

Bone Health in Patients with Epilepsy: A Community-based Pilot Nested Case–control Study

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Abstract

Background: Antiepileptic drugs (AEDs) adversely affect bone health and there are reports describing association of alternations of bone and mineral metabolism in epileptic patients. **Objectives:** This study was undertaken to evaluate the bone profile (bone mineral parameters and bone mineral density [BMD]) of patients with epilepsy and compare them to their age-, gender-, and socioeconomic status-matched healthy controls in a community. **Materials and Methods:** This was a nested case–control study conducted in fifty individuals, which included 25 cases (age above 18 years and on AEDs for at least 3 years) for which 25 controls were selected from the same community. Bone mineral parameters (serum calcium, proteins, phosphorous, alkaline phosphate, parathyroid hormone, and Vitamin D) and BMD were measured. **Results:** There was significant hypocalcemia ($P = 0.003$), hypoproteinemia ($P = 0.014$), hyperparathyroidism ($P = 0.048$), and increased levels of serum alkaline phosphatase ($P = 0.019$) in cases as compared to controls. The difference was insignificant in the serum levels of Vitamin D and phosphorous among both the groups. Vitamin D was significantly low in female patients as compared to males ($P = 0.043$). There was no significant difference in BMD at the lumbar spine and femur neck among both the groups. Mean duration of epilepsy was longest in patients with osteoporosis (23.6 years), and increasing duration of epilepsy was associated with reduction in age- and sex-corrected total BMD mean Z-score anteroposterior spine. There was negative correlation between cumulative drug load and T-score of patients with epilepsy. **Conclusion:** Patients on long-term AED treatment have altered bone profile as evident from biochemical parameters and reduced BMD. There is a need for more extensive research and that too on a larger sample size.

Keywords: Antiepileptic drugs, bone mineral density, bone mineral parameters

INTRODUCTION

Epilepsy is a major health problem in developing countries and is the second most common neurological disorder after headache in India.^[1] The prevalence of active epilepsy is estimated to be between 6.2 and 7.6/1000 population in developed countries and 5–10/1000 population in resource-poor countries.^[2] There are very few incidence studies from India, and the most recent one suggests an age-standardized incidence rate of 27.3/100,000 per year.^[3] The mainstay of treatment of epilepsy is long-term antiepileptic drugs (AEDs), often for a long duration. The use of AEDs has acute and chronic adverse effects that have considerable impact on the quality of life of people with epilepsy.^[4] A large body of evidence indicates an association between AEDs and bone abnormalities ranging from disorders of bone mineral metabolism to decrease in bone mineral density (BMD) to an increased fracture risk.^[5,6] It has been

seen that the fracture risk is 2–6 times greater in people with epilepsy compared with the general population.^[7]

AEDs have been identified as an independent risk factor for low bone density and secondary osteoporosis.^[8] The chronic treatment regime and polytherapy in epilepsy compromises bone mass. Other risk factors include female gender, postmenopausal status, sedentary lifestyle, smoking, excessive alcohol intake, inadequate sun exposure, intestinal malabsorption, liver disease, anorexia nervosa, hyperthyroidism, and hyperparathyroidism and some medications such as glucocorticoids, chemotherapeutics, and anticoagulants like heparin, etc.^[9] The various possible

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mechanisms of AED-related bone disease include hepatic induction of cytochrome P450 enzymes leading to increased metabolism of Vitamin D, direct action of AEDs on osteoblasts, impaired calcium absorption, inhibition of response to parathyroid hormone (PTH), hyperparathyroidism, reduced reproductive sex organs activity, and reduced Vitamin K.^[10] The most common biochemical abnormalities that occur are hypocalcemia, hypophosphatemia, elevated serum alkaline phosphatase, and reduced serum levels of biologically active Vitamin D metabolites and hyperparathyroidism.^[10,11] The effect of AEDs on the bone can also be modified by a number of factors like exposure to sunlight and poor dietary intake of calcium and Vitamin D.^[12] Although few of the studies present conclusive evidence, most of the studies have found some association between the use of AEDs and low BMD. This study was undertaken to evaluate the bone profile (biochemical and radiological) of patients with epilepsy and compare them to their age-, gender-, and socioeconomic status-matched healthy controls in a community.

MATERIALS AND METHODS

This was a nested case-control study conducted in fifty individuals who visited the urban health centre of a Tertiary Care Medical College, in Ludhiana, an industrial city in Punjab in Northwest India. The study was carried out after approval from the institutional ethics committee.

Selection of cases and controls: in the study area, there were a total of 114 patients with epilepsy who attended neurology clinic and underwent epileptological assessment by a neurologist. After obtaining informed consent, out of these 114 patients, we selected those 25 cases for which an age-, gender-, and socioeconomic status-matched healthy controls (with no known neurological disorder or history of seizures or epilepsy) were available from the same community. Patients of age more than 18 years and on AED treatment for at least 3 years were included in the epilepsy group. On the same day of the interview, blood samples were collected for measurement for various biochemical tests, and at the same visit, BMD measurements of the lumbar spine and femur were done using dual energy X-ray absorptiometry (DEXA) scan. Individuals not consenting for giving blood sample, having nonepileptic seizures and those unable to understand the implications of the consent were excluded.

The socioeconomic status of the consenting individuals was calculated using the scale provided by the office of economic advisor, Department of Industrial development, Ministry of Industries, Government of India. Information recorded in the pro forma included the patient's demographic profile, age at diagnosis, duration of epilepsy, seizure semiology, history of any surgery, substance abuse, and a detailed history of AED treatment.

Biochemical measurements

Fifteen milliliters of peripheral venous blood was withdrawn under aseptic conditions and was used for estimation of serum

calcium, phosphorus, alkaline phosphate (ALP), and serum proteins. These were analyzed by Cobas 6000 autoanalyzer by Roche kits. Fresh, clear, and unhemolyzed samples were used. The serum was separated in a refrigerated centrifuge at 4°C and stored at -20°C until analysis for the estimation of 25-hydroxyvitamin D (25(OH)D) and PTH. For estimation of levels of 25(OH)D and PTH, immunoassay analyzer Cobas e411 was used. The equipment was precalibrated and used the electroluminescence technology. The minimum detection limit for PTH was 1 pg/ml (normal range 15–65 pg/ml) and for 25(OH)D was 5 ng/ml with measuring range of 3–70 ng/ml. The preferred level for 25(OH)D is recommended to be ≥ 30 ng/ml. In this protocol, vitamin D deficiency was defined by serum levels of 25(OH)D < 20 ng/ml. Insufficiency was defined as 25(OH)D between 20 and 30 ng/ml.

Bone mineral density

BMD was measured by Lunar Prodigy Advance densitometer using DXA software enCORE™ 2007 version 11.40.004, General Electric using DEXA. BMD is calculated from bone mineral content and area of bone scanned (g/cm^2). The results are reported in terms of T-scores or Z-scores.

Amount of AEDs used was semi-quantified by defining cumulative drug load. It was calculated as total duration of epilepsy multiplied by the current number of AEDs the patient was taking. This surrogate measure of cumulative AED load was used because no standard measure for chronic treatment with multiple drugs during many years was available.^[13]

Statistical analysis

The bone profile of the epileptic patients was compared with that of controls using unpaired *t*-test and Chi-square test. The values are presented as means \pm standard deviation (SD) and described as statistically significant at $P < 0.05$.

RESULTS

A total of fifty individuals who consented for the study were evaluated during the study which included 25 pairs of patients with epilepsy and 25 age-, gender-, and socioeconomic status-matched controls (1:1). The mean age (\pm SD) of the patients was 37.7 ± 13.9 years. The mean BMI of patients was $21.75 \text{ kg}/\text{m}^2$. Fifty-six percent in epilepsy group and 44% in control group were below matriculation. Socioeconomic status was comparable between two groups with 76% of patients belonging to lower middle class.

In the epilepsy group, generalized tonic-clonic seizure was the most commonly observed semiology (44%). At the time of the study, 32% of patients were on monotherapy in which carbamazepine was the commonly used AED, and 68% of the patients were on multiple drug regimens using combination of phenytoin and phenobarbitone most frequently. Further drug evaluation showed that 76% of people were taking only enzyme-inducing AEDs (EIAEDs), 12% only nonenzyme-inducing drugs (NEIAEDs), and 12% taking both. For assessing the risk factors for osteoporosis, out of the

15 male patients, 9 had positive history of substance abuse in which alcohol and tobacco (smoking) were among the most commonly abused substances [Table 1].

Biochemical measurements

The results of biochemical measurements of the cases compared to the control group are shown in Table 2. There was significant hypocalcemia, hypoproteinemia, hyperparathyroidism, and increased levels of serum alkaline phosphatase in patients with epilepsy as compared to the age-, gender-, and socioeconomic status-matched controls. The difference was insignificant in the serum levels of Vitamin D and phosphorous among both groups. 25(OH)D deficiency (<20 ng/ml) was seen in 84% ($n = 21$) in both epilepsy and control group, 25(OH)D insufficiency (20-30 ng/ml) in 16% ($n = 4$) in epilepsy group compared to 12% ($n = 3$) in control group and 25(OH)D preferred level (>30 ng/ml) in 4% ($n = 1$) in control group. Furthermore, it was seen that 25(OH)D was significantly low in female patients as compared to males ($P = 0.043$). In the epilepsy group, mean serum level of PTH was 63.3 ± 38.08 pg/ml and was significantly higher than the control group ($P = 0.048$). When the patients were divided into tertiles of PTH: ([a] PTH >60 [$n = 11$], [b] 30–60 [$n = 13$], [c] <30 [$n = 1$]), it was observed that patients in the highest tertiles had lower levels of serum calcium ($P = 0.047$).

Bone mineral density

The mean BMD in both the groups is shown in Table 3. It is reported at the region of the lumbar spine and femur neck as g/m^2 . BMD evaluation using DEXA scan showed osteoporosis in 20% ($n = 5$) and osteopenia in 40% ($n = 10$) in the cases as compared to 4% ($n = 1$) osteoporosis and 56% ($n = 14$) osteopenia in control group ($P = 0.189$).

On comparison of the bone profile of patients taking EIAEDs with those taking non-EIAEDs, no significant difference was seen in biochemical parameters except for serum ALP which was significantly higher in patients on EIAEDs ($P = 0.05$). With DEXA scan, 16% of the patients had osteoporotic BMD and 47% had osteopenia in the patients on EIAEDs as compared to 67% of osteopenia in the patients taking NEIAEDs.

Mean duration of epilepsy was longest in patients with osteoporosis (23.6 years) than in patients with osteopenia (19.4 years) and 12.7 years in patients with normal BMD. There was significant difference ($P = 0.059$), when patients with normal BMD and those with osteoporosis were compared in relation to duration of epilepsy. It was observed that increasing duration of epilepsy was associated with reduction in age- and sex-corrected total BMD mean Z-score anteroposterior (AP) spine ($n = 25$, $r^2 = 0.162$) [Figure 1].

Cumulative drug load was calculated as total duration of epilepsy multiplied by the current number of AEDs; the patient was taking at the time of study. It was observed that the patients with osteoporosis have the highest cumulative drug load followed by those with osteopenia and normal BMD, i.e.,

Table 1: Demographic details of cases

Characteristics	Values
Age, years (mean±SD)	37.7±13.9
Gender (%)	
Male	15 (60)
Female	10 (40)
Socioeconomic group	76% in lower middle class
Age of onset of epilepsy, years (mean±SD)	19.24±11.75
Duration of epilepsy, years (mean±SD)	17.54±11.26
Monotherapy, n (%)	8 (32)
Polytherapy, n (%)	17 (68)
EIAED, n (%)	19 (76)
NEIAED, n (%)	3 (12)
EIAED and NEIAED, n (%)	3 (12)
Smokers	4
Alcoholics	5

NEIAED = Nonenzyme inducing anti-epileptic drug, SD = Standard deviation

Table 2: Biochemical evaluation: Cases versus controls

Biochemical parameter (normal range)	Mean±SD		P
	Cases	Controls	
Serum calcium (8.6-10.2 mg/dL)	9.3±0.54*	9.7±0.39	0.003
Serum phosphorous (2.7-4.5 mg/dL)	3.4±0.50	3.5±0.67	0.264
Serum proteins (6.6-8.7 g/dL)	7.2±0.52*	7.6±0.43	0.014
Serum alkaline phosphatase (40-129 U/L)	102.2±27.77*	85.5±20.42	0.019
Serum Vitamin D (30-80 ng/mL)	12.3±5.9	13.2±7.24	0.614
Serum PTH (15-65 pg/mL)	63.3±38.08*	46.7±14.58	0.048

* $P < 0.05$ is considered significant. SD = Standard deviation, PTH = Parathyroid hormone

Table 3: Bone mineral density with Z-score and T-score of the lumbar spine and femur in cases and controls

Site	Mean±SD		P
	Cases	Controls	
BMD lumbar spine (g/m^2)	1.08±0.14	1.09±0.10	0.73
BMD femur neck (g/m^2)	0.91±0.15	0.95±0.09	0.29
Z-score AP spine	-0.95±1.10	-0.83±0.85	0.667
Z-score femur neck	-0.51±1.01	-0.23±0.69	0.253
T-score AP spine	-1.07±1.20	-0.97±0.87	0.737
T-score femur neck	-1.08±1.14	-0.84±0.73	0.373

SD = Standard deviation, BMD = Bone mineral density, AP = Anteroposterior

there was negative correlation between cumulative drug load and T-score of patients with epilepsy [Figure 2].

DISCUSSION

This is the first such study to the best of our knowledge from northern India which looked into changes in bone metabolic

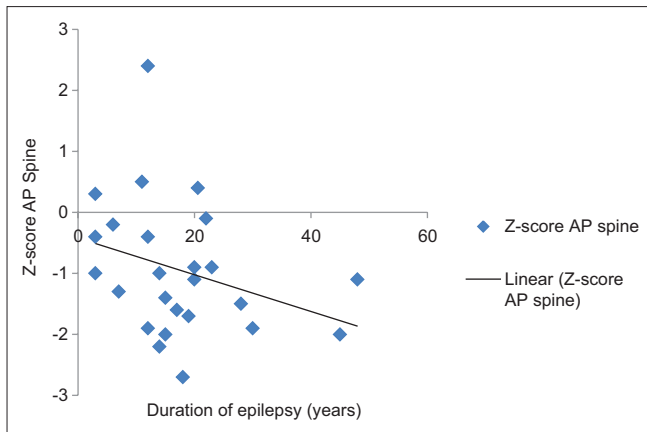


Figure 1: Increasing duration of epilepsy associated with reduced z-bone mineral density

parameters and bone density in patients who were on antiepileptic therapy. Among users of AEDs, we observed significant hypocalcemia, hypoproteinemia, hyperparathyroidism, and increased levels of serum alkaline phosphatase when compared to their age-, gender-, and socioeconomic status-matched controls. In his study, Pack reported that hypocalcemia affects between 3% and 30% of persons with epilepsy receiving AEDs.^[14] In the present study, 8% of the AED users had serum calcium below normal range although there were no significant differences in serum phosphorus and Vitamin D levels between a control group and AED users.

Several theories on the mechanism of AED-associated bone disease have been proposed, but no single one explains all the reported findings. The most common explanation is that AEDs such as carbamazepine that induce hepatic cytochrome P450 enzymes cause increased conversion of Vitamin D to inactive metabolites in the liver microsomes. The decreased biologically active Vitamin D leads to decreased absorption of calcium in the gut, resulting in hypocalcemia and an increase in circulating PTH.^[11] Hyperparathyroidism leads to increased bone resorption and ultimately reduced BMD and increased fracture risk.^[15,16] Further insight was gained when those taking EIAEDs were specifically analyzed and compared to those on NEIAEDs. Only significant difference was found in levels of serum ALP that was found raised in the patients on EIAEDs ($P < 0.05$), with not much difference in other parameters. Hence, these results suggest that AEDs may affect the bone metabolism through some other mechanisms in addition to enzyme induction.

As 25(OH)D deficiency is very common in the general population, it is difficult to demonstrate that AED use specifically plays a role in the Vitamin D deficiency. In a study by Menon, it was observed that serum 25(OH)D levels declined from 29 ± 1.3 – 17.2 ± 1.6 ng/ml ($P < 0.001$) within 6 months of initiation of AED therapy.^[17] In the present study, the mean 25(OH)D level in the cases was 12.3 ± 5.90 ng/ml and in the control group was 13.26 ± 7.24 ng/ml; the difference between the two was nonsignificant. Narang *et al.* in his study conducted

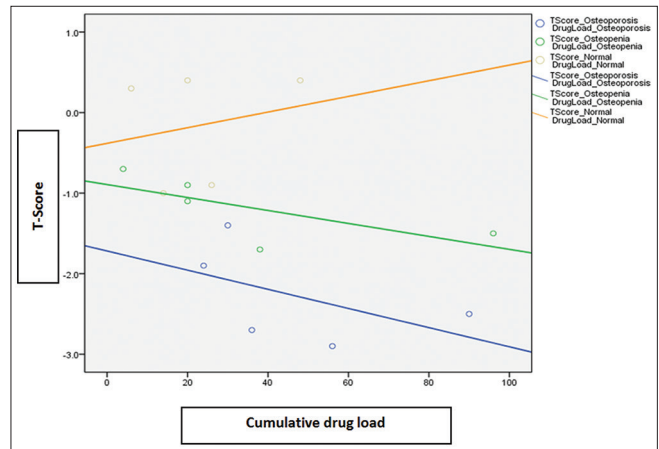


Figure 2: Cumulative drug load and T-score

in North India found mean 25(OH)D levels in healthy controls, 29.5 ± 7.17 ; in osteoporotic patients 22.6 ± 5.75 .^[18] Hence, in our study, mean 25(OH)D level in both patient and control group was far below the normal range. Therefore, 25(OH)D deficiency in persons with epilepsy may be due to baseline high rates in the general population or to other accepted etiologies rather than due to AED use.

The study by Krishnamurthy *et al.* documented that serum biochemical changes which may predispose the subjects to development of osteomalacia appear within 3 months of starting AED monotherapy. It suggested that simultaneous coadministration of calcium and 25(OH)D in recommended daily allowance dosage may be beneficial in limiting the changes in calcium and Vitamin D metabolism in patients on AEDs.^[19]

Kulak *et al.* in a cross-sectional study measured BMD at the lumbar, femur, and forearm and reported osteopenia and osteoporosis in 53.4% and 10.3% patients, respectively.^[20] Lado *et al.* measured the BMD of patients who had received AEDs for more than 3 years and found osteopenia in 39% and osteoporosis in 16% of the patients.^[21] This prevalence of low BMD is in concordance to findings of our study with 40% osteopenia and 20% osteoporosis in patients with epilepsy taking AEDs for more than 3 years. In the present study, the BMD was lower in patients on AEDs in the lumbar spine and femur neck region as compared to the controls, but this difference was not significant. However, Koshy *et al.* found significantly reduced BMD at the femur neck region in patients on AEDs for more than 6 months.^[22]

Sheth *et al.* in his study found that increasing duration of epilepsy was associated with a progressive reduction in BMD compared to controls.^[23] In the present study, also, it was observed that increasing duration of epilepsy was associated with reduction in age- and sex-corrected total BMD mean Z-score AP spine. Cumulative drug load, a surrogate parameter independent of the type of AEDs used, provides a strong association between long-term treatment with multiple AEDs and osteoporosis.^[13] In this study, we observed that the

patients with osteoporosis have the highest cumulative drug load followed by those with osteopenia and normal BMD, i.e., there was negative correlation between cumulative drug load and T-score of patients with epilepsy.

Further research is needed to elucidate the biological mechanism of AEDs that alters the bone profile and contribute to osteoporosis. At present, treatment decisions lie with the individual clinician, using the available medication options for treating bone disease, including calcium and Vitamin D supplementation, etc. Such therapeutic maneuvers are likely to avoid fractures in the future.

CONCLUSION

In this nested case-control study, we observed that patients with epilepsy taking AEDs for more than 3 years have altered bone profile as evident from biochemical parameters and reduced BMD at the femur neck and lumbar spine region. The accumulated evidence shows that there is a need for more extensive research and that too on a larger sample size.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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