Two randomized vitamin D trials in ambulatory patients on anticonvulsants

Impact on bone

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Abstract—*Objective:* To investigate the effects of two doses of vitamin D given over 1 year on bone density in ambulatory patients on long-term antiepileptic drug (AED) therapy. *Methods:* We conducted two parallel, randomized, controlled trials in 72 adults (18 to 54 years old) and 78 children and adolescents (10 to 18 years) on long-term AED therapy. They received either low-dose vitamin D 400 IU/day or high-dose vitamin D 4,000 IU/day (adults) and 2,000 IU/day (children/adolescents). Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry. *Results:* In adults, baseline BMD was lower than that of age- and gender-matched controls vs either a Western or an ethnically identical population. After 1 year, there were significant increases in BMD at all skeletal sites compared to baseline in the high-, but not in the low-dose treatment group. However, BMD at 1 year remained below normal. In children, baseline BMD was normal vs age- and gender-matched controls and showed significant and comparable increases in both treatment groups. *Conclusions:* In ambulatory adults on antiepileptic drugs, high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites. In children, both doses resulted in comparable increases in bone mass.

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The effects of long-term antiepileptic drug (AED) therapy on bone metabolism are well established and span the spectrum from osteomalacia to osteoporosis and to high bone turnover with normal bone density.[1-7] Our group has reported that polypharmacy and the use of enzyme-inducing drugs were risk factors for decreased bone density in ambulatory patients.[3]

Several mechanisms have been proposed to explain the deleterious effects of AEDs on bone. These include hepatic induction of cytochrome P-450 (CYP450) hydroxylase enzymes leading to accelerated vitamin D catabolism, impaired calcium absorption, a direct effect of AEDs on bone cells, calcitonin deficiency, and resistance to parathyroid hormone.[8,9] Vitamin D supplementation would address at least two of the above-proposed mechanisms and has been advocated as a potential therapy to counteract the negative effect of AEDs on bone. However, there are few prospective trials of vitamin D supplementation in patients on AEDs, and the results are conflicting.[10-14] All these cited studies were limited by their short duration (varying between 1 and 6 months), small number of subjects studied,[11,13,14] use of older technology with measurements limited to the forearm only,[10,11,13,14] and inclusion of institutionalized adolescents.[13] Although most studies[10,11,13] except one[14] demonstrated an increase in bone density, the optimal dose of vitamin D to be used is still unclear. Currently, there are no dose-ranging studies to assess the optimal dose of vitamin D to be used, and no widely accepted guidelines for vitamin D supplementation in ambulatory patients on long-term AED treatment.

In this study, we compared the effects of maintenance dose vs replacement physiologic dose vitamin D on bone mineral density (BMD) in ambulatory patients on anticonvulsant medications. This matter is particularly relevant in view of the increasing recognition of hypovitaminosis D worldwide in general[15] and in sunny countries in particular.[16,17]

Methods. *Study design.* The study consisted of two parallel, 1-year, prospective, randomized, dose-ranging trials conducted in two groups of ambulatory patients: one group of adults and one of children and adolescents 10 to 18 years old, on long-term anticonvulsant medication therapy. Subjects were randomly allocated to maintenance vs physiologic replacement doses of oral vitamin D. The maintenance dose in both age groups was 400 IU/day, and the physiologic replacement dose was 4,000 IU/day in adults and 2,000 IU/day in children. In view of the well-recognized effect of AEDs on vitamin D metabolism and the low vitamin D levels in our Lebanese population in general[16,17] and in patients with epilepsy in particular,[3] the use of a placebo was deemed unethical.

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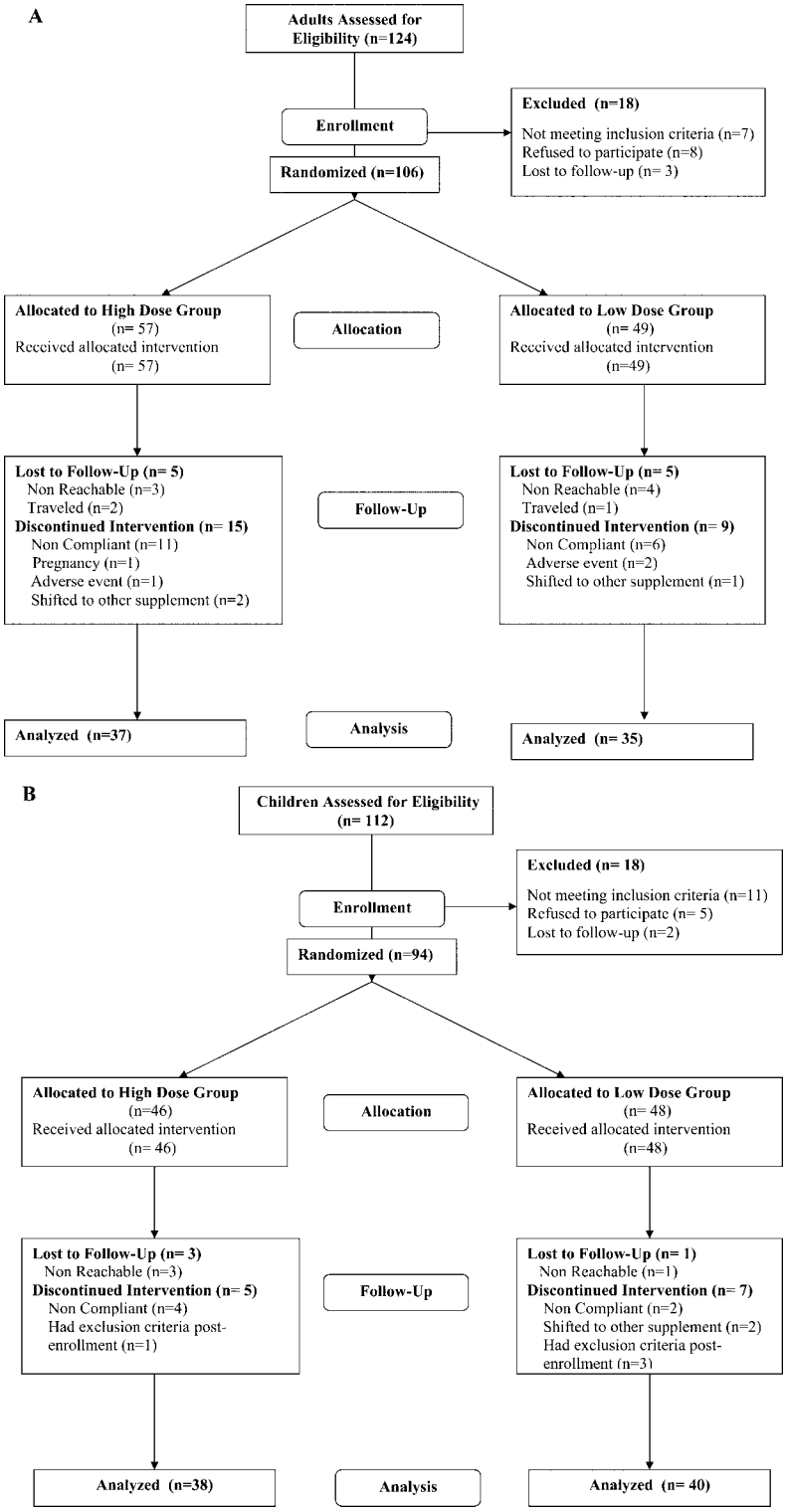

Figure 1. Flow diagram of participants through each stage of the trial in adults (A) and children (B).

Therefore, increases in BMD in the pediatric age group were compared to those of schoolchildren of a similar age group assigned to receive placebo in a randomized, double-blind vitamin D trial.[17]

Treatment assignment for both the adult and pediatric groups was based on a coin toss for the first patient, performed by the study coordinator, and subsequently by alternating treatment assignment for subsequent study subjects. Alternating assignment was based on the allocation status of the last randomized subject who was still in the study at the time of randomizing the additional study subjects. In adults, more subjects were allocated to the high-dose group to make up for the higher discontinuation rate in that group, in large part due to failure to follow up (figure 1), to ensure balanced number in both arms.[18]

The maintenance dose of 400 IU/day corresponds to the current adequate intake (AI) of vitamin D in adults.[19] The high dose in children (2,000 IU/day) was chosen in view of safety data and the desirable levels of serum 25-hydroxyvitamin D (25(OH)D) levels demonstrated in the study of schoolchildren of the same age group receiving the same dose.[17] The high dose in adults (4,000 IU/day) was chosen as it was demonstrated to be safe and to result in desirable serum 25(OH)D levels.[20]

The vitamin D preparation used was sterogyl ergocalciferol

(D_2) 2,000,000 IU/100 mL, 400 IU/drop (Hoechst, Hoechst Marion Roussel, France). Adults took either one drop (400 IU/day) or 10 drops (4000 IU/day) of sterogyl per day, and children either one drop (400 IU/day) or five drops (2,000 IU/day) of sterogyl per day, as assigned by the random allocation protocol. Due to the lack of compatible solvent (as confirmed by the local representative of Hoechst Marion Roussel), the same number of drops could not be delivered to the two treatment groups, and therefore the study subjects and coordinator could not be blinded. However, the investigator reading dual-energy x-ray absorptiometry scans was blinded to subjects' treatment.

Sample size calculation. The sample size calculation was computed taking cortical sites into consideration (total hip BMD in adults and total body bone mineral content [BMC] in children) because cortical sites would be most severely affected in diseases of abnormal vitamin D metabolism. In adults, to demonstrate a difference of 7% (SD 11%) in the percentage of change in total hip BMD between the maintenance and physiologic vitamin D groups, 40 subjects per treatment arm would be needed (power 80%, $\alpha = 0.05$ (GraphPad Instat, version 2.04a, Graphpad Software Inc., San Diego, CA). In children, to demonstrate a difference of 7% (SD 11%) in the percentage of change in total body BMC between the maintenance and physiologic vitamin D groups, 40 subjects per treatment arm would be needed (power 80%, $\alpha = 0.05$, GraphPad Instat, version 2.04a, Graphpad Software Inc.).

This would translate into a total of 160 subjects (80 adults and 80 children). We aimed to recruit 200 subjects to allow for potential dropouts. The study was not powered to implement subgroup analyses to evaluate the impact of type of AED, enzyme-inducing AEDs (EIAEDs), and non–enzyme-inducing AEDs (non-EIAEDs) on efficacy of intervention, in either the adults or children.

Study groups. We enrolled 200 patients with epilepsy presenting to neurologists in the outpatient clinics at the American University of Beirut Medical Center between April 2001 and January 2003 in the study. Fifty subjects were discontinued from the study as detailed in the "Compliance and Adverse Events" section. Seventy-two adults (age ranging between 18 and 60 years) and 78 children and adolescents (age ranging between 10 and 18 years) completed the study (figure 1).

Inclusion criteria were patients aged 10 years or older diagnosed with epilepsy and on long-term anticonvulsant therapy for at least 6 months, presenting to the American University of Beirut Medical Center to any of the neurologists on staff. Exclusion criteria were age younger than 10 years (children younger than 10 years were excluded because of lack of completely satisfactory data on vitamin D dosing and toxicity in this age group), gastric or bowel surgery, renal disease, liver disease, chronic diarrhea, hypothyroidism, mental retardation, multiple fractures, or intake of medications other than anticonvulsants known to affect bone metabolism including vitamin A, vitamin D (within <6 months), anabolic steroids, bisphosphonates, glucocorticoids, thiazides, or calcitonin.

Data collection. Screening assessments consisted of a complete medical history, physical examination, routine blood work including hematology and chemistry tests, as are usually performed in routine clinic visits. If the patient was eligible, anthropometric measurements including weight and height were taken. Subjects were weighed to the nearest 0.1 kg in light clothes, and height was measured to the nearest 0.5 cm with the person barefoot. A questionnaire was administered to assess type and duration of AED therapy, lifestyle, and activity habits. Patients were questioned on the date of starting and discontinuing the intake of different AEDs.

AEDs taken by the patients were classified as enzyme-inducing AEDs (EIAEDs) or non-EIAEDs. The EIAEDs in our study were phenytoin (Dilantin, Epanutin), phenobarbital (Gardenal, Luminal sodium), carbamazepine (Tegretol), and primidone (Mysoline). The non-EIAEDs were valproic acid (Depakene, Depakote), lamotrigine (Lamictal), clonazepam (Rivotril, Klonopin), gabapentin (Neurontin), topiramate (Topamax), ethosuximide (Zarontin), and vigabatrin (Sabril). Patients on multiple medications were classified in the EIAED group if at least one of the medications they were taking at the time of the study was enzyme inducing. Medication history was reassessed at 6 and 12 months.

Dietary calcium intake was assessed using a Food Frequency Questionnaire completed by the patients, targeting dairy items (milk, yogurt, cheese, strained yogurt, pizza, and ice cream). The use of this questionnaire was based on a previously validated dietary calcium questionnaire in Lebanese youths demonstrating that dairy products provided almost 80% of total daily calcium intake.[21] This is consistent with the National Health and Nutrition Examination Survey II survey results, demonstrating that dairy products were the major sources of calcium.[22,23]

Blood was drawn for hormonal assays at baseline and 12 months. All samples were stored at −70°C until analyzed. BMD was measured at 0 and 12 months.

The study protocol was approved by the Institutional Review Board at the American University of Beirut, and informed consent was obtained from the subjects (if adults) or their legal guardian (if children).

Compliance and adverse events. Compliance, intake of vitamin D, and adverse events were assessed every 3 months. We examined the sterogyl bottles and compared the expected amount consumed vs the actual amount consumed of vitamin D. Compliance was assessed as measured amount/expected amount x 100.

Patients were discontinued from the study if they had compliance <75% in any 3-month period or if they missed one follow-up appointment and unable to reschedule within 2 weeks (figure 1). Therefore, the analyses presented are per-protocol analyses.

Assays. Serum 25(OH)D was measured by a competitive protein-binding assay with inter- and intra-assay coefficient of variation (CV) <13% for the value of 47 ng/mL (Diasorin Incstar; Diasorin, Saluggia, Italy).

Dual-energy x-ray absorptiometry. Methods used. BMD determinations were performed at 0 and 12 months using a dual-energy x-ray absorptiometry densitometer (Hologic 4500A, Hologic, Bedford MA). The lumbar spine (L1-4), the hip, and 1/3 radius were measured in adults and the lumbar spine and total body in children. Using the densitometer's software, BMD values were compared to age-matched controls as provided by the manufacturer's database. In addition, BMD values were compared to age-, gender-, and ethnicity-matched controls from the Lebanese population from a database compiled at our institution.[17,24]

In vivo quality control was derived from same-day duplicate measurements performed on 329 patients during the study period. The CV% mean ± SD for the spine duplicates was 0.85 ± 0.72%, 0.83 ± 0.76%for the total hip, 1.46 ± 1.19% for the femoral neck, 1.13 ± 0.91% for the trochanter, and 0.95 ± 0.74% for 1/3 radius. For the total body measurements, the CV% mean ± SD performed on 30 duplicates were as follows: 0.91 ± 0.69% for total body BMD and 0.9 ± 0.77% for total body BMC. These values fell within the range of values we and others have reported.[25]

T score and *z* score calculation. The *T* score represents the number of SDs from a reference group of young subjects. For adults, two *T* scores were calculated: one was calculated using the mean and SD from the densitometer Western database (Hologic 45000A software version 11.2) and one using the mean and SD of an identical ethnic group.[24] The *T* scores for the lumbar spine, total hip, and 1/3 radius were calculated using the universally accepted following formula: *T* score = subject's BMD − peak mean BMD/SD. *T* scores of adult subjects with epilepsy were compared to zero to determine whether BMD in the study group differed significantly from that of peak bone mass using a Western and an ethnically matched database. For children, *z* scores were derived from the densitometer's Western normative database (Hologic 4500 A, software version 11.2).

Statistical analyses. Primary efficacy outcomes were the percentage of change in BMD at the lumbar spine, hip, and forearm in adults and the percentage of change in BMD and BMC at the lumbar spine and total body in children, the most established skeletal sites in these subgroups.

Primary analyses consisted of comparison of the percentage of change in BMD or BMC between the two treatment groups at 1 year, using a Student *t* test. Secondary analyses consisted of comparison of the percentage of change in BMD or BMC from baseline as compared to zero (no change) within each treatment group, using a Student *t* test. In adults, BMD stabilizes and then decreases progressively with aging. Therefore, a significant increase in BMD compared to baseline or no change would be reflective of a favorable response to therapy. In growing children, BMD is anticipated to increase in parallel with their growth. Therefore, increases, as opposed to no change or decreases, would be considered a favorable response. In addition, in the pediatric age group, secondary analyses evaluated treatment efficacy in each of

Table 1 *Baseline characteristics of the adult study group overall and by treatment arm*

	Adults, N = 72			
	All, N = 72	High dose, n = 36	Low dose, n = 36	*p* Value between low and high dose
Sex, M/F	33/39	15/21	18/18	0.48
Age, y	28.7 ± 9.7	25.6 ± 8.0	31.8 ± 10.4	0.01
BMI, kg/cm^2	25.9 ± 4.8	24.9 ± 4.9	26.9 ± 4.6	0.07
Calcium intake, mg/day	608 ± 467	569 ± 357	646 ± 559	0.49
25(OH)D, ng/mL	13.4 ± 7.1	13.7 ± 8.0	13.1 ± 6.9	0.72
Duration of therapy, y	10.8 ± 9.5	8.5 ± 6.7	13.1 ± 11.4	0.04
BMD				
Lumbar spine BMD	0.97 ± 0.11	0.97 ± 0.10	0.98 ± 0.12	0.81
T score	−0.87 ± 1.06*	−0.86 ± 0.95*	−0.87 ± 1.18*	0.96
Total hip BMD	0.90 ± 0.13	0.90 ± 0.13	0.91 ± 0.14	0.67
T score	−0.58 ± 0.93*	−0.64 ± 0.81*	−0.52 ± 1.04*	0.59
Femoral neck BMD	0.8 ± 0.12	0.79 ± 0.11	0.80 ± 0.13	0.74
T score	−0.70 ± 0.97*	−0.75 ± 0.83*	−0.64 ± 1.09*	0.69
Trochanter BMD	0.68 ± 0.11	0.67 ± 0.10	0.68 ± 0.11	0.54
T score	−0.5 ± 0.94*	−0.58 ± 0.83*	−0.43 ± 1.02*	0.45
1/3 radius BMD	0.70 ± 0.07	0.70 ± 0.06	0.70 ± 0.07	0.96
T score	−0.85 ± 1.05*	−0.86 ± 1.10*	−0.85 ± 1.03*	0.97
Type of seizure, no. (%)				0.10
Generalized	28 (43%)	17 (55%)	11 (32%)	
Focal	35 (54%)	14 (45%)	21 (62%)	
Both	2 (3%)	0	2 (6%)	
Type of therapy, no. (%)				0.19
EIAED	51 (71%)	23 (64%)	28 (78%)	
Non-EIAED	21 (29%)	13 (36%)	8 (22%)	
Mode of therapy, no. (%)				0.81
Single	35 (49%)	18 (50%)	17 (47%)	
Multiple	37 (51%)	18 (50%)	19 (53%)	

Results are expressed as mean ± SD or as proportions.

* $p < 0.05$ compared to 0. A *T* score <0 denotes a mean BMD that is less than the mean for young adults (age range 20 to 29 years old) as provided by manufacturer's database.

BMI = body mass index; 25(OH)D = 25-hydroxyvitamin D; BMD = bone mass density; EIAED = enzyme-inducing antiepileptic drug; non-EIAED, non–enzyme-inducing antiepileptic drug.

the two treatment groups compared to healthy controls, as detailed in the "Study Design" section. Analysis of variance was used for this comparison. Exploratory subgroup analyses by gender were conducted both in the adult and the pediatric age groups.

Results are expressed as mean ± SD, unless mentioned otherwise. All analyses were done separately for adults (18 years and older) and pediatric (children/adolescents 10 to 18 years) patients using SPSS version 12 software (SPSS, Chicago, IL). Comparisons of continuous variables between various subgroups of subjects were performed using a two-tailed Student *t* test and a χ^2 test for categorical variables. Baseline variables that were found to be significantly different in the bivariate analysis were entered into a linear regression model to assess the independent effect of each on the percentage of change in BMD. Significance was set at $p < 0.05$.

Results. *Clinical characteristics of study subjects.* Adults. The adult study group included 72 participants (figure 1A, table 1), 39 women and 33 men. Mean age (± SD) was 28.7 ± 9.7 years, and mean duration of AED therapy was 10.8 ± 9.5 years. In adults, the major seizure etiologies were idiopathic (39%), cryptogenic/congenital (36%), trauma (16%), infection (6%), neoplasm (1.5%), and cerebrovascular (1.5%). The majority of adults (71%) were taking EIAEDs, and they were equally distributed between mono- and polytherapy (table 1). Among adult patients, 22 were on valproate, 15 on lamotrigine, 8 on topiramate, 6 on gabapentin, 5 on clonazepam, 37 on carbamazepine, 17 on phenytoin, 13 on phenobarbital, and 3 on primidone.

None of the baseline characteristics differed between the two treatment arms, except for age and duration of therapy, which were greater in the group assigned to low-dose therapy (table 1).

Children. The pediatric group included 78 participants

Table 2 *Baseline characteristics of the pediatric study group overall and by treatment arm*

	Children with epilepsy				
	All, N = 78	High dose, n = 38	Low dose, n = 40	*p* Value low vs high dose	Healthy matched* Lebanese subjects
Sex, M/F	71/37	22/16	19/21	0.36	56/55
Age, y	13.2 ± 2.0	13.0 ± 1.8	13.4 ± 2.1	0.27	13.3 ± 2.0
BMI, kg/cm^2	21.2 ± 4.5	21.1 ± 4.5	21.4 ± 4.6	0.73	20.8 ± 4.1
Calcium intake, mg/day	547 ± 334	585 ± 346	511 ± 321	0.33	736 ± 341†
25(OH)D, ng/mL	18.1 ± 8.1	18.0 ± 9.1	18.2 ± 7.1	0.91	15.3 ± 6.8†
Duration of therapy, y	5.2 ± 4.6	4.9 ± 4.0	5.4 ± 5.1	0.63	
BMD					
Lumbar spine BMD, g/cm^2	0.77 ± 0.17	0.74 ± 0.15	0.80 ± 0.18	0.11	0.76 ± 0.15
z score	−0.23 ± 1.2	−0.4 ± 0.01†	0.07 ± 1.34	0.23	0.36 ± 0.88
Subtotal body BMD, g/cm^2	0.84 ± 0.12	0.82 ± 0.11	0.87 ± 0.12	0.08	0.85 ± 0.11
Subtotal body BMC, g	1,217 ± 480	1,141 ± 395	1,289 ± 461	0.13	1,231 ± 400
Type of seizure no. (%)					
Generalized	23 (31%)	10 (28%)	13 (34%)	0.55	
Focal	51 (69%)	26 (73%)	25 (66%)		
Type of therapy, no. (%)					
EIAED	41 (53%)	24 (63.2%)	17 (42%)	0.07	
Non-EIAED	37 (47%)	14 (38.8%)	23 (57.5%)		
Mode of therapy, no. (%)					
Single	50 (64%)	24 (63%)	26 (65%)	0.86	
Multiple	28 (36%)	14 (37%)	14 (35%)		

Results are expressed as mean ± SD or proportion.

* Study group of 111 children from a previous study, age and ethnically matched, as described in detail in reference 17.
† $p<0.05$ compared to overall group of children with epilepsy.
‡ $p < 0.05$ compared to 0. A *z* score <0 denotes a mean BMD that is lower and a *z* score >0 higher than the mean of age-matched controls as provided by manufacturer's database.

BMI = body mass index; 25(OH)D = 25-hydroxyvitamin D; BMD = bone mass density; BMC = bone mineral content; EIAED = enzyme-inducing antiepileptic drug; non-EIAED = non–enzyme-inducing antiepileptic drug.

(figure 1B, table 2), 41 boys and 37 girls with a mean age of 13.2 ± 2 years and duration of therapy of 5.2 ± 4.6 years. In children, the etiologies for epilepsy were idiopathic (52%), cryptogenic/congenital (38%), trauma (7%), and cerebrovascular (3%). The proportions of children on EIAEDs and non-EIAEDs were almost identical (table 2). Fifty (64%) were on monotherapy and 28 (36%) on polytherapy. Among this age group, 39 were on valproate, 17 on lamotrigine, 8 on topiramate, 2 on clonazepam, 2 on gabapentin, 30 on carbamazepine, 6 on phenytoin, and 5 on phenobarbital.

None of the baseline characteristics differed between the two treatment arms in the pediatric age group (table 2).

Baseline vitamin D and BMD values. Adults. The mean 25(OH)D level was 13.4 ± 7 ng/mL (table 1). Thirty-four percent of the patients were in the deficient range (<10 ng/mL), 46% in the insufficient range (10 to 20 ng/mL), and 20% were normal. Similar proportions were noted in the high- and the low-dose groups. The mean 25(OH)D level did not differ between patients on EIAEDs (12.75 ± 6.32 ng/mL) and those on non-EIAEDs (15.00 ± 8.65 ng/mL) ($p = 0.29$). The mean 25(OH)D was not correlated with duration of AED therapy for EIAEDs ($p = 0.09$) or non-EIAEDs ($p = 0.87$) (data not shown).

BMD at all skeletal sites in the whole group and in each of the high- and the low-dose subgroups, was decreased vs normal young controls as provided by the manufacturer's database ($p < 0.05$ at all skeletal sites, table 1). It was also lower than that of young controls matched for gender and ethnicity ($p < 0.05$ at all skeletal sites; data not shown). Except at the femoral neck, BMD was not different between patients on EIAEDs and those on non-EIAEDs (lumbar spine: 0.96 ± 0.12 g/cm^2 and 1.01 ± 0.09 g/cm^2; hip: 0.89 ± 0.13 g/cm^2 and 0.94 ± 0.13 g/cm^2; femoral neck: 0.78 ± 0.11 g/cm^2 and 0.85 ± 0.13 g/cm^2; trochanter: 0.66 ± 0.09 g/cm^2 and 0.72 ± 0.11 g/cm^2; radius: 0.71 ± 0.07 g/cm^2 and 0.68 ± 0.05 g/cm^2) ($p > 0.05$ in all sites except the femoral neck: $p = 0.02$). BMD was not correlated with duration of AED therapy at any site for EIAEDs or non- EIAEDs ($p > 0.05$) except at the lumbar spine (data not shown).

Children. The mean 25(OH)D level was 18.1 ± 8.1 ng/mL (table 2). Fifteen percent were in the deficient range, 44% in the insufficient range, and 41% were in the normal range (with the high-dose group not different from

the low-dose group). The mean 25(OH)D level did not differ between children on EIAEDs (17.68 ± 8.87 ng/mL) and those on non-EIAEDs (18.59 ± 7.27 ng/mL) ($p = 0.62$). Mean 25(OH)D was not correlated with duration of AED therapy for EIAEDs ($p = 0.64$) or non-EIAEDs ($p = 0.11$; data not shown). BMD in the whole group was not significantly different from manufacturer's normative database (z score not significantly different from zero). However, when analyzed separately, the high-dose group had at baseline a significantly lower lumbar spine BMD than manufacturer's subjects (table 2). Compared to age, gender, and ethnically matched controls, children with epilepsy had similar lumbar spine, subtotal body BMD, and subtotal body BMC (table 2). BMD was not different between patients on EIAEDs and those on non-EIAEDs (lumbar spine: 0.77 ± 0.16 g/cm^2 for EIAEDs and 0.78 ± 0.18 g/cm^2 for non-EIAEDs; subtotal body BMD: 0.85 ± 0.12 g/cm^2 and 0.84 ± 0.12 g/cm^2; subtotal body BMC: 1,238 ± 449 g and 1,192 ± 421 g) ($p > 0.05$ in all comparisons). BMD was not correlated with duration of AED therapy at any site for EIAEDs or non-EIAEDs ($p > 0.05$) (data not shown).

Compliance with medication dosing and adverse events. From the original study cohort, 34 adults (21 in the high-dose and 13 in the low-dose group) and 16 children (eight in the high-dose and eight in the low-dose group) were dropped from the study (figure 1). Reasons for drop out in adults were noncompliance in 17, inability to reach the patients in seven, travel in three, switching to other supplements in three, adverse experiences in three, and pregnancy in one. In the high-dose group, the adverse experience attributed by the patient to be secondary to vitamin D was gastrointestinal discomfort. In the low-dose group, the adverse experiences attributed by the patients to be secondary to vitamin D included back pain and poor tolerability to the drug in a patient with multiple allergies. Reasons for dropouts in children included noncompliance in six, inability to reach the patients in four, discovery of exclusion criteria after study enrollment in three, shifting to another supplement in two, and inability to lie still for BMD in one. Dropouts were not different with respect to demographic characteristics from included patients ($p > 0.05$) in all baseline characteristics (data not shown).

The mean amount of vitamin D actually consumed by patients was essentially on target for patients assigned the replacement doses and above targets for patients assigned maintenance doses. In adults, the mean intake of vitamin D consumed in the high-dose group was 3,627 ± 453 IU/day (target 4,000 IU/day), and the amount consumed in the low-dose arm was 745 ± 319 IU/day (target 400 IU/day). In children, corresponding numbers were 2,068 ± 366 IU/day (target 2,000 IU/day) and 712 ± 264 IU/day (target 400 IU/day).

25(OH)D levels at 1 year of therapy. Adults. Vitamin D levels increased on the average by 53% in the low-dose treatment arm from a mean of 13.1 ± 6.2 ng/mL to 17.5 ± 7.3 ng/mL ($p < 0.001$) and by 150% in the high-dose treatment arm from a mean of 13.8 ± 8.1 ng/mL to 26.3 ± 9 ng/mL ($p < 0.0001$). The mean 25(OH)D level at 1 year of therapy was higher in the high-dose vs the low-dose group, ($p < 0.0001$). In the low-dose group, only 14% of the patients were vitamin D deficient, 55% insufficient, and 31% had normal levels, at 1 year. In the high-dose group, none of the patients were vitamin D deficient, 31% had vitamin D insufficiency, and the majority (69%) were in the normal range ($p < 0.01$ by χ^2 test).

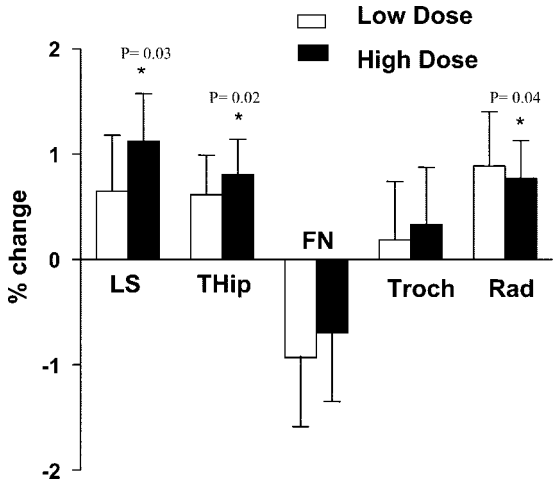

*Figure 2. Percentage of change in BMD (mean ± SEM) in adults compared to baseline in the lumbar spine (LS), hip (THip), femoral neck (FN), trochanter (Troch), and 1/3 radius (Rad). *Percentage of change from baseline that is significantly different from zero in the lumbar spine, total hip, and radius in the high-dose group.*

Children. Vitamin D levels increased on the average by 30% in the low-dose treatment arm from a mean of 18.2 ± 7.1 ng/mL to 21.3 ± 8.54 ng/mL ($p = 0.012$), and by 54% in the high-dose treatment arm from 18.0 ± 9.1 to 22.9 ± 8.4 ng/mL ($p = 0.001$). Mean 25(OH)D levels at 1 year did not differ between the two treatment groups ($p = 0.4$). At 1 year, in the overall pediatric group, only 6% were deficient, 44% insufficient, and 50% normal. Comparable proportions were noted in the high- and the low-dose groups.

Changes in BMD at 1 year of therapy. Adults. At 1 year, there was no difference in the percentage of change in BMD between the two treatment groups. However, BMD increased significantly in the lumbar spine, total hip, and 1/3 radius (three of five sites) in adults assigned to high-dose vitamin D (figure 2), whereas BMD did not change compared to baseline in the low-dose group (figure 2).

Children. At 1 year, BMD increased significantly in the lumbar spine, subtotal body BMC, and subtotal body BMD, both in the high-dose and low-dose vitamin D groups (figure 3). The percent change from baseline was increased in both treatment groups ($p < 0.001$). There were no treatment differences between the two groups (figure 3). When compared to healthy subjects assigned to placebo in a previous vitamin D trial at our center[17] (and matched for age, gender, and ethnicity), subjects with epilepsy in both treatment groups had bone mass increases comparable to those of healthy controls at all three sites (table 3). Specifically, these were for the low-dose group: lumbar spine, BMD 7.6 ± 5.5%; subtotal body BMD, 2.3 ± 3.2%; and subtotal body BMC, 8.6 ± 8.9%. The changes for the high-dose group were 7.8 ± 6.4% for the lumbar spine, 3.2 ± 0.6% for subtotal body BMD, and 12.2 ± 8.9% for subtotal body BMC. For matched control subjects (as described in the "Study Design" section), the changes were 8.1 ± 6.2% for the lumbar spine, 3.6 ± 3.9% for subtotal body BMD, and

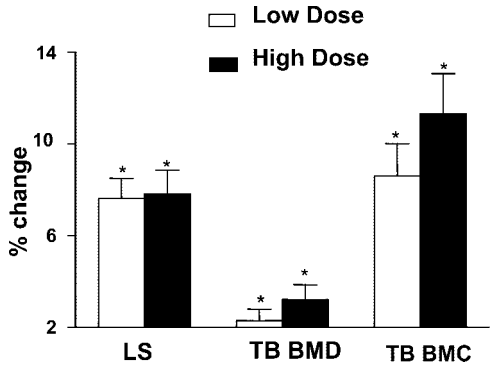

*Figure 3. Percentage of change in bone mass (mean ± SEM) in children compared to baseline in the lumbar spine and in total body BMD/BMC. *Percentage of change from baseline in bone mass that is significantly different from zero at all sites: lumbar spine (LS), total body (TB BMD), and total body BMC (TB BMC) in both treatment groups ($p < 0.001$).*

12.3 ± 9.2% for subtotal body BMC (table 3). When analyses were split by gender, boys with epilepsy, but not girls, had trends for lower increases in bone mass at the three skeletal sites that almost reached significance at the subtotal body BMC. The post hoc analyses of variance showed that the trend was driven by the difference between the low-dose group and controls (table 3).

BMD at 1 year of therapy. Adults. The BMD at all skeletal sites was still significantly lower than both normal young adult controls compared to the manufacturer's database and to the population age-matched controls ($p < 0.05$ at all skeletal sites, data not shown), in both treatment arms.

Children. All BMD values in the low-dose group and subtotal body BMD and subtotal body BMC in the high-dose group were still in normal range compared to manufacturer's database (data not shown). The lumbar spine BMD in the high-dose group was still, as it was at baseline, significantly lower than controls of the manufacturer's database (data not shown).

Analysis for potential confounding variables. Linear regression analysis, correcting for the confounding variables that were significantly different at baseline between the two study arms at the bivariate level (age and duration of therapy in adults), demonstrated that the variables did not influence the effect of the different doses on the percentage of change in BMD at any site (data not shown).

Discussion. Ambulatory adults on AEDs had low bone density vs age- and gender-matched controls. High-dose, but not low-dos, vitamin D increased BMD significantly at several skeletal sites, but did not normalize it at 1 year. In children on AEDs, BMD was similar to that of age- and gender-matched controls, and there were no differences in BMD increases between the two groups. The efficacy of low-dose vitamin D therapy compared to no treatment could not be assessed because of the absence of a placebo group, the inclusion of which was considered unethical.

Few short-term studies have examined the impact of vitamin D therapy in outpatient adults on anticonvulsant therapy, and thus there were contradictory conclusions (table 4). An earlier study showed a 4% increase in forearm BMC in 116 patients given 2,000 IU/day of vitamin D_2 along with 515 mg of calcium over 3 months.[10] Similar increases were noted in forearm BMC of six patients with epilepsy given 4,000 IU/day of vitamin D_3 without any calcium supplementation.[11] A third study demonstrated that 120,000 IU of vitamin D_3 given as a single dose to 30 adults on anticonvulsant therapy resulted in significant increases in ultrasound-derived variables.[12] Conversely, two studies showed no benefit of vitamin D therapy on bone mineral mass.[14,26] In the first study, 50,000 IU of vitamin D was administered daily for 6 months to nine patients.[26] In the second, 4,000 IU vitamin D given as D_2 or D_3 and 500 mg of calcium were given daily for 6 months to 30 patients

Table 3 *Changes in bone density and bone mass at 1 year in controls vs children with epilepsy, overall and by gender*

	Control children*	Children with epilepsy on low-dose vitamin D	Children with epilepsy on high-dose vitamin D	p†
All, no.	111	40	38	
% Change in lumbar spine BMD	8.1 ± 6.2	7.6 ± 5.5	7.8 ± 6.4	0.92
% Change in subtotal body BMD	3.6 ± 3.9	2.3 ± 3.2	3.2 ± 4.0	0.18
% Change in subtotal body BMC	12.3 ± 9.2	8.6 ± 8.9	12.2 ± 8.9	0.08
Boys, no.	56	19	22	
% Change in lumbar spine BMD	9.6 ± 6.7	9.3 ± 6.3	7.6 ± 6.6	0.47
% Change in subtotal body BMD	4.7 ± 4.3	3.0 ± 3.9	3.7 ± 4.2	0.28
% Change in subtotal body BMC	15.8 ± 8.4	10.5 ± 10.6	12.9 ± 8.8	0.065
Girls, no.	55	21	16	
% Change in lumbar spine BMD	6.5 ± 5.1	6.1 ± 4.2	8.1 ± 6.4	0.46
% Change in subtotal body BMD	2.5 ± 3.1	1.6 ± 2.2	2.5 ± 3.7	0.55
% Change in subtotal body BMC	8.7 ± 8.8	6.9 ± 6.8	11.2 ± 9.3	0.31

* Control children, age and ethnically matched, randomized to placebo for 1 year as described in detail in reference 17.
† p value for analysis of variance analysis between the three groups.

Table 4 *Comparative studies using vitamin D therapy for AED-related osteopenia*

Study	Design	Patient age, y, mean ± SD, (range)	Study groups	Doses of vitamin D	Duration of vitamin D therapy	Results (BMD, BMC, levels)
Adult studies						
Bachrach[27]	Not controlled, not blinded	Epileptic age: 45.4, nonepileptic age: 47.4 institutionalized women	9 institutionalized women on AED for 10–15 y and 10 institutionalized nonepileptic women controls	1 oral dose of 50,000 IU of vitamin D in the 2 groups	At 3 and 6 mo	No change in bone mass in both groups
Christiansen et al.[10]	Randomized, not mentioned whether blinded	21–70	116 epileptics on vitamin D, 110 epileptics on placebo, 20 normal controls (10 on placebo and 10 on vitamin D)	2,000 IU/d D_2, placebo; all received 390 mg/d Ca lactate and 125 mg/d $CaHPO_4$	3 mo	4% increase in forearm BMC in epileptics on vitamin D, no increase in normals on vitamin D or in placebo groups
Hahn and Halstead[11]	Not blinded, not controlled	30.1 ± 4.1 for patients, 28.7 ± 3.2 for controls	6 epileptic adults, 15 normal age-matched controls	4,000 IU/d D_3	4 mo	5.3% increase in forearm BMC compared to baseline
Tjellesen et al.[14]	Randomized, double blinded	40.4 (20–68)	30 epileptic outpatients on CBZ for at least 1 y divided to 2 groups: given vitamin D_2 or vitamin D_3	4,000 IU/d D_2 or D_3; all received 0.5 g/d Ca	24 wk	Normal bone mass at baseline, no change after vitamin D_2 or D_3 supplementation
Pedrera et al.[12]	Not blinded, not controlled	53 ± 15 y	30 adults on AEDs for at least 10 y, 30 normal controls	120,000 IU oral D_3 oncein patients only	1 mo	3.9% increase in AD-SOS of the phalanx in epileptics compared to baseline
Current study	Randomized, not blinded except for reading bone density, which was blinded	28.7 (18–54)	72 adults on AEDs (36 high dose and 36 low dose)	400 IU/d D_2; 4,000 IU/d D_2	1 y	Favorable effect on BMD in the high-dose group, neither dose corrected the decrease in BMD
Pediatric studies						
Silver et al.[13]	Randomized, not mentioned whether blinded	14 (10–16)	33 institutionalized adolescent epileptic patients, 32 matched nonepileptic patients (each group divided to placebo and vitamin D)	200 IU/d D or placebo for normal and epileptics for 12 wk; 3,000 IU/wk D_3 for epileptics for an additional 12 wk	24 wk	200 IU/d resulted in decreases in AlkP, 3,000 IU/wk resulted in early increase in AlkP, presumably a reflection of increased osteoblastic activity, healing of rickets in 3 children
Current study	Randomized, not blinded except for reading bone density, which was blinded	13.2 (10–18)	78 children on AEDs (38 high dose, 40 low dose)	400 IU/d D_2, 2,000 IU/d D_2	1 y	Both the low and high dose had similar increases in BMD (trend for higher increases in the high-dose group).

AED = antiepileptic drug; BMD = bone mineral density; BMC = bone mineral content; CBZ = carbamazepine; AD-SOS = amplitude-dependent speed of sound; AlkP = alkaline phosphatase.

with epilepsy on carbamazepine.[14] The above contradictory results could probably be explained by differences in the severity of bone disease at study entry, differences in study durations, and differences in the doses of vitamin D used. Indeed, previous studies showing positive effects of vitamin D supplementation were conducted in patients with hypocalcemia, low vitamin D levels, subclinical osteomalacia, or low

bone mass.[10-12] Conversely, the most recent negative study was conducted in patients with normal BMD, and in that study, vitamin D levels were not provided.[14]

In our study, the majority of study subjects had baseline vitamin D levels <20 ng/mL and the mean BMD of the study group was below that of controls. Our study is unique because of its duration of 1 year and the fact that it compared a low-maintenance dose with a higher dose of vitamin D, a particularly important point in view of the lack of widely accepted recommendations regarding vitamin D therapy. Whereas high-dose vitamin D resulted in significant increases in adults, both at the lumbar spine and hip, the difference at 12 months between the high- and low-dose groups was not significant. In view of the smaller than anticipated difference in BMD between the two treatment groups (in the range of 1% rather than 7%), our study turned out to be underpowered to detect treatment differences between the two groups. In addition, the presence of a placebo group would have been critical to the assessment of the benefit, if any, from low-dose vitamin D. We, however, believed that the use of a placebo would have been inappropriate due to the high prevalence of hypovitaminosis D in the population in general[16,17] and in patients with epilepsy in particular.[3]

The only study reporting on the efficacy of vitamin D therapy in the pediatric age group was conducted over 12 weeks in a group of adolescents with more severe disease than observed in our patients (table 4). Indeed, those patients were institutionalized adolescents and several had clinically overt bone disease.[13] In contrast, our current study evaluated outpatient noninstitutionalized children with normal BMD at baseline and demonstrated comparable increases in BMD and BMC in both treatment arms. Because of the absence of a placebo group, we cannot rule out that the increases noted in children may have been due to growth itself rather than to vitamin D supplementation.[17] However, comparison of results in this study to those achieved in age-, gender-, and ethnically matched children[17] but with no epilepsy revealed comparable BMD increases,[17] especially at the higher physiologic doses. Conversely, the increases with the maintenance dose tended to be lower, and the difference between them and ethnically age-matched subjects almost reached significance. In view of the actual difference in the percentage of change in subtotal BMC (3.61 ± 8.9%) between the low- and high-dose groups in children, we would have needed 50 subjects per treatment arm to detect the difference between the two groups as significant (power 80%, $\alpha = 0.05$). In addition, subgroup analyses in boys suggest that the increases in children with epilepsy were suboptimal, specifically in the low-dose maintenance group. Possible putative modest increases in BMD in response to vitamin D therapy in both of our study groups may have been overshadowed by the substantial increases in bone mass due to growth and puberty.[17] The lack of a significant difference between the two treatment arms in children could also be due to the fact that the doses of vitamin D actually consumed did not result in vitamin D levels that were different at 1 year, between the two arms of the study. Other possibilities for the lack of a treatment effect in the pediatric age group include short disease duration, normal baseline BMD, and the fact that a smaller proportion of children in the study were on EIAEDs compared to adults.

There are multiple potential mechanisms accounting for the pathophysiology of AED-induced bone disease. Not all are related to abnormalities in vitamin D metabolism, the latter being most commonly implicated in bone disease of patients on EIAEDs.[8-10] It is thus possible that the multifactorial nature of AED-induced osteopathy may explain, at least in part, the inability of vitamin D therapy to completely normalize BMD in adults. The other potential explanation is that longer treatment periods and larger doses of vitamin D would be needed to completely normalize BMD. It is likely that patients who benefit the most from vitamin D therapy are those on EIAEDs with low vitamin D levels and low BMD. Our study population included patients taking a variety of AEDs and was not powered to dissect the above-proposed possibilities.

Limitations of the study also include that it was not blinded and did not include placebo for the reasons presented above. However, the lack of increases in BMD in a previous study in adults with epilepsy assigned to placebo,[10] as opposed to increases in BMD in study subjects on high-dose vitamin D, underscores the importance of vitamin D supplementation at both doses in subjects with epilepsy. The calcium intake of study subjects was suboptimal, and the study did not include calcium supplementation. However, it was meant to be a vitamin D rather than a calcium/vitamin D trial. There are limitations to the use of dual-energy x-ray absorptiometry in a growing skeleton, and several methods adjusting for lean mass, height, bone age, and Tanner staging have been suggested. However, none of these adjustments are incorporated in the densitometer software, and no optimal method has been reached to address such limitations.[27] Finally, we were only able to implement per-protocol analyses because patients who did not take their medications did not return for follow-up BMD assessment. However, these patients' characteristics did not differ from those who completed the study.

The optimal dose of vitamin D to be given to patients with epilepsy has been, to date, unclear. Several lines of evidence, including the current study, suggest that a high doses may be preferable to lower doses, both in adults and children. Based on the increased prevalence of hypovitaminosis D and the fundamental role that vitamin D plays in

skeletal homeostasis, estimates for optimal replacement doses of vitamin D and optimal vitamin D levels have been proposed for the general population.[15,20] It has been suggested that for normal adults, 25(OH)D levels >20 ng/mL and in some estimates as high as 30 ng/mL would be optimal.[15] The consumption of doses of 4,000 IU/day pf vitamin D would be needed in healthy adults to achieve such targets.[20] In our study, in adults with epilepsy after 1 year of vitamin D therapy, the mean 25(OH)D level was below the above-mentioned target levels in patients given low-dose vitamin D, whereas it reached a mean of 26.3 ± 9 ng/mL in subjects consuming on average 3,627 IU/day. Targets for optimal vitamin D levels have not been defined for healthy children. However, a previous study from our center demonstrated substantial increases in bone mass in adolescent school girls given vitamin D[17] that tended to be higher in those given the equivalent of 2,000 IU/day of vitamin D (the same dose as used in the current study) than in those given placebo. The mean vitamin D levels reached in the school study, while consuming the same dose of vitamin D (2,000 IU/day) and for the same duration (1 year) was 38 ± 31 ng/mL, a level well above that achieved in our current study. This is consistent with the well-recognized observations of accelerated metabolism of vitamin D and decreased absorption in subjects taking AEDs.[9]

Indeed, a recent study suggested that doses as high as 50,000 IU of vitamin D monthly would be needed to normalize vitamin D levels.[28]

There are currently no widely accepted guidelines for treating diseases of bone metabolism in epilepsy.[29] It was recently recommended that patients should be treated with an escalating regimen of vitamin D, with doses varying between 400 and 15,000 IU/day, depending on the type of AED-induced osteopathy.[30] Doses between 400 and 2,000 IU/day were proposed for prophylaxis at the start of AED therapy, 2,000 to 4,000 IU/day for treatment of osteopenia/osteoporosis, and 5,000 to 15,000 IU/day for 3 to 4 weeks for the treatment of osteomalacia, if present. Another review suggested general measures for patients on AEDs for >6 months that include physical activity, a balanced diet, smoking cessation, moderate intake of alcohol and caffeine, and supplementation with 1,000 to 1,500 mg of calcium and 400 IU of vitamin D daily.[1]

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