

Bone mineral density following long-term use of antiepileptic drugs in a tropical Asian country

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ABSTRACT – The objective of this study was to investigate bone mineral density (BMD) in Thai epileptics who had been receiving long-term, antiepileptic drugs. Subjects were epileptic patients aged 15 to 50 years who had been taking antiepileptic drugs for longer than six months. All were free of disease and none was taking any medication that might interfere with bone metabolism other than antiepileptic drugs. BMD at the left femoral neck and spine was measured with dual energy X-ray absorptiometry. Demographic data, basic laboratory studies and history of clinical epilepsy were obtained. One hundred and thirty patients (63 males and 67 females) were included. Mean age (+ SD) was 31.9 ± 9.7 year. There were 79 patients receiving monotherapy and 51 patients receiving polytherapy. All patients had normal serum calcium. Thirteen patients had slightly low serum phosphate levels. The BMD at the femoral neck had a mean Z-score -0.15 ± 1.17 and the mean Z-score at the lumbar spine was -0.56 ± 1.03 . Thirty one patients had osteopenia at the spine and 30 patients at the femoral neck. Three patients had osteoporosis of the spine and 1 patient of the femoral neck. There was found to be no significant correlation between age, sex, body mass index, duration of treatment and type of antiepileptic drug with bone mineral density at the femur and spine. The mean BMD of long-term antiepileptic users was lower than that of the sex and age-adjusted mean.

Key words: bone mineral density, antiepileptic drugs, tropical Asian country

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Since the late 1960s, antiepileptic drugs have been known to be associated with abnormal bone mineral meta-

bolism. Epileptic patients also have been known to have an increased risk of fracture (Jaglal *et al.* 1995, Vester-

gaard *et al.* 1999, Cummings *et al.* 1995). The increased fracture risk may be due to (1) more frequent trauma due to seizure activity (Sheth *et al.* 1995), and (2) a decreased bone mineral density (BMD) (Elliott and Jacobson 2006). Early reports suggested that 12% to 65% of epileptic patients have abnormal bone mineral density (Hahn *et al.* 1972, Mosekilde *et al.* 1977, Petty *et al.* 2005, Stephen *et al.* 1999). Enzyme inducers and non-enzyme inducers cause abnormalities in calcium metabolism, including hypocalcemia, hypophosphatemia, elevated serum alkaline phosphatase, serum parathyroid hormone and low vitamin D (Pack *et al.* 2003, Andress *et al.* 2002, Boluk *et al.* 2004, Christiansen *et al.* 1973, Richens and Rower 1970, Tolman *et al.* 1975, Berr *et al.* 1983, Marshall *et al.* 1996, Farhat *et al.* 2002). The consequences of fractures include hospitalization, loss of independence and death. Vertebral and hip fractures are associated with the most significant morbidity and mortality (Berr *et al.* 1983). It has been reported that every SD unit of T-score below 0 represents a doubling of risk of fracture (Marshall *et al.* 1996).

Several studies have reported that people with epilepsy, who are taking antiepileptic drugs, have low bone mineral density compared with healthy controls (Pack *et al.* 2005, Kulak *et al.* 2007, Kim *et al.* 2007, Kulak *et al.* 2004, Tjellesen and Christiansen 1982, Tekgul *et al.* 2006). However, these studies were conducted mostly in western countries, which differ from tropical countries with respect to food, seasons and sun exposure, all of which are closely linked to vitamin D₂ and vitamin D₃. In addition, there are marked cultural differences. Thailand is a tropical Asian country situated in 15° 00' Northern latitude and 100° 00' Eastern Longitude. Thailand has three seasons; cool (November through February), hot (March through June) and rainy (July through October). Almost every day in the cool and hot seasons is a sunny day. Even in the rainy season in Thailand, it rarely rains for more than an hour at a time. The mornings are usually sunny, but a thunderstorm or two might occur late afternoon or at night. The diet in Thailand is different from that in Western countries. Thailand has a rice-dependent population. The Thai lifestyle involves mostly home-prepared meals, which are low fat and with a high vegetable and fruit content. Thai people have three meals a day. Generally, in Western countries, the number of daily meals has decreased, with breakfast being the most commonly skipped meal and dinner being the main meal of the day. Furthermore, the typical Western diet is high in fat and low in fruit and vegetables (Sukalakamala and Brittin 2006, Matsuda-Inoguchi *et al.* 2000, Kajiadphai-Taungbodhitham 2007, Craven and Hawks 2006).

We conducted a cross-sectional study of bone mineral density in Thailand to identify the main factors influencing low bone mineral density in ambulatory, epileptic patients on long-term antiepileptic drugs.

Patients and methods

This cross-sectional study was performed involving epileptic patients in a tertiary care, referral center in the South of Thailand from November 2004 to December 2006.

Patients

The authors enrolled 15-50 year-old epileptic patients who had been treated with antiepileptic drug(s) for more than six months in the general medical and neurological clinics of Songklanagarind Hospital. Songklanagarind Hospital is the only tertiary medical center and the largest referral center in the South of Thailand.

In this report, the terminology adopted is in accordance with the International League Against Epilepsy's classification of seizure and epileptic syndromes (Engel 2001). Inclusion criteria were: Thai national with epilepsy with no chronic medical illness other than epilepsy, taking no medication except antiepileptic drug(s), with an active daily life (performed activity of daily living without assistance), no history of amenorrhoea, hysterectomy or oophorectomy, and who did not drink alcohol.

Exclusion criteria were pregnancy, being unable to read and converse in the Thai language, having significant disabilities such as mental retardation, ataxia, paresis, and other motor disability, learning disability, language disorder, hearing or visual disability, psychosis or psychiatric disease, or having significant a medical disorder other than epilepsy. From a total of 224 epileptic patients seen at Songklanagarind Hospital during the study period, ninety four patients were excluded from the study (21 had a neurological disability with or without abnormal menstruation, 27 had other medical problems with or without abnormal menstruation, two had uncertain data for their epilepsy, 29 were taking other medications which interfered with bone minerals, five were aged more than 50 years, five had been taking medication for less than six months and five had received adjunctive therapy with other antiepileptic drug for less than six months). The data from 130 patients were used for analysis.

Procedure

All patients completed a questionnaire covering age, age-at-onset of epilepsy, duration of treatment, duration of epilepsy, occupation and medication. All of them completed the questionnaire in one session. Variables from the patients were rechecked with family members by independent interviewers and with the medical record and, in some cases, by contacting their physicians. Blood samples were taken for albumin, calcium and phosphate determination on a HITACHI 971 automatic analyzer during the same hospital visit.

Weight and height were measured. Bone mineral density of the lumbar spine and left femur was measured by dual-energy X-ray absorptiometry (DXA) (DPX MD. Soft-

ware version: 4.6, Lunar corporation, USA) and reported as a T-score (the difference in standard deviation units between the measured bone density value and the peak bone density in the normal reference population), and the Z-score (SD from age-sex-specific score). The areas selected for determination of BMD were the neck of the left femur and lumbar (L1-L4) vertebrae.

The World Health Organization (WHO) (Kanis *et al.* 1996) defines normal bone mineral density as a T-score greater than -1.0, osteopenia as a T-score between -1 and -2.49, and osteoporosis as a T-score equal to or less than -2.5. Body mass index was calculated [body weight (kg)/height (m)²]. A body mass index below 18.5 was classified as a low body mass index, between 18.5 – 22.9 as normal and higher than 23 as overweight, in accordance with World Health Organization (WHO) recommendations (World Health Organization 2000).

The enzyme-inducing antiepileptic drugs were phenytoin, phenobarbital and carbamazepine. The non-enzyme inducers were valproic acid, lamotrigine, clonazepam, topiramate, gabapentin. Patients on both enzyme inducer and non-enzyme inducer drugs were classified as receiving combination drugs. Patients taking only one medication were classified as receiving monotherapy and taking more than one medication as receiving polytherapy. The Ethics Review Committee of the Faculty of Medicine, Prince of Songkhla University, approved the study and informed consent was sought and obtained from all patients.

Statistical analysis

Characteristics of the study patients were described in terms of mean and standard deviation for continuous variables, and number and percentage for categorical variables. Bone mineral density T-scores and Z-scores of the neck of the femur and the lumbar spine were compared across categories of independent variables using Student's t-test or analysis of variance, as appropriate.

Results

Basic demographic and clinical characteristics of the patients are shown in *table 1*. A total of 130 patients were analyzed. Mean age (\pm SD) was 31.9 ± 9.7 years. Sixty three were male and 67 female. Seventy nine of the 130 patients were receiving monotherapy and 51 polytherapy; 71 patients were taking only enzyme-inducers, 28 taking only non-enzyme-inducers and 31 were taking a combination of the two.

The mean duration of treatment with antiepileptic drugs used at the time of the study was 6.63 ± 4.63 years (range 0.5–25 years); 70 had a normal value for body mass index; 12 had a low body mass index and 48 were overweight. The mean BMD of the patients is shown in *table 1*. The Z-score and T-score for the spine were significantly lower

than for the femur ($p = 0.001$ and $p = 0.024$, respectively). Thirty one patients had a T-score below -1.0 at the femoral neck. By contrast, at the lumbar spine 34 patients had a T-score below -1.0. The mean Z-scores were -0.56 ± 1.03 at the lumbar spine and -1.15 ± 1.17 at the femoral neck (*table 1*). The youngest patient with osteoporosis of the femur was a 27-year-old who had been taking combination antiepileptic drugs for 12 years. The youngest with osteoporosis of the spine was 30 years old and had been taking combination antiepileptic drugs for eight years.

At the femoral neck, males had a mean T-score that was not significantly different from the females ($p = 0.222$). There was no significant relationship between T-score and age ($p = 0.241$), body mass index ($p = 0.635$), type of antiepileptic drug (enzyme inducer or non-enzyme inducer) ($p = 0.104$), or duration of therapy ($p = 0.061$). As regards the Z-score for the femoral neck, there was no significant relationship with age ($p = 0.299$), sex ($p = 0.174$), body mass index ($p = 0.639$), duration of therapy ($p = 0.075$), type of antiepileptic drug ($p = 0.098$) or mode of administration of the antiepileptic drugs ($p = 0.133$). At the lumbar spine, the T-score and Z-score showed no significant difference with age, sex, body mass index, duration of epilepsy or type and mode of administration of antiepileptic drug.

Discussion

Ethnic differences in bone mass have been observed in some studies (Gilsanz *et al.* 1998, Wang *et al.* 1997, Nelson *et al.* 1997). We have shown for the first time, to our knowledge, the values for bone density in patients receiving long-term antiepileptic drug treatment in a tropical Asian country. Thailand is a tropical country with all-year sun exposure. All participants lived normal lives. All patients had had fewer than three seizures in the six months prior to the study. About a quarter of the patients (23%) had a BMD (T-score) lower than one SD below normal at the femoral neck, which suggests osteopenia and osteoporosis, and 26% had a BMD T-score lower than one SD at the spine. Pack *et al.* studied epileptic patients aged 19–50 years in the USA and found that 40.2% had osteopenia and 10.3% had osteoporosis, whereas in a healthy population 15.3% were expected to have osteopenia and 0.6% to have osteoporosis (Pack *et al.* 2003). Our study shows a lower prevalence of osteoporosis and osteopenia than Pack *et al.* This difference may be explained by differences in ethnicity, diet, sun exposure, and culture. In our study, the patients who had bone mineral density T-scores below -1 at the left femur had a mean age of 35 ± 8.4 years, and below -1 at the spine of 34 ± 8.4 years. This finding might suggest a greater risk of future osteoporotic fractures in later life.

Table 1. Bone mineral density and chemical data by demographic and treatment categories.

Variable	Frequency N (%)	Calcium	Phosphorus	Hip		Spine	
				Z	T	Z	T
Overall	130 (100%)	9.38 ± 0.45	3.56 ± 0.87	-0.15 ± 1.17	-0.19 ± 1.12	-0.56 ± 1.03*	-0.30 ± 1.27*
gender							
Male	63 (48.46)	9.47 ± 0.44	3.31 ± 0.63	-0.01 ± 1.15	-0.15 ± 1.29	-0.60 ± 1.23	-0.56 ± 1.34
Female	67 (51.54)	9.31 ± 0.44	3.81 ± 0.90	-0.28 ± 0.88	-0.25 ± 0.93	-0.53 ± 1.10	-0.04 ± 1.15
Age (years)							
15-25	38 (29.23)	9.50 ± 0.47	3.79 ± 0.78	-0.17 ± 1.00	0.13 ± 1.15	-0.82 ± 1.06	-0.45 ± 0.89
26-35	44 (33.85)	9.33 ± 0.45	3.49 ± 0.53	-0.32 ± 1.04	-0.30 ± 1.13	-0.46 ± 0.99	-0.25 ± 1.21
36-45	35 (26.92)	9.36 ± 0.42	3.60 ± 1.25	0.00 ± 1.10	-0.19 ± 1.12	-0.45 ± 1.53	-0.22 ± 1.56
46-50	13 (10.00)	9.35 ± 0.41	3.08 ± 0.68	0.10 ± 0.83	-0.40 ± 1.04	-0.40 ± 0.85	-0.46 ± 1.23
BMI (kg/m²)							
< 18.5	12 (9.23)	9.44 ± 0.40	3.57 ± 0.64	-0.44 ± 0.98	-0.61 ± 1.01	-0.75 ± 1.18	-0.99 ± 0.76
18.5-22.9	70 (53.85)	9.39 ± 0.44	3.68 ± 1.04	-0.11 ± 1.19	-0.32 ± 1.23	-0.47 ± 1.32	-0.51 ± 1.43
> 23	48 (36.92)	9.38 ± 0.47	3.40 ± 0.61	-0.12 ± 0.79	0.06 ± 0.94	-0.63 ± 0.91	0.13 ± 0.99
Duration of epilepsy (years)							
< 1	7 (5.39)	9.41 ± 0.47	3.54 ± 0.76	0.14 ± 0.31	-0.20 ± 0.80	-0.84 ± 1.01	-0.50 ± 0.63
2-5	23 (17.69)	9.53 ± 0.31	3.68 ± 0.78	0.29 ± 1.25	-0.03 ± 1.29	-0.69 ± 1.62	-0.36 ± 1.83
6-10	24 (18.46)	9.42 ± 0.50	3.63 ± 0.74	-0.23 ± 1.02	-0.21 ± 1.06	-0.50 ± 0.98	-0.36 ± 1.17
> 25	76 (58.46)	9.33 ± 0.46	3.51 ± 0.95	-0.23 ± 1.00	-0.23 ± 1.13	-0.51 ± 1.08	-0.26 ± 1.22
Type of AED							
EIAED	71(54.61)	9.34 ± 0.42	3.47 ± 0.66	-0.14 ± 0.98	-0.18 ± 1.13	-0.64±1.07	-0.44 ± 1.24
Non-EIAED	28(21.54)	9.68 ± 0.39	3.59 ± 0.78	0.17 ± 1.17	0.11 ± 1.17	-0.42±1.46	0.16 ± 1.28
Combination	31(23.85)	9.25 ± 0.44	3.76 ± 1.28	-0.43 ± 0.98	-0.50 ± 1.01	-0.49±1.09	-0.37 ± 1.28
AED treatment							
Monotherapy	79 (60.77)	9.41 ± 0.43	3.51 ± 0.68	-0.02 ± 1.03	-0.07 ± 1.14	0.57 ± 1.22	-0.24 ± 1.32
Polytherapy	51 (39.23)	9.35 ± 0.47	3.65 ± 1.11	-0.32 ± 1.01	-0.38 ± 1.07	-0.55 ± 1.09	-0.39 ± 1.21

Bone mineral density depends on many factors, one of which is age. However, in our patients there was no correlation between age and BMD.

We have demonstrated that BMD of the spine had a lower T-score than that for the femur ($p = 0.024$), in contrast with the findings of Farhat *et al.* (2002), who showed no significant difference between spine, hip and total BMD. Again, Petty *et al.* in twin pairs, showed no significant differences between lumbar spine, hip and femur (Petty *et al.* 2005). There are several theories explaining how antiepileptic drugs might cause decreased bone mineral density. Some studies have suggested that antiepileptic drugs (phenytoin, carbamazepine, phenobarbital) induce cytochrome p450 enzyme activities, which accelerate vitamin D catabolism, resulting in hypocalcemia, increased bone turnover and loss of cortical bone leading to osteopenia or osteoporosis (Ecevit *et al.* 2004), but another study showed a conflicting result (Sheth 2002). Our cases had normal

serum calcium, and 13 patients had slightly low serum phosphatase (2.1-2.6 mg), among whom 10 were taking enzyme inducers, two a combination and one a non-enzyme inducer. A non-enzyme-inducing antiepileptic drug (valproate) was reported to induce a decrease in bone mineral density, but there is no association between BMD changes and parathyroid hormone (PTH) (Christiansen *et al.* 1973). Other mechanisms include a direct effect of antiepileptic drugs on bone cells, impairment of calcium absorption, inhibition of response to PTH, secondary hyperparathyroidism and calcitonin deficiency. It is hypothesized that valproate-induced bone loss is mediated by the resorption activity of bone rather than by formation abnormalities (Sato *et al.* 2001). Our study analyzed the effect of antiepileptic drugs, enzyme-inducers ($n = 73$), non-enzyme inducers ($n = 26$) and combinations ($n = 31$). All three groups showed a decrease in Z-score below 0 at the lumbar spine. The enzyme-inducer drugs should lower

BMD more than the combination and non-enzyme-inducer drugs, however, the differences were not significant ($p = 0.53$).

There are several data in the literature comparing bone density in patients receiving monotherapy and polytherapy. Our study, which involved a larger sample size than previous studies and which was designed to identify risk factors for low bone density, suggests that polytherapy and monotherapy may not differ in their activity, either at the lumbar spine or at the femur. Farhat *et al.* studied 71 adults and children and found antiepileptic use and duration of antiepileptic drug treatment to be significantly associated with low BMD (2002). We included 130 patients who had been taking antiepileptic drugs more than six months. The mean duration of treatment was 6.63 years ($SD \pm 4.63$, range 0.5-25 years). Surprisingly, our findings showed no significant correlation between the duration of treatment and BMD. Similarly, in a case-control study by Stephen (1999), the duration of treatment was not an independent factor for reduction in BMD.

An important limitation of our study is the lack of vitamin D measurements. It has been suggested that antiepileptic drugs enhance vitamin D catabolism, *e.g.* via the induction of the cytochrome P450 system (Pascucci *et al.* 2005). However, studies of the role of vitamin D in patients receiving antiepileptic drugs have yielded conflicting results (Kim *et al.* 2007, Andress *et al.* 2002, Verrotti *et al.* 2000, Verrotti *et al.* 2002). Brämsswing *et al.* have found that seasonal variations in vitamin D levels are in line with the seasonal fluctuations in vitamin D status (Brämsswing *et al.* 2003). Homocysteine has also been suggested as a mechanism of bone loss in epilepsy (Elliott *et al.* 2007). In future research, we plan to investigate the relationships between vitamin D levels, PTH, homocysteine levels and bone mineral density in ambulatory epileptics. □

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