Effect of antiepileptic drugs on bone density in ambulatory patients

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Abstract—*Background:* Long-term antiepileptic drug (AED) use causes multiple abnormalities in calcium and bone metabolism that have been most extensively described in institutionalized patients. The objective is to determine the effect of AED on vitamin D levels and bone density in ambulatory patients and to compare the effects of enzyme-inducing and -noninducing AED and of single vs multiple therapy on bone density. *Methods:* A cross-sectional evaluation was conducted of 71 patients (42 adults and 29 children/adolescents) on anticonvulsant therapy for at least 6 months who presented to neurologists at a tertiary referral center. Bone mineral density (BMD) as well as serum 25 hydroxy–vitamin D (25-OHD) levels were measured. A detailed questionnaire assessing calcium intake as well as previous and current intake of antiepileptic medications was administered to all patients. *Results:* Over 50% of adults and children/adolescents had low 25-OHD levels, but this finding did not correlate with BMD. Antiepileptic therapy decreased BMD in adults. Generalized seizures, duration of epilepsy, and polypharmacy were significant determinants of BMD, more so at skeletal sites enriched in cortical bone. Subjects on enzyme-inducing drugs such as phenytoin, phenobarbital, carbamazepine, and primidone tended to have lower BMD than those on noninducers such as valproic acid, lamotrigine, clonazepam, gabapentin, topamirate, and ethosuximide. *Conclusion:* Epilepsy and its therapy, including the newer drugs, are risk factors for low bone density, irrespective of vitamin D levels. Skeletal monitoring with the institution of appropriate therapy is indicated in patients on chronic antiepileptic therapy.

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Chronic therapy with antiepileptic drugs (AED) causes abnormalities in calcium metabolism, including hypocalcemia, hypophosphatemia, elevated levels of serum alkaline phosphatase and serum parathyroid hormone, reduced serum levels of biologically active vitamin D metabolites, radiologic evidence of rickets, and histologic evidence of osteomalacia.[1-4] The mechanism of these abnormalities is unclear. It has been suggested that the drugs such as phenytoin accelerate vitamin D metabolism or directly inhibit intestinal calcium absorption.[5-7]

Early reports suggested that 20 to 65% of epileptic patients receiving anticonvulsants developed signs of rickets or osteomalacia, especially if institutionalized.[1,4,8,9] In the outpatient population, although alterations in biochemical indices of mineral metabolism have been reported, the impact of AED on bone mineral density (BMD) remains uncertain, with conflicting results.[10-16] Furthermore, several studies have failed to demonstrate the expected sparing of bone by newer so-called enzyme-sparing drugs such as valproate.[10,12,14,15] Finally, no single study has systematically assessed the impact of age, multiplicity, and type of AED on vitamin D levels and BMD in ambulatory patients.

We studied the prevalence of vitamin D deficiency and insufficiency in ambulatory patients on AED, BMD in patients on AED and the impact of chronicity of intake of AED on bone density; the relation between vitamin D levels and BMD; the effects of AED type (those that induce hepatic microsomal enzymes or enzyme inducers compared with noninducers); and the mode of therapy (single vs multiple) on bone density and vitamin D level.

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Methods. *Study design.* This cross-sectional study evaluated the effect of long-term AED therapy on bone density in a group of ambulatory epileptic patients who presented to our center between November 1998 and January 2000. All patients attending neurology clinics were offered study participation. BMD was measured in all subjects. 25 Hydroxy–vitamin D (25-OHD) level, a primary end point of the study, was measured in 62 of 71 patients. A questionnaire assessing calcium intake and previous and current intake of antiepileptic and other medications was administered to all subjects. The study was approved by the Institutional Research Committee and Ethical Com-

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mittee, and informed consent was obtained from all patients.

Subjects. Seventy-one ambulatory epileptic patients aged 5 to 64 years (mean ± SD: 24 ± 14 years) on chronic AED therapy for at least 6 months were included in the study. Of these, 42 patients were adults (i.e., older than 18 years of age; 22 women and 20 men) with a mean age 33 ± 12 years, and 29 were children/adolescents (12 girls and 17 boys) with a mean age of 11 ± 4 years. Patients with conditions known to affect bone metabolism such as hepatic or renal disorders, hypothyroidism, or malabsorption or those with a history of intake of pharmacologic amounts of medications that can affect bone turnover (e.g., vitamin A, anabolic steroids, bisphosphonates, glucocorticoids, thiazides, calcitonin) were excluded from the study.

Vitamin D levels. Definition of vitamin D deficiency and insufficiency. Serum 25-OHD level, an index of body stores of vitamin D, was measured by a competitive protein-binding assay using the Diasoren Incstar kit (Diasorin, Saluggia, Italy). For 25-OHD, the manufacturer's normal range is 9 to 47 ng/mL, the lower limit is 5 ng/mL, the intra-assay coefficient of variance percentage (CV%) is <11%, and the interassay CV% is <13% at a serum concentration of 47 ng/mL.

Based on the suggested cutoff values for adults, vitamin D deficiency was defined as 25-OHD less than 10 ng/mL and insufficiency as 25-OHD between 10 and 20 ng/mL.[17]

BMD. BMD of the lumbar spine, total hip, femoral neck, and trochanter as well as total body bone mineral content (BMC) and BMD were measured in adult patients. Lumbar spine and total body BMD and BMC were assessed in children/adolescent patients, because the software necessary for measurement of other skeletal sites was not available for this age group. BMD was measured using a Lunar DPX-L densitometer (Lunar, Madison, WI). In our laboratory, the in vivo precision at our center, expressed as the CV%, is 1.2 ± 0.8% at the lumbar spine, 1.0 ± 0.8% at the hip, 1.8 ± 1.2% at the femoral neck, and 1.7 ± 1.3% at the trochanter as calculated from duplicate BMD measurements performed on the same day in 27 to 35 subjects. These numbers are comparable to those we have previously reported.[18] Using the American database provided by the densitometer, T scores (number of SD below peak bone mass) were calculated in adults only, and Z scores (number of SD below age- and sex-matched controls) were calculated in adults and children. In adults, osteopenia and osteoporosis were determined according to the World Health Organization (WHO) operational BMD definition for these terms.[19] Osteoporosis was defined as a BMD T score at any site less than −2.5, and osteopenia was defined as a BMD T score between −1 and −2.5. Because children have not reached peak bone mass yet, the WHO operational definition of osteoporosis does not apply to the pediatric age group.

Classification of AED according to their enzyme-inducing effect. Patients on multiple therapy were classified in the enzyme-inducing drug group if at least one of the medications they were taking at the time of the study was an enzyme inducer.

The enzyme-inducing antiepileptics in our study were phenytoin (Dilantin, Epanutin), phenobarbital (Gardenal, Luminal sodium), carbamazepine (Tegretol), and primidone (Mysoline). The noninducers were valproic acid (Depakene, Depakote), lamotrigine (Lamictal), clonazepam (Rivotril, Klonopin), gabapentin (Neurontin), topamirate (Topamax), and ethosuximide (Zarontin).

Table 1 *Baseline characteristics of study subjects*

Variables	All subjects (n = 71)	Adults (n = 42)	Children (n = 29)
Sex, F/M	34/37	22/20	12/17
Age, y	24.1 ± 14.4	33.0 ± 12.2	11.3 ± 3.8
Body mass index, kg/m^2	23 ± 5	26 ± 4	19 ± 5
Total calcium intake, mg/d, (N = 65)	620 ± 496	541 ± 468	732 ± 521
Duration of therapy, y	7 ± 8	9 ± 10	5 ± 4
25Hydroxy–vitamin D, ng/mL (n = 62)	17 ± 13	15 ± 11	20 ± 14
Type of seizures, n (%)			
Generalized		17 (42)	19 (66)
Focal		24 (58)	10 (34)
Type of therapy, n (%)			
Enzyme inducers		32 (76)	18 (62)
Nonenzyme inducers		10 (24)	11 (38)
Mode of therapy, n (%)			
Single		23 (55)	15 (52)
Multiple		19 (45)	14 (48)
Osteoporosis, n (%)*			
Spine and/or hip		1 (2)	NA
Osteopenia, n (%)*			
Spine and/or hip		25 (59)	NA

Results are expressed as mean ± SD unless otherwise indicated.

* Defined per the World Health Organization operational definition (i.e.) bone mineral density T score <−2.5 for osteoporosis and a bone mineral density T score between −1 and −2.5 for osteopenia.

NA = not applicable.

Statistical analyses. Results are expressed as mean ± SD unless specified otherwise. All analyses were done separately for adult (≥18 years old) and children/adolescent patients (<18 years old) using SPSS version 10 software (SPSS, Chicago, IL). Comparisons of continuous variables between various subgroups of subjects were performed using a two-tailed *t*-test. The associations between the outcome variables and the covariates were examined using bivariate analyses (Pearson's correlation, χ^2 test, and Student's *t*-test). The outcome variables analyzed in adults were lumbar spine, total hip, femoral neck, trochanter, and total body BMD, BMC, and vitamin D. In children/adolescents, the outcome variables were limited to lumbar spine and total body BMD, BMC, and vitamin D. Significance was set at $p < 0.05$.

Results. *Clinical characteristics of the study groups.* Baseline demographic and clinical characteristics of study subjects are shown in table 1. Forty-two percent of adults and 66% of children/adolescents had generalized seizures. Twelve patients in the study group overall (n = 7 adults and n = 5 children/adolescents) had intractable epilepsy,

defined as lack of seizure control with more than two first-line AED, with an average of more than one seizure per month for 18 months.[20] All adults had normal activity levels, and only two children were homebound (data not shown). The anatomic or other abnormalities leading to the seizure disorder in adults were as follows: idiopathic (22), congenital/cryptogenic (6), cerebrovascular disease (5), neoplasm (3), trauma (3), cerebral palsy (1), infection (1), and undiagnosed cause (n = 1). The numbers for children/adolescents were as follows: idiopathic (18), congenital/cryptogenic (7), cerebral palsy (3), and infection (1).

The mean duration of AED used at the time of study was 9 ± 10 years in adult patients and 5 ± 4 years in children/adolescents: 76% of adults and 62% of children/adolescents were taking enzyme-inducing antiepileptics, and 45% of adults and 48% of children/adolescents were on multiple AED therapy. Mean calcium intake was below recommended guidelines in both age groups.[21] Vitamin D level was 15 ± 11 ng/mL in adult patients compared with 20 ± 14 ng/mL in the younger age group. In both age groups, the mean serum calcium and phosphorus levels were normal when measured (n = 32, data not shown).

Prevalence of vitamin D insufficiency and deficiency. The mean 25-OHD level was in the insufficient range in the overall study group as well as in adults (see table 1). Over two-thirds of adult patients (77%) had low vitamin D levels; specifically, 34% had 25-OHD levels less than 10 ng/mL, and 43% had 25-OHD levels between 10 and 20 ng/mL. Over one-half of children/adolescent patients (62%) had low vitamin D levels; specifically, 35% had 25-OHD levels less than 10 ng/mL, and 27% had 25-OHD levels between 10 and 20 ng/mL. In children, there was no correlation between duration of AED therapy and 25-OHD level. Surprisingly, serum 25-OHD levels were positively correlated with duration of AED in adults only ($r = 0.42$, $p = 0.013$).

BMD. The mean BMD of the study subjects is shown in table 2. In adults, BMD at all skeletal sites was lower compared with both young adults and age-matched controls as provided by the manufacturer's database ($p < 0.05$ at all skeletal sites except the total body). A substantial proportion of adults (59%) had osteopenia at either the spine or hip (see table 1). Subgroup analysis by sex yielded essentially similar findings (data not shown). In children, BMD was lower at the spine but higher at the total body when compared with that of age-matched controls; however, these differences were not significant. There was a significant negative correlation between duration of AED use and BMD in adults (but not in children) noted at the total hip ($r = -0.38$) and femoral trochanter ($r = -0.41$) as well when total body BMD was measured ($r = -0.45$) (figure). Patients having focal seizures had higher total body BMD than patients having generalized seizures ($p = 0.02$); these findings were not explained by shorter duration of therapy or use of monotherapy in the group with focal seizures (data not shown). There were, however, no significant differences in spine and hip BMD between these two groups. Similarly, no differences in spine, hip, or total body BMD were observed between patients having intractable epilepsy and those who did not (data not shown). In the pediatric age group subgroup comparisons of BMD between patients with generalized and focal seizures yielded no significant differences. Similarly, no BMD differences were found between patients having intractable epilepsy and those who did not or between patients who were homebound and those who had a normal activity level (data not shown).

Table 2 *Baseline bone mineral density (BMD) for all study subjects*

Site of bone mass	Adults (n = 42)	Children (n = 29)
Lumbar spine BMD, g/cm^2	1.14 ± 0.16	0.82 ± 0.27
Z score	−0.43 ± 1.15*	−0.42 ± 1.80
T score	−0.50 ± 1.20*	
Hip BMD, g/cm^2	0.95 ± 0.13	NA
Z score	−0.65 ± 0.78*	
T score	−0.69 ± 0.98*	
Femoral neck BMD, g/cm^2	0.92 ± 0.15	NA
Z score	−0.57 ± 0.96*	
T score	−0.71 ± 1.11*	
Trochanter BMD, g/cm^2	0.79 ± 0.16	NA
Z score	−0.72 ± 0.94*	
T score	−0.75 ± 1.06*	
Total body BMD, g/cm^2	1.17 ± 0.10	0.97 ± 0.14
Z score	−0.11 ± 0.83	0.47 ± 1.22
T score	−0.11 ± 0.99	
Total body BMC, g	2,690 ± 487	1,533 ± 807

Results are expressed as mean ± SD.

* $p < 0.05$ compared with zero: a $Z < 0$ denotes a mean BMD that is lower than that of age-matched controls, and a T score < 0 denotes a mean BMD that is less than that of young adults (age range: 20–29 years) as provided by densitometer's database.

NA = not available in densitometer's software; BMC = bone mineral content.

Impact of type/mode of AED on vitamin D levels and BMD in adults. Enzyme-inducing and -noninducing therapy. No significant difference in 25-OHD levels was observed between patients on enzyme-inducing and -noninducing AED (additional material can be found on the *Neurology* Web site; go to www.neurology.org and scroll down the Table of Contents to find the title link for this article). Adults taking enzyme-inducing AED were on therapy for a longer period compared with those taking noninducing drugs; that difference was not significant (additional material can be found on the *Neurology* Web site; go to www.neurology.org). Patients taking enzyme-inducing AED had lower BMD of the spine, total hip, femoral neck, trochanter, and total body; however, these differences were not significant (additional material can be found on the *Neurology* Web site; go to www.neurology.org).

Single and multiple AED therapy. Patients on single therapy had lower vitamin D levels than those on multiple therapy ($p < 0.05$) (table 3). Adults taking a single AED were on therapy for a shorter period and had a significantly higher mean BMD of the total hip and trochanter than those taking multiple AED (see table 3).

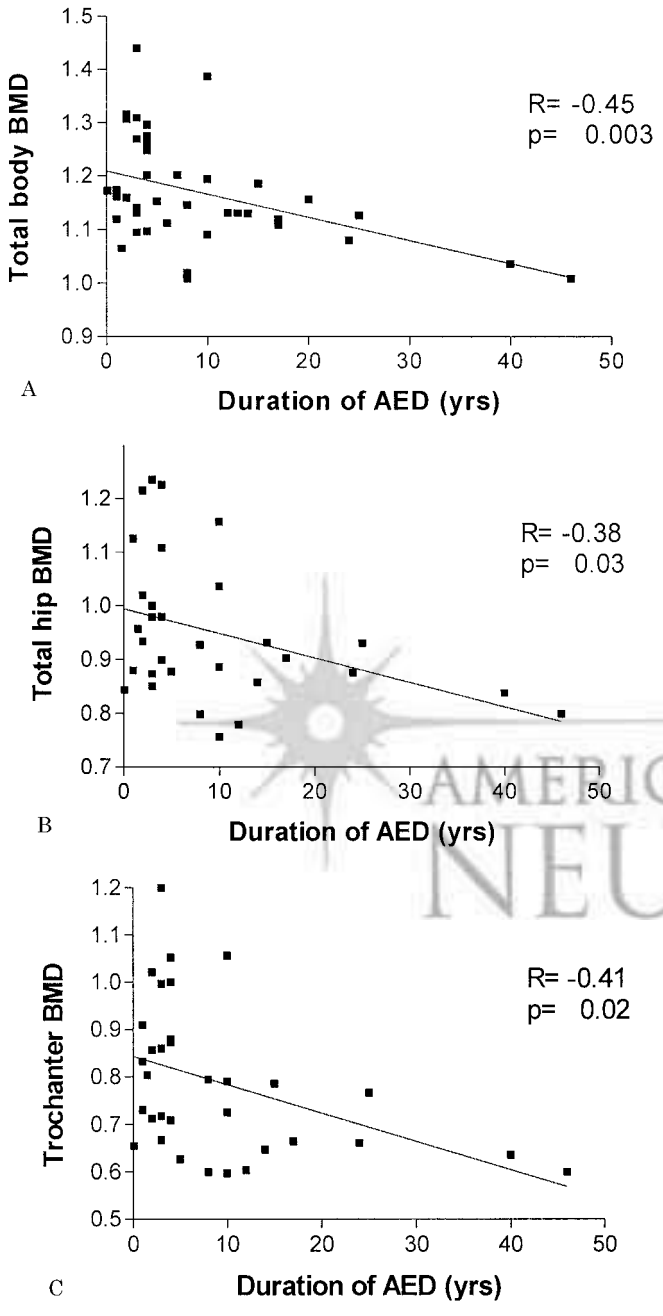

Figure. Correlation between duration of antiepileptic drug (AED) and bone mineral density (BMD) at the total body (A), total hip (B), and trochanter (C) in adult patients.

Impact of type/mode of AED on vitamin D levels and BMD in children/adolescents. Enzyme-inducing and -noninducing therapy. Mean 25-OHD level was lower among patients on enzyme-inducing AED, but this difference was not significant (table 4). No significant difference in BMD of the lumbar spine and total body BMD or BMC was observed between patients on enzyme-inducing and -noninducing therapy (see table 4).

Single and multiple AED therapy. Patients taking single therapy had higher vitamin D levels, BMC, and BMD of the lumbar spine and total body than patients taking multiple AED; however, these differences were not significant (additional material can be found on the *Neurology* Web site; go to www.neurology.org). Subgroup analysis by sex revealed that boys taking a single AED had a higher BMD at the lumbar spine ($p = 0.003$) and total body ($p = 0.03$) than patients taking multiple therapy (data not shown).

Discussion. In our study of ambulatory adults and children/adolescents on chronic AED therapy, a significant proportion (>50%) of patients in both age groups had low 25-OHD levels. Epilepsy and its therapy are associated with a low BMD in adults of both sexes, independent of vitamin D levels. Patients with generalized seizures had a lower total BMD than those with focal seizures. Duration and multiplicity of antiepileptic therapy were significant negative determinants of BMD, and patients taking enzyme-inducing medications tended to have a lower BMD than those taking noninducing drugs.

Although vitamin D levels were below 20 ng/mL in more than one-half of our patients, they did not correlate with BMD in our study. It has been reported that certain drugs such as phenytoin and phenobarbital cause induction of hepatic microsomal enzymes, resulting in increased catabolism of 25-OHD and the classic bone changes of osteomalacia.[5] Abnormalities in calcium and bone metabolism are not always associated with low levels of 25-OHD.[6] Indeed, other reported mechanisms of action of classic AED on calcium metabolism include direct inhibition of intestinal calcium absorption.[7] Several studies evaluating vitamin D levels in ambulatory patients have yielded conflicting results.[2,6,8,22-24] These differences may be explained by differences in season, diet, sun exposure, and latitude of the area in which the study was conducted, for example. In our sunny country, we have recently demonstrated a high prevalence of vitamin D insufficiency in healthy adults and adolescents.[25,26] Although a control group would have helped to sort out whether there is a direct effect of AED on vitamin D levels, we believe that the lack of correlation between vitamin D levels and BMD in our study confirms a non-vitamin D–mediated mechanism of action of AED on the skeleton as has been previously suggested. Indeed, skeletal abnormalities and histomorphometric or low BMD have been described in ambulatory patients on antiepileptic treatment in the absence of low vitamin D levels.[6,8,16,24] A direct effect of phenytoin and carbamazepine on osteoblast proliferation has also been suggested.[27] The positive correlation between vitamin D and duration of therapy with AED in adults as well as the higher levels in patients taking multiple therapy as opposed to single therapy and on enzyme inducers compared with noninducers may reflect concomitant therapy with vitamin D; however, this was not adequately assessed.

In our study, bone density in adult patients (but not in children/adolescents) on chronic AED therapy was decreased, on average, by one-half to three-quarters of 1 SD (5 to 7%) compared with age- and sex-matched controls, a finding that may suggest a

Table 3 *Serum 25 hydroxy-vitamin D (25-OHD) levels and bone mineral density (BMD) in adult patients taking single or multiple therapy*

Variable	All adults	Single therapy (n = 23)	Multiple therapy (n = 19)	*p* Value
Duration of therapy, y	9 ± 10	6 ± 6	13 ± 12	0.01
25-OHD, ng/mL	15 ± 11	11 ± 7	20 ± 13	0.02
Lumbar spine BMD, g/cm^2		1.14 ± 0.19	1.15 ± 0.13	NS
Hip BMD, g/cm^2		1.00 ± 0.13	0.90 ± 0.12	0.03
Femoral neck BMD, g/cm^2		0.95 ± 0.17	0.89 ± 0.12	NS
Trochanter BMD, g/cm^2		0.85 ± 0.16	0.71 ± 0.11	0.01
Total body BMD, g/cm^2		1.19 ± 0.09	1.14 ± 0.10	NS
Total body BMC, g		2,815 ± 474	2,539 ± 471	NS

Values are expressed as mean ± SD.

BMC = bone mineral content; NS = not significant.

greater risk of future osteoporotic fractures in later life. Although we have used the densitometer manufacturer database as a control rather than locally recruited controls, it is the appropriate comparison, because the WHO operational definition of osteoporosis was defined using the American databases, and it is in that population that the relation between BMD and fracture risk was validated.[19] The lack of a consistent effect of AED in children as compared to adults in our study may be a result of the smaller sample size and shorter duration of antiepileptic therapy. Other studies have shown comparable decrements in BMD in adults taking chronic AED therapy that were more pronounced at cortical sites (i.e., the hip) as we have demonstrated.[13,15,16,24] In our analyses, duration of antiepileptic therapy was inversely and significantly correlated with BMD, findings that suggest the disease itself or the associated therapy is instrumental in the deleterious skeletal profile. Nevertheless, two previous studies in adults have failed to demonstrate an effect of therapy duration on BMD in adults taking AED for 6 to 43 years in one and 7 to 36 years in the other.[12,13] These findings are possibly explained by the long mean/median duration of therapy in those studies, whereby most of the deleterious skeletal effect may have already taken place, akin to findings in patients on chronic glucocorticoid therapy.[12,13,27,28] Indeed, a close examination of the data in the figure suggests a sharper drop in BMD early on and a taper thereafter, especially of the total hip.

Whereas there is a paucity of data in the literature comparing bone density in patients taking single and multiple antiepileptic therapy, our findings suggest that multiple drugs may also be an important risk factor for low bone mass in adult patients, an effect that may have been confounded by therapy duration. Our results in adults and those of Holloway et al.[24] suggest that the detrimental skeletal effect of the classic AED could be somewhat curtailed with the enzyme-sparing medications. Such findings are at odds with those of two previous studies, however.[12,15] Indeed, Sato et al.[15] compared metacarpal BMD in 80 adult patients taking either valproate or Dilantin for 7 to 10 years and did not show any difference between the two groups. Similarly, Stephen et al.[12] were unable to show any protective effect of nonenzyme inducers on either spine or hip BMD in over 70 adults patients who had epilepsy for 7 to 36 years.[12] Furthermore, such evaluations in the pediatric age group have shown similarly conflicting results.[10,11,14] An important limitation of all studies is their cross-sectional nature, and a further limitation of pediatric studies is their relatively short duration

Table 4 *Serum 25 hydroxy-vitamin D (25-OHD) levels and bone mineral density (BMD) in children/adolescents taking enzyme-inducing or -noninducing antiepileptic therapy*

Variable	All children	Nonenzyme inducing (n = 18)	Enzyme inducing (n = 11)	*p* Value
Duration of therapy, y	5 ± 4	3 ± 3	6 ± 4	0.05
25-OHD, ng/mL	20 ± 14	22 ± 18	18 ± 11	NS
Lumbar spine BMD, g/cm^2		0.79 ± 0.31	0.84 ± 0.24	NS
Total body BMD, g/cm^2		0.93 ± 0.15	0.99 ± 0.14	NS
Total body BMC, g		1,302 ± 724	1,692 ± 845	NS

Values are expressed as mean ± SD.

BMC = bone mineral content; NS = not significant.

of therapy, with a maximum of 4 years.[10,11,14] Indeed, the only published longitudinal study evaluating the impact of AED on BMD revealed a further decrease in both spine and hip BMD by 5 to 7% in a small number of adult patients followed over 7 years.[13]

The accumulating evidence regarding the impact of AED on skeletal health calls for a systematic evaluation of some of the questions posed today. The respective impact of epilepsy per se (type and duration) and the use of AED (class and single vs multiple) on skeletal health is only possible through the implementation of large multicenter studies. Furthermore, there is a pressing need to elucidate the impact of AED on skeletal health in children/adolescents at a critical time for bone mass accrual. It is only through such evidence-based medicine that guidelines regarding the monitoring of skeletal health of patients on antiepileptic therapy would be possible.[29-32]

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