Arch Iran Med 2009; 12 (6): 550 – 554

Original Article

Bone Density of Ambulatory Adult Patients Receiving Long-term Anticonvulsant Drug Therapy

Nahid Ashjazadeh MD*, Ali Zamani MD**,***, Mehrzad Pourjafar MD†, Gholamhossein R. Omrani MD•**,***

Background: Chronic antiepileptic therapy has been associated with metabolic bone diseases including osteomalacia and osteoporosis. The object of this study was to assess the effect of first line anticonvulsants on bone density and vitamin D levels in Iranian ambulatory patients.

Methods: We conducted a cross-sectional study assessing bone density with dual energy X-ray absorptiometry at the hip and lumbar spine in 90 outpatients receiving anticonvulsants and 90 normal subjects matched for age, sex, and body mass index. Plasma total calcium, intact parathyroid hormone, total alkaline phosphatase in addition to 25 hydroxy vitamin D were also determined in both groups.

Results: The mean (±SD) bone density in patients treated with antiepileptic drugs was lower at the spine (T Score= -084±1.18 vs. -0.5±1.18, *P*< 0.05) and femoral neck (T Score= -0.83±1.11 vs. -0.46±1.1, *P*<0.05), compared to the control group of subjects. In addition, serum total alkaline phosphatase was significantly higher in patients (246.5±127 vs. 190±65.3, *P*=0.004), but the total calcium, parathyroid hormone and 25 hydroxy vitamin D did not differ significantly between patients and controls.

Conclusion: Our results suggest that maintenance therapy with antiepileptic drugs may decrease bone mass. These data also suggest a higher bone turnover rate in those receiving anticonvulsants.

Archives of Iranian Medicine, Volume 12, Number 6, 2009: 550 – 554.

Keywords: Antiepileptic drugs • bone mineral density • bone turnover • osteoporosis • osteopenia

Introduction

An association of skeletal abnormalities, namely florid rickets and osteomalacia, with chronic antiepileptic therapy was described approximately three decades ago.[1] The exact mechanisms by which anticonvulsants may interfere with bone and mineral metabolism remain unclear. First generation antiepileptic drugs (AEDs) such as phenytoin, phenobarbital and carbamazepine are thought to be hepatic enzyme inducers and by doing so may lead to altered vitamin D metabolism, vitamin D deficiency and subsequently secondary hyperparathyroidism and osteomalacia.[1] But there are controversial data regarding the level of vitamin D and its metabolites during antiepileptic therapy.[1–5] While some data are indicative of reduced 25(OH) vitamin D levels,[2–3] others demonstrated no significant reduction[4–5] associated with use of these drugs in epileptics. Also in two major studies,[5–6] bone histomorphometry were compatible with a high bone turnover state resembling the histologic features of primary hyperparathyroidism instead of showing absent mineralization which is characteristic of osteomalacia. Furthermore, the skeletal consequences of each antiepileptic drug may vary, as newer AEDs such as valproic acid are not enzyme inducers.[1,7]

Therefore, we selected a large group of

Authors' affiliations: *Department of Neurology, Nemazee Hospital, Shiraz University of Medical Sciences, **Division of Endocrinology and Metabolism, Department of Medicine, Nemazee Hospital, Shiraz University of Medical Sciences, ***Endocrine & Metabolism Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, †Department of Neurology, Kowsar Hospital, Shiraz, Iran.

•Corresponding author and reprints: Gholamhossein R. Omrani MD, Endocrine & Metabolism Research Center, Shiraz University of Medical Sciences, Zand Ave., Shiraz 71937-11351, Iran.
E-mail: hormone@sums.ac.ir
Accepted for publication: 19 July 2009

outpatients on first line anticonvulsants to elucidate the effects of AEDs, used as monotherapy or in combination, on bone health status in an Iranian population. Also the levels of parathormone (PTH) and vitamin D were evaluated in them.

Patients and Methods

All patients in the age range of 20 – 50 years who were on AEDS maintenance therapy and consecutively referred to our neurology outpatient clinic were invited to take part in this study. Patients were excluded if they had known risk factors for decreasing bone density including a history of menopause or oligoamenorrhea, heavy cigarette smoking (i.e. using 20 cigarettes or more a day for more than five years), diseases or medications[8] known to influence calcium metabolism or bone mass; also excluded were those with abnormal renal or thyroid function tests. All patients were using AEDs for at least one year. All were clinically in remission (i.e. seizure free for at least one year) at the time of investigation and provided written informed consent.

The patients were individually matched for age (±3 years), sex and body mass index (BMI) [±1 kg/m²] with randomly selected healthy controls who were participating in an ongoing national osteoporosis survey in the local community.[9] None of the healthy women had a history of oligoamenorrhea or menopause in the past or at the time of study, and none of the healthy participants were using medications known to affect bone density, including calcium or vitamin D supplements.

Bone mineral density (BMD) was evaluated with a lunar dual-energy X-ray absorptiometer at the lumbar spine and femoral neck in all patients and controls. All BMD measurements were made by a single machine using fast scan mode (DPX-IQ, Lunar Co., Madison, WI) with strict adherence to the procedures and instructions in the operator's manual. Instrument variation was determined regularly using a lunar spine phantom with coefficient of variation (CV) less than 0.5%. The *in vivo* CV was less than 1.3% for the lumbar spine and 1.2% for the femoral neck. BMD was expressed as T-scores, provided by bone densitometer's software for both groups after comparing them with a young normal population database of the same sex and race.

After a 12 hr overnight fast, blood samples were obtained in cases and controls and separated serum was kept frozen at -20°C until the time of analysis. Calcium (Ca), phorphorous (P), creatinine (Cr), total alkaline phosphatase (ALP) and albumin were determined with standard automated equipment. Total Ca was corrected for variance in serum albumin[10] by the following formula: corrected total Ca (mg/dL)=measured Ca (mg/dL)+ 0.8×[4-Alb (g/dL)]. The intact PTH was measured using an immunoradiometric assay (Diasorin, Stillwater, MN; normal range, 13 – 54 Pg/mL). Serum 25(OH) vitamin D was determined by radioimmunoassay (Biosource, Belgium).

BMD and lab values were compared with the use of unpaired Student's *t*-test and a *P*-value of <0.05 was considered statistically significant. Results were expressed as mean and standard deviations (SD). Correlations between parameters were determined using Pearson or Spearman's rank test depending on the type of data. Chi-squared test was used for comparing proportions of those with osteopenia between cases and controls. To evaluate the relation between parameters such as duration of AED therapy and number of drug(s) (polytherapy versus monotherapy) on bone density; a stepwise linear multivariate regression analysis was performed to assess the presence of interaction with age, sex, BMI, PTH, and 25(OH) vitamin D as potential confounders in patients.

Results

A total of 90 patients (mean age: 31.3±9.9, female/male ratio=58/32) with epilepsy and 90 controls (mean age: 35.1±8.5, female/male ratio=58/32) were studied. The BMI of cases were 24.2±4 and those of controls were 25±3. The average duration of anticonvulsant therapy was 11.5 (±7.4) years with a range of 1 – 35 years. At the time of study, 47(52%) patients were on monotherapy and 43(48%) were on a multiple drug regimen. The most common AEDs used by patients were carbamazepine (74%) followed by sodium valproate (31%), phenobarbital (21%), and phenytoin (12%). Only three patients were on lamotrigine or clonazepam.

The corrected total Ca (9.8±0.5 vs. 9.79±0.4 mg/dL), P (3.6±0.2 vs. 3.9±0.4 mg/dL), PTH (26±11.7 vs. 28±8 pg/mL) and 25(OH) vitamin D (60.5±35.9 vs. 59.8±34.9 ng/mL) levels of the patient group were not statistically different from those of the control group. The mean serum total

ALP was significantly higher in subjects than their controls (246.5±127 vs. 190±65.3, *P*=0.004). No correlation was found between the PTH and serum levels of Ca (r=0.1, *P*=0.6), 25(OH) vitamin D (r =0.2, *P*=0.9) or ALP (r=0.4, *P*=0.5) in either group. Also no significant relationship existed between 25(OH) vitamin D and ALP (r= -0.1, *P*=.08), P (r=0.4, *P*=0.6) or Ca (r=0.1, *P*=.09) in both groups.

Mean T-scores of the lumbar spine and femoral neck were significantly lower in patients (Table 1). Subgroup analysis showed that T-scores at the aforementioned sites were significantly lower in both female and male patients compared to their counterparts in the control group. Those on longer duration of AEDs (>5 yr, 84% of patients) had lower T-scores of the femoral neck compared to those receiving AEDs less than five years (*P*=0.03). But the lumbar spine T-score was not different between these two groups (*P*=0.14). Also a weak inverse correlation was found between duration of AEDs therapy and T-score of the femoral neck (r= -0.33, *P*=0.001). No significant relationship was found between duration of AEDs therapy and lumbar spine T-score (r= -0.2, *P*=0.09). When WHO criteria were applied, osteopenia or osteoporosis (T-score< -1.0) of at least one site was detected in 58 patients (64.4%) as compared to 39 controls (43.3%).The odds ratio for osteopenia in those on AED therapy, as compared to controls, was 2.4 (95% confidence interval, 1.3 – 4.3).

Those patients on multiple AEDs had a lower bone density compared to those on monotherapy (-1.28 vs. -0.64, *P*=0.024 for lumbar spine and -1.12 vs. -0.53, *P*=0.018 for femoral neck). Table 2 shows the results of linear regression analysis to assess the effects of duration of AED therapy and polytherapy versus monotherapy on patients' bone density. In multivariate analysis, the independent risk factor for osteopenia at the lumbar spine was polytherapy but not duration of therapy; whereas the independent risk factor for osteopenia at the femoral neck was duration of therapy (Table 2).

Discussion

We have demonstrated that epileptic patients treated with anticonvulsant medications have significantly decreased BMD and increased total ALP compared with normal controls. The higher serum total ALP may suggest accelerated skeletal turnover. Individuals with higher rates of bone turnover have been shown to lose bone at a much faster rate than subjects with normal or low bone turnover.[11–12] Several clinical trials have indicated that a concomitant increase in BMD and decrease in bone turnover markers, including ALP and osteocalcin, occurred in postmenopausal women when they were given antiresorptive agents such as bisphosphonates and hormone replacement therapy.[13–14] Although we did not measure markers of bone resorption in our study, several studies found an increased marker of bone resorption and formation in those on AEDs.[15–16] Therefore, because of coupling, higher levels of total ALP in our patients may be secondary to higher rates of bone resorption in them. Secondary hyperparathyroidism has been implicated in the pathogenesis of skeletal changes seen in patients on AEDs and may account for the observed higher total ALP in our study group, but we could not demonstrate any difference between levels of PTH and 25(OH) vitamin D in patients and their controls. In addition, high bone turnover has been demonstrated with AED use despite normal levels of PTH.[7,17] On the other hand, increased total ALP may be due to increased hepatic fraction of ALP as has been shown by others.[5,18–19]

Although most studies indicate the presence of osteopenia in those receiving AEDs, the underlying pathophysiology remains uncertain.[1,20] Several mechanisms might be considered as contributing to this phenomenon.[1,20] Traditionally,

Table 1. Comparison of bone mineral density in patients on antiepileptic drugs and age, sex, and body mass index matched controls*

	Patients			Controls		
Bone measured	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**
Lumbar spine (L_2–L_4) T Score #	-0.84±1.44[a]	-1.22±0.9[b]	-0.7±0.44[c]	-0.50±1.18	-0.86± 0.6	-0.3±0.21
Femoral neck T Score	-0.83±1.11[d]	-1.03±0.7[b]	-0.73±0.4[c]	-0.46±1.10	-0.56±0.3	-0.41±0.19

* Plus-minus values are means±SD; #values for "T Score" are the numbers of standard deviations from the mean density derived from a sex and race matched young adult population (20 – 45 years) provided by lunar database; [a]*P*=0.01 comparing all cases to all controls at the lumbar spine; [b]*P*=0.02 comparing AED treated men with normal men; [c]*P* =0.02 comparing AED treated women with normal women; [d]*P*=0.02 comparing all cases to all controls at the femoral neck

Table 2. Effects of duration of antiepileptic drug therapy and polytherapy versus monotherapy on mean bone density values, linear regression analysis

	Lumbar spine		Femoral neck	
Independent variable	**β***	***P* value**	**β ***	***P* value**
Age (years)	-0.1	0.3	0.02	0.8
Sex (female vs. male)	0.9	0.4	0.06	0.5
PTH (pg/mL)	0.01	0.9	0.09	0.4
25(OH) vit D (ng/mL)	0.2	0.1	0.2	0.08
ALP (IU/L)	-0.2	0.07	-0.09	0.4
Duration of AED use (years)	-0.1	0.4	-0.05	0.001
Polytherapy vs. monotherapy	-0.7	0.02	-0.2	0.06

* β, partial regression coefficients adjusted for the other independent variables; ALP=alkaline phosphatase; AED=antiepileptic drugs

vitamin D deficiency, hypocalcemia and secondary hyperparathyroidism are considered to be the primary mechanisms of AED-induced bone loss. However, vitamin D deficiency has not been noted in all studies that document bone disease in patients treated with AEDs.[5,15–16,21] Also valproic acid does not induce hepatic enzymes and would not be expected to reduce BMD by this mechanism.[7,22–23] In addition, some studies demonstrate low BMD independent of vitamin D levels[21,24–26] similar to what is found by us in this study.

In recent years, depression has been proposed as an independent risk factor for osteoporosis.[27] Suggested pathophysiological mechanisms include: hypersecretion of corticotropin releasing hormone and hypercortisolism, growth hormone deficiency and increased concentration of interleukin 6 in depressed patients.[27] As most epileptic patients are confronted with problems such as unemployment,[25] social withdrawal and emotional deprivation, depression is more common in them than in the general population.[28–29] Whether or not the presence of depression is an independent risk factor for inducing osteoporosis in patients on anticonvulsants needs further investigation.

This study has some limitations. First, we relied on retrospective data collection from patients' files regarding the duration of AEDs therapy and the medications that they used up to the time of the study. Second, we could not eliminate the possibility of prior consumption of other medications that may affect bone metabolism in studied patients. Finally we had no precise longitudinal data on the level of physical activity and daily calcium intake in participants. However, self-reports of current exercise patterns and daily calcium intake were relatively similar in both groups. The contribution of different physical activities or calcium intake to the measured decrease in bone density remains uncertain.

In conclusion, our results suggest that continuous therapy with AEDs may enhance bone loss. In addition to traditional approaches to prevent bone loss, such as providing calcium and vitamin D supplements and using antiresporptive agents, treatment of depression and recognition of other not yet known risk factors for bone loss in epileptic patients should be addressed.

References

1 Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. *Epilepsy Behav.* 2004; **5:** S3 – S15.

2 Hahn TJ, Hendin BA, Scharp CR, Boisseu VC, Haddad JG. Serum 25-hydroxycalciferol levels and bone mass in children on chronic anticonvulsant therapy. *N Engl J Med*. 1975; **292:** 550 – 554.

3 Stamp TCB, Round JM, Haddad JG. Plasma levels and therapeutic effect of 25-hydroxycholecalciferol in epileptic patients taking anticonvulsant drugs. *Br Med J*. 1972; **4:** 9 – 12.

4 Wark JD, Larkins RG, Perry-Keen D, Peter CT, Ross DL, Sloman JG. Chronic diphenylhydantoin therapy does not reduce plasma 25-hydroxy-vitamin D. *Clin Endocrinol*. 1979; **11:** 267 – 274.

5 Weinstein RS, Bryce GF, Sappington LJ, King DW, Gallagher BB. Decreased serum ionized calcium and normal vitamin D metabolite levels with anticonvulsant drug treatment. *J Clin Endocrinol Metab*. 1984; **58:** 1003 – 1009.

6 Mosekilde L, Melsen F. Dynamic differences in trabecular bone remodeling between patients after jejuno-ileal bypass for obesity and epileptic patients receiving anticonvulsant therapy. *Metab Bone Dis Relat Res*. 1980; **2:** 77 – 82.

7 Sato Y, Kondo I, Ishida S, Motooka H, Takayama K, Tomita Y, et al. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. *Neurology*. 2001, **57:** 445 – 449.

8 Tannirandorn P, Epstein S. Drug-induced bone loss. *Osteoporosis Int*. 2000; **11:** 637 – 659.

9 Omrani GR, Masoompour SM, Hamidi A, Mardanifard HA, Taghavi SM, Talezadeh P, et al. Bone mineral density in the normal Iranian population: a comparison with American reference data. *Arch Osteoporos*. 2006; **1:**

29 – 35.
10 Portale AA. Blood calcium, phosphorus and magnesium. In: Favus MJ, Christakos S, Kleerekoper M, et al, editors. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. New York: Raven Press; 1993; 87 – 90.
11 Riggs BL, Melton LJ III, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: Evidence that decreases in bone turnover and increases in bone mass both determine anti fracture efficacy. *Bone*. 1996; **18:** 197S – 201S.
12 Melton LJ III, Khosla S, Atkinson EJ, O'fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. *J Bone Miner Res*. 1997; **12:** 1083 – 1091.
13 Greenspan SL, Resnick NM, Parker RA. Early changes in biochemical markers of bone turnover are associated with long term changes in bone mineral density in elderly women on Alendronate, hormone replacement therapy, or combination therapy: a three-year, double-blind, placebo–controlled, randomized clinical trial. *J Clin Endocrinol Metab*. 2005, **90:** 2762 – 2767.
14 Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zolendronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007; **356:** 1809 – 1822.
15 Valimaki MJ, Tjihonen M, Laitinen K, Tahetela R, Karkkainen M, Lamberg-Allardt C, et al. Bone mineral density measured by dual-energy X-ray absorptiometry and novel markers of bone formation and resorption in patients on anti-epileptic drugs. *J Bone Miner Res*. 1994; **9:** 631 – 637.
16 Verroti A, Greco R, Latini G, Margese G, Chiarelli F. Increased bone turnover in epileptic patients treated with carbamazepine. *Ann Neurol*. 2000; **47:** 385 – 388.
17 Feldkamp J, Becker A, Witte OW, Scharff D, Scherbaum WA. Long-term anticonvulsant therapy leads to low bone mineral density: evidence for direct drug effects of phenytion and carbamazepine on human osteoblast-like cells. *Exp Clin Endocrinol Diabetes*. 2000; **108:** 37 – 43.
18 Hahn TJ, Hendin BA, Scharp CR, Haddad JG Jr. Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol level in adults. *N Engl J Med*. 1972; **287:** 900 – 904.
19 Richens A, Rowe DJF. Disturbances of calcium metabolism by anticonvulsant drugs. *Br Med J*. 1970; **4:** 73 – 76.
20 Ali II, Schuh L, Barkley GL, Gates JR. Antiepileptic drugs and reduced bone mineral density. *Epilepsy Behav*. 2004; **5:** 296 – 300.
21 Pack AM, Morrell MJ, Marcus R, Holloway L, Flaster E, Done S, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. *Ann Neurol*. 2005; **57:** 781 – 786.
22 Sheth RD, Wesolowski CA, Jacob JC, Penney S, Hobbs GR, Riggs JE, et al. Effect of carbamazepine and valproate on bone mineral density. *J Pediatr*. 1995; **127:** 256 – 262.
23 Gough H, Goggin T, Bissessar A, Baker M, Crowley M, Callaghan N. A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. *Q J Med*. 1986; **230:** 569 – 577.
24 Andress DL, Ozuna J, Tirschwell D, Grande L, Johnson M, Jacobson AF, et al. Antiepileptic drug-induced bone loss in young male patients who have seizures. *Arch Neurol*. 2002; **59:** 781 – 786.
25 Kulak CAM, Borba VZC, Bilezikian JP, Silvado CE, Paola L, Boguszewski CL. Bone mineral density and serum levels of 25 OH vitamin D in chronic users of antiepileptic drugs. *Arq Neuropsiquiatr*. 2004; **62:** 940 – 948.
26 Farhat G, Yamout B, Mikati MA, Demirjian S, Sawaya R, El-Hajj Fuleihan G. Effect of antiepileptic drugs on bone density in ambulatory patients. *Neurology*. 2002; **58:** 1348 – 1353.
27 Cizza G, Ravn P, Chrousos GP, Gold PW. Depression: a major, unrecognized risk factor for osteoporosis? *Trends Endocrinol Metab*. 2001; **12:** 198 – 203.
28 Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry*. 2003; **54:** 388 – 398.
29 Kanner AM. Depression in epilepsy: a complex relationship with unexpected consequences. *Curr Opin Neurol*. 2008; **21:** 190 – 194.