osteomalacia are not as prevalent as once thought, especially in the ambulatory, noninstitu-

tionalized population who experience seizures.^{11,12} Biopsy evidence of normal bone mineralization or increased bone turnover¹² is more characteristic of ambulatory patients of both sexes who have seizures and is consistent with bone serum markers demonstrating increased bone turnover.¹³

Despite the indirect evidence that AEDs may directly affect bone remodeling, there is little known about the sustained effects of AEDs on bone mineral density (BMD). Specifically, BMD has only been examined in small groups of patients who have seizures^{5,11,13} and longitudinal assessments in adults have not been reported. This study prospectively examined the relationship between femoral neck BMD and AED therapy in ambulatory, male patients who have seizures and determined potential risk factors in patients demonstrating ongoing bone loss.

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PATIENTS AND METHODS

PATIENTS

There were 103 consecutive male veteran patients who were asked to participate in the study. All were active outpatients enrolled in the Seizure Clinic at the Seattle Veterans Affairs Puget Sound Health Care System, Seattle, Wash. Only male patients were recruited because of the small number of female veterans in this clinic population and only patients younger than 55 years were included to minimize the influence of age-related effects on bone loss. Twenty-two patients either declined or were unable to undergo serologic testing or to obtain a x-ray film. Eighty-one men, aged 25 to 54 years (mean age, 45 years), participated in the study after giving informed written consent. Each patient completed a questionnaire detailing his fracture history, habits (cigarette smoking and alcohol intake), comorbid conditions, medications, and dietary intake of calcium and vitamin D. Data regarding the duration of AED therapy were derived from these questionnaires and from pharmacy and clinic records. The study was approved by the Human Subjects Division of the University of Washington, Seattle.

MEASUREMENTS

Bone mineral density of the femoral neck was measured by dual-energy x-ray absorptiometry (DEXA) using a densitometer (Hologic QDR-4500A; Hologic Inc, Waltham, Mass). At this measurement site, the precision (coefficient of variation) is 1.2% according to the manufacturer. Measurements of the levels of serum total calcium, phosphate, alkaline phosphatase, γ -glutamyl-transpeptidase, and aspartate transaminase were performed by an autoanalyzer; their normal ranges, respectively, are 8.4 to 10.2 mg/dL (2.1-2.6 mmol/L), 3.5 to 4.5 mg/dL, 50 to 110 U/L, 15 to 40 U/L, and 16 to 45 U/L. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were determined by saturation analysis (SmithKline Laboratories, Philadelphia, Pa); their normal ranges, respectively, are 10 to 45 ng/mL and 15 to 60 pg/mL. Serum intact parathyroid hormone (SmithKline) and free testosterone

(Diagnostics Product Corp, Los Angeles, Calif) levels were determined by radioimmunoassay; the luteinizing hormone level was measured by an enzyme-linked immunosorbent assay (Bayer Diagnostics, Tarrytown, NY); their normal ranges, respectively, are 15 to 54 pg/mL, 9 to 45 ng/mL, and 3 to 11 mIU/mL. A serum sample was lacking for measurement of the following levels: 1,25-dihydroxyvitamin D, 7 patients; parathyroid hormone, 4; testosterone, 3; 25-hydroxyvitamin D, 1; and phosphate, 1.

STATISTICAL ANALYSIS

Univariate analysis of associations between femoral neck BMD and the predefined risk factors was performed using nonparametric methods. The Wilcoxon rank sum test was applied with dichotomous risk factors and the Spearman rank correlation test was used with continuous risk factors. Controlling for the influence of age, the effect of years of receiving AED therapy on femoral neck BMD was analyzed using multivariate linear regression. All of the potential risk factors were entered into a linear regression model and all associations with $P > .10$ were then removed in a backward stepwise fashion. A separate interaction term was included in the regression models to account for the possibility that the effect of AEDs on femoral neck BMD may be modified by the age at the time of BMD determination. Age at the time of DEXA scanning, number of years receiving AEDs, and their interaction term were all modeled as continuous linear variables. Regression diagnostics were performed to identify outliers for closer inspection. To ensure that the observed associations were not being driven by a few extreme values, the linear regression was performed a second time excluding the outliers.

A second analysis was performed on patients who had 2 DEXA scans (separated by at least 12 months) for femoral neck BMD after excluding those for whom treatment for bone loss had been started. Nonparametric analyses were used to assess associations with age at the time of the DEXA scans and the annual change and annual percentage of change in femoral neck BMD were the outcome measures.

Statistical significance was defined as $P < .05$. All analyses were performed using STATA, Version 6.0 (Stata Corp, College Station, Tex). All data are given as mean (SD).

RESULTS

The mean age of the study population was 45 (7) years and the mean duration of AED therapy was 18 (10) years (**Table 1**). The mean femoral neck BMD for the group was 0.80 (0.13) g/cm². Thirty-eight patients (47%) had osteopenia of the femoral neck as defined by a T score greater than 1.0 SD below that of young healthy control subjects. The average calcium and vitamin D intakes for the group were 1162 mg/d and 285 U/d, respectively. At the time of the study the patients were taking the following medications: phenytoin sodium, 46 patients; carbamazepine, 31; valproic acid, 19; lamotrigine, 9; gabapentin, 12; and phenobarbital, 7. Forty-eight patients were taking AEDs as monotherapy (phenytoin in 58%) and 33 patients (41%) were taking more than 1 AED (polytherapy).

Serologic studies revealed that no patient was frankly hypocalcemic, although 9 patients (11%) were vitamin

D deficient (25-hydroxyvitamin D level, <10 ng/mL) and 32 (40%) had elevated parathyroid hormone levels. Twenty patients (25%) had hypogonadism as defined by having either an elevated luteinizing hormone level (9 patients) or only a low free testosterone level (11 patients). There were 42 patients (52%) who were current cigarette smokers and 26 (32%) who had a history of heavy alcohol intake (≥ 6 drinks/d for >1 year); none were heavy users of alcohol at the time of the study.

Few comorbid conditions were identified that may have affected BMD. Four patients had type 2 diabetes mellitus, 1 had rheumatoid arthritis, 1 had liver disease, 1 had sarcoidosis, and 1 had panhypopituitarism. Only 7 patients were taking medications known to influence calcium metabolism—glucocorticoids, 3; furosemide, 1; and thiazide diuretics, 3; and only 5 patients were taking hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) for hypercholesterolemia during the study.

Nineteen patients (23%) had suffered 25 fractures since being treated with AEDs. The sites of fracture were arms (8 patients), ribs (3 patients), hands (2 patients), legs (5 patients), feet (6 patients), and hip (1 patient). Seven fractures (28%) were related to a seizure and 7 resulted from high energy impacts (motor vehicle collision, falling from roof or ladder). The crude fracture rate was 1.9 fractures per 100 patient-years of observation and the non-seizure-related fracture rate was 1.4 fractures per 100 patient-years.

Univariate analyses of femoral neck BMD (**Table 2**) revealed a significant association with cigarette use, and the associations with age, the number of years receiving AED therapy, hypogonadism, and alcohol use approached but did not reach statistical significance. All of the characteristics in Table 2 were then entered into a linear regression model and characteristics with $P > .1$ were then removed in a stepwise fashion. As summarized in **Table 3**, the final model retained only age, number of years receiving AED therapy, and the interaction term. To interpret the model with the interaction term, the sample was divided into 3 similar-sized groups based on age (25-44 years, 28 patients; 45-49 years, 30 patients; and 50-54 years, 23 patients) and the femoral neck BMD was plotted against the number of years receiving AED therapy for each age group. As shown in the **Figure**, the relationship between femoral neck BMD and time receiving AED therapy was apparent only in the youngest age group after the regression lines were adjusted for residual confounding by age (group 1).

Regression diagnostics identified 2 patients who might be considered outliers. The first was 25 years old at the time of DEXA scanning, had been receiving AEDs for 2 years, and had had a femoral neck BMD of 1.240 g/cm². The other was 39 years old at the time of DEXA, had been receiving AEDs for 33 years, and had had a femoral neck BMD of 0.760 g/cm² (see solid circles in the **Figure**). When the linear regression was performed a second time without these outliers, the P values for age at the time of DEXA, the number of years receiving AEDs, and their interaction all remained statistically significant with $P < .05$ (data not shown).

The second set of analyses looked at the change in femoral neck BMD in the subset of patients who had undergone 2 DEXA scans. Of the 81 patients in the cohort, 67 had follow-up DEXA scanning. However, 13 of these patients were excluded from the subsequent analysis because bone antiresorptive therapy had been started before the second DEXA scan by their referring physicians. We, therefore, analyzed the remaining 54 patients according to the previously defined age groups (**Table 4**). In only the youngest age group (aged, 25-44 years) was there a significant change in femoral neck BMD with a mean loss of 1.8% per year (range, 0.1%-4.3% per year; $P < .003$). In addition, the correlations between annual change in femoral neck BMD and age (Spearman $R = 0.33$, $P = .02$) and the percentage of annual change in femoral neck BMD and age (Spearman $R = 0.30$, $P = .03$) were both significant. The patients in the youngest age group had received AEDs for a significantly shorter time (median duration, 11 vs 17 and 28 years, respectively, in the 2 older age groups, $P < .001$, Kruskal-Wallis rank sum test).

Table 1. Characteristics of the Patient Population*

Characteristic	Mean (SD)
Age, y	45 (7)
Duration of AED therapy, y	18 (10)
Dietary calcium intake, mg/24 h	1162 (626)
Dietary vitamin D intake, U	285 (373)
Femoral neck BMD, g/cm ²	0.80 (0.13)
Serologic test results	
Calcium level, mg/dL	9.1 (0.5)
Phosphate level, mg/dL	3.4 (0.5)
Alkaline phosphatase level, U	105 (40)
25-Hydroxyvitamin D level, ng/mL	28 (14)
1,25-Dihydroxyvitamin D level, pg/mL	39 (11)
Parathyroid hormone level, pg/mL	49 (22)
Free testosterone, pg/mL	13 (5)
Luteinizing hormone, mIU/mL	7 (5)

*AED indicates antiepileptic drug; BMD, bone mineral density. To convert calcium intake to millimoles per day, multiply by 0.025; calcium to millimoles per liter, by 0.25; 25-hydroxyvitamin D to nanomoles per liter, by 2.496; 1,25-dihydroxyvitamin D to picomoles per liter, by 2.6; parathyroid hormone to picomoles per liter, by 0.1053; and luteinizing hormone to international units per liter, by 1.0.

Table 2. Univariate Associations With Femoral Neck BMD in 81 Male Patients Who Have Seizures*

Characteristic	Spearman R	P Value
Dichotomous		
Cigarette smoking		.03
History of alcohol excess		.06
Vitamin D deficiency†		.50
Hypogonadism‡		.06
Continuous		
Age	-0.21	.06
Duration of AEDs	-0.21	.06
Serum PTH	-0.02	.85
Serum calcium	0.02	.86
Serum LH	-0.17	.12

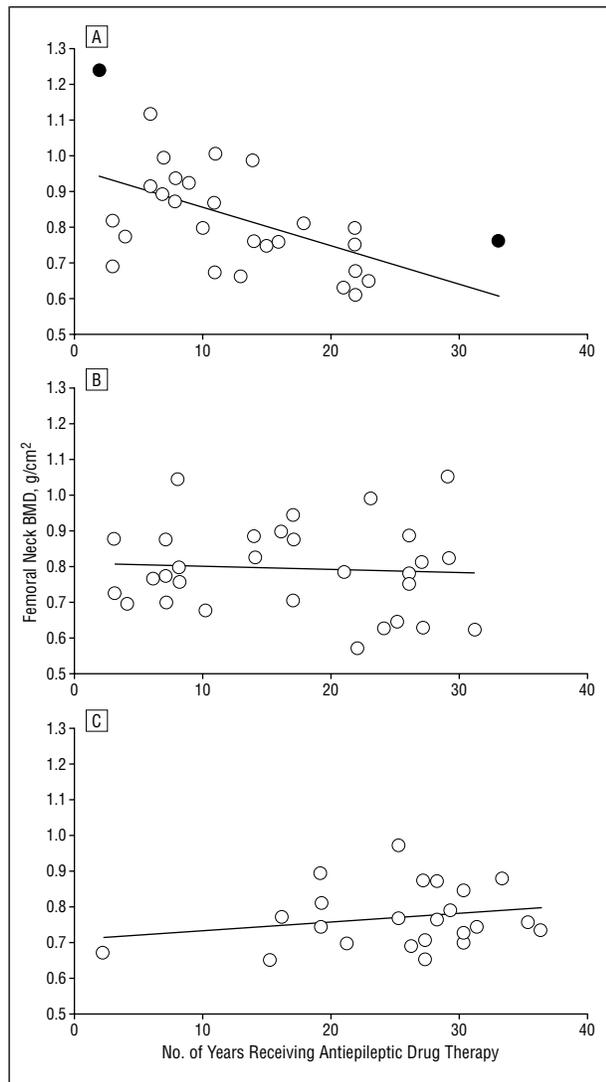
*BMD indicates bone mineral density; AEDs, antiepileptic drugs; PTH, parathyroid hormone; and LH, luteinizing hormone.
 †A vitamin D deficiency was defined as a 25-hydroxyvitamin D level less than 10 ng/mL.
 ‡Hypogonadism was defined as an LH level exceeding 11 mIU/mL or a free testosterone level lower than 9 pg/mL.

Table 3. Multivariate Linear Regression Analysis*

Characteristic	Coefficient (95% CI)	P Value
Age at the time of DEXA	-0.015 (-0.022 to -0.008)	<.001
Years on AEDs	-0.035 (-0.058 to -0.012)	.003
Interaction variable†	0.0007 (0.0002 to 0.0012)	.003

*CI indicates confidence interval; DEXA, dual-energy x-ray absorptiometry; AEDs, antiepileptic drugs. Femoral neck bone mineral density is the dependent variable, overall model $P < .001$, adjusted $R^2 = 0.22$.
 †The interaction variable is between age and the number of years the patient was receiving AEDs.

To determine possible risk factors associated with the loss of BMD in the youngest age group, we performed univariate and multivariate analyses of the group who underwent 2 DEXA scans (54 patients) and found



Relationship between femoral neck bone mineral density (BMD) and the number of years receiving antiepileptic drug therapy in 81 men who have seizures. A, Group 1 includes patients from the ages of 25 to 44 years; B, group 2, patients from the ages of 45 to 49 years; and C, group 3, patients from the ages of 50 to 54 years. Two outliers in group 1 (A), identified by regression diagnostics, are indicated by solid circles.

that only age at the time of DEXA scan and the duration of AED therapy were significantly associated with the decrease in femoral neck BMD. After adjusting for age, there were no associations between calcium or vitamin D intake, or polytherapy (>1 AED, 18 of 54 patients) and decline in femoral neck BMD. There was no evidence that a specific type of AED was more important in causing bone loss although most patients were taking either phenytoin (30 of 54 patients) and/or carbamazepine (22 of 54 patients) (Table 4).

COMMENT

To our knowledge, we have shown for the first time that young male patients who have seizures sustain significant bone loss at the femoral neck while receiving AED therapy. The finding that 47% had a BMD lower than 1 SD below normal (osteopenia) at this site indicates that

a substantial number are at an increased risk for hip or other skeletal fractures.¹⁴⁻¹⁶ In this regard, one of our study patients had already suffered a fall-related hip fracture. Moreover, a recent evaluation of noninstitutionalized patients with epilepsy showed a 4-fold increased risk of femoral neck fractures when compared with age- and sex-matched healthy controls.¹⁷ Since not more than 16% of the healthy US male population in this age group is expected to be osteopenic,¹⁸ our patient population has more than a 2.5-fold increased prevalence of bone loss at the hip. Surprisingly, the patients who were continuing to lose bone were those in the younger age group (mean age, 38 years) who had been receiving AEDs the shortest length of time (median, 11 years; 95% confidence interval, 7.2-14.7 years). The older patients (mean age, 50 years), in contrast, seemed to have stabilized their bone loss despite being on comparable amounts and types of AEDs during the longitudinal assessment period.

Risk factors that have previously been associated with bone loss in patients who have seizures have included vitamin D deficiency, hypocalcemia, and secondary hyperparathyroidism.^{2,3} In our study only 11% had low vitamin D levels and these were not associated with low BMD values after multivariate analysis. This may be attributable to our patients' relatively high intake of dietary calcium and vitamin D. While cigarette use and a history of heavy alcohol use were identified as potential additional risk factors in the initial analysis, the more rigorous multivariate regression analysis excluded these factors for being as important as age and time on AEDs.

These results agree with recent smaller studies suggesting that certain AEDs have a direct effect on bone turnover¹²⁻¹⁴ and support the notion that AEDs can cause bone loss without inducing vitamin D deficiency-related osteomalacia. This is the first study, however, to quantify ongoing bone loss in a large group of ambulatory young male patients who have seizures. While the study was not designed to determine the mechanism of AED-induced bone loss, our finding that the younger patients had the highest rate of bone loss suggests that bone cell activity in the young adult male skeleton may be more susceptible to the direct effects of AEDs. Few studies have examined bone biopsy specimens from men in this age range so it is unclear whether rates of bone formation and osteoblast activity are normal or increased.^{11,12} However, recent studies that have evaluated serum bone markers in young men receiving phenytoin and/or carbamazepine (mean age, 38 years) therapy indicated that the parameters for bone formation and bone resorption were higher than in age-matched controls,¹³ suggesting that these AEDs directly stimulate bone turnover. Moreover, recent *in vitro* studies have shown that AEDs directly stimulate osteoblast activity.¹⁹ Thus, it is possible that the younger male skeleton with enhanced bone turnover from AED therapy may require a substantially higher calcium intake to adequately suppress bone resorption and optimize bone mineralization. Alternatively, the AED effect may involve the same mechanism that causes age-related bone loss that could accelerate this process in younger patients.

Table 4. Longitudinal Change in Femoral Neck BMD According to Age*

Variable	Age Group, y		
	25-44	45-49	50-54
Age, mean (SE)	38 (1)	48 (1)	52 (1)
No. of patients	18	20	16
Interval (SE), mo	20 (2)	20 (1)	18 (2)
Femoral neck BMD % of change/y, (CI)	-1.8 (-3.1 to -0.9)†	-0.9 (-2.0 to 1.0)	-0.7 (-1.5 to 0.5)
AEDs‡			
Type			
Phenytoin	8	11	11
Carbamazepine	7	7	8
Phenobarbital	2	0	0
Valproic acid	3	1	4
Gabapentin	5	1	4
Lamotrigine	1	0	0
Polytherapy, No. (%) of patients	8 (44)	2 (10)	9 (56)

*Same age groups as seen in Figure 1. BMD indicates bone mineral density; CI, confidence interval; and AEDs, antiepileptic drugs.

† $P = .003$.

‡These AEDs were taken during the longitudinal assessment.

Despite our finding that 25% of the population had either primary (an elevated luteinizing hormone level) or secondary (low testosterone without an elevated luteinizing hormone level) hypogonadism, we found no association between femoral neck bone loss and gonadal status. While this seems somewhat surprising in light of the known effects of testosterone in stimulating bone accretion,^{20,21} we believe that the mechanisms involved with AED-induced alterations in testosterone metabolism may include compensatory protective effects on bone remodeling. For example, it is known that serum levels of sex hormone-binding globulin are often elevated in patients who are taking AEDs that result in a decreased free testosterone index or bioactive testosterone level.²²⁻²⁵ However, it was recently shown that serum estradiol levels are elevated in male patients who have seizures and who are taking phenytoin,²⁶ possibly as a consequence of AED-induced stimulation of aromatase²⁷ that converts testosterone to estradiol. Thus, it is possible that raised estradiol levels in some patients who have seizures may function to protect bone against low bioactive testosterone levels. Because we did not measure the sex hormone-binding globulin or estradiol levels in our patients, we cannot determine whether their fluctuations were associated with femoral bone loss. Future studies on bone loss in male patients who have seizures should include these measurements to help resolve this issue and to determine whether testosterone treatment with the aromatase inhibitor, testolactone,²⁷ would be an effective therapy for AED-induced bone loss.

While the evaluation of fracture risk was not an end point of this study, the crude fracture rate in our patients was similar to that of a recent study by Vestergaard et al.¹⁷ They demonstrated a 30% increased risk for nonseizure-related fractures in 348 patients when compared with a large control population.¹⁷ For non-seizure-related fractures their crude fracture rate of 1.6 fractures per 100 patient-years of observation is similar to our crude fracture rate of 1.4 fractures per 100 patient-

years. We attribute their higher fracture rate, in part, to their inclusion of older patients (up to 80 years of age) and women (50%), some of whom may have suffered from postmenopausal osteoporosis.¹⁷ The locations of the fractures were similar in the 2 studies with fractures of the arms, lower legs, and feet accounting for more than 50% of the fractures in both studies.

CONCLUSIONS

Young male patients who have seizures are susceptible to significant bone loss in the hip during long-term AED therapy. Bone loss in this region may be related to a direct effect of AEDs in stimulating bone turnover. We recommend DEXA scanning of the hip to identify susceptible younger patients who may suffer from accelerated bone loss. Future studies should examine potential mechanistic roles for testosterone and estradiol in the bone loss of these patients and determine whether the newer AEDs are also associated with bone loss in the hip.

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