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# How safe is bone health in patients on newer or enzyme inhibitor antiepileptic drugs?

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## ARTICLE INFO

## ABSTRACT

*Background:* Data on the effect of enzyme inhibitors and newer anti-epileptic drugs (AEDs) on bone health is limited with conflicting results.

*Aim:* We compared the effects on bone health of patients exposed to enzyme inducer versus enzyme inhibitor AEDs and newer versus older AEDs.

*Methods:* We prospectively studied 51 patients on AEDs for more than two years and equal age and sex matched controls from March 2017 to September 2018. Biochemical bone mineral markers and bone mineral density (BMD) were measured and analysed between patients versus controls and between various sub-groups based on enzymatic effect, generation and number of AEDs.

*Results:* Of 51 patients,11(21.5%) had osteopenia and 3(5.9%) had osteoporosis. T-score ($-0.75 \pm 1.22$ versus $0.004 \pm 1.0$, $p < .001$) and Z-score at femur neck ($-0.38 \pm 1.08$ versus $0.002 \pm 0.81$, $p < .001$) were found to be significantly lower in patients compared to controls. Relative risk for low BMD was higher in patients on polytherapy compared to monotherapy (RR = 1.37,CI = 0.69–2.74).Higher relative risk for low BMD was noted with; clobazam (RR = 1.51,CI = 0.82–2.78), oxcarbazepine (RR = 1.33,CI = 0.68–2.59), phenobarbitone (RR = 1.31,CI = 0.26–6.7) and leviteracetam (RR = 1.18,CI = 0.45–3.06) mono or polytherapy and valproate monotherapy (RR = 3.5,CI = 1.09–11.29). No significant difference was noted with regards to mean dosage or metabolic or radiological markers of bone health between patients on enzyme inducer versus inhibitors and newer versus older AEDs. A significant negative correlation was found between cumulative drug load and femur T-score (r2 = $-0.27$, p = .04).

*Conclusion:* Bone health in epilepsy is adversely affected by chronic exposure to AEDs; irrespective of the enzymatic effect or generation of AEDs. Complex pharmacodynamic mechanisms of AEDs as well as pharmacokinetic interactions between various AED polytherapies affects bone health.

## 1. Introduction

Epilepsy is one of the most common neurological diseases affecting nearly 50 million people worldwide, with nearly 80% living in low and middle-income countries and more than half of cases beginning in childhood [1]. The prevalence of epilepsy in India is reported to be 5.59/1000 population [2] and a most recent study regarding incidence suggests an age adjusted incidence rate of 27.3/100,000 per year [3].Most patients require therapy with antiepileptic drugs (AEDs) for years, sometimes lifelong [4]. AEDs are found to be associated with significant effects on bone metabolism leading to decreased bone mineral density (BMD), altered bone turnover, and increased fracture risk [5–8].AEDs, particularly enzyme inducing drugs are known to increase catabolism of 25-hydroxyvitamin D3 by inducing hepatic P-450 enzyme system, leading to decreased dietary calcium absorption, increased parathyroid hormone (PTH) levels, and resultant low BMD [9,10]. However, few studies have shown that non-enzyme-inducing AEDs can also cause significant reduction in BMD [11,12]. The literature on the effect of newer AEDs on bone metabolism is limited with conflicting results.

Most studies on bone health in epilepsy are limited by small populations, biased subject selection, lack of control population and being cross sectional, complicating their interpretation [13]. Also, very little is known about the effect of enzyme inhibitors and newer AEDs as compared to older ones.

With this background, we undertook this study with the following objectives:

i) To assess the effects of AEDs on BMD and bone metabolism.
ii) To compare the effects on bone health between patients exposed to enzyme inducer versus enzyme inhibitor AEDs.
iii) To assess whether newer AEDs are safer than older AEDs with regards to effect on bone health.

## 2. Materials and methods

### 2.1. Study design and subjects

This hospital based prospective case-control study was conducted over one year from March 2017 to September 2018 at a tertiary care referral centre for epilepsy in India.

Patients > 18 years of age exposed to AEDs for at least two years who were seen in the outpatient department or admitted for video-telemetry consecutively and appropriate age and gender matched controls were included. We excluded subjects having psychogenic non-epileptic seizures, non-ambulant or on assisted ambulation, type I diabetes, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition or malabsorption, chronic liver disease, chronic kidney disease and patients who were already on calcium or vitamin D supplementation.

Informed consent was obtained from all participants. The Institutional Ethics Committee approved the study. All relevant data including demographic profile, socio-economic status, age at diagnosis, duration of epilepsy, epilepsy classification as per ILAE [14], treatment history, with dose and duration of AED exposure over the past six months were collected according to a structured proforma. A composite score for socioeconomic status (CSES) was arrived at for each participant by summing the 5 individual scores: education, occupation of the individual as well as their spouse/parent and their family income; with the lowest possible score being 5 and the highest being 50 (higher score indicating better socioeconomic status).

### 2.2. Biochemical measurements

Blood samples were collected for various biochemical tests of bone metabolism which included serum calcium, phosphorus, alkaline phosphate (ALP), 25-hydroxyvitamin D3 [25(OH)D3], serum calcitonin and parathyroid hormone (PTH) levels. Serum levels of calcium, phosphorus and ALP were analysed by Cobas, Integra 400plusauto-analyzer by Roche kits. Immunoassay analyzer Cobas e411 was used for estimation of levels of 25(OH)D3 and PTH. The equipment was pre-calibrated and used the electroluminescence technology.

### 2.3. Dual energy X-ray absorptiometry

BMD measurements of the lumbar spine and femur were performed using dual energy X-ray absorptiometry (DEXA) scan. Lunar prodigy advance densitometer was used to measure BMD using DXA software enCORE™ 2007 version 11.40.004. Bone mineral content and area of bone scanned ($g/cm^2$) are used to calculate BMD. BMD results were expressed in the form of T score or Z-score which are defined as the difference in number of standard deviations (SDs) from the mean BMD of a normally distributed, healthy adult reference population [14]. Z-score = T-score - Reference T-score. T score or Z-score above −1 was considered normal, a score between −1 and −2.5 was classified as

osteopenia, and a score below −2.5 was classified as osteoporosis [15].All DEXA scans were interpreted by a Senior Research Fellow(AC) having radiological expertise.

### 2.4. Exposure to AED(s)

Semi-quantification of AED(s) used was done using cumulative drug load which is defined as total duration of epilepsy multiplied by the current number of AEDs the patient was taking [16]. The highest dose of a drug (milligrams per day) that was used anytime i.e. prescribed daily dose(PDD) was taken as the exposure for that drug. To make comparisons between various AEDs, we also described the dose as a ratio of PDD to daily defined dose(DDD). The DDD as defined by the World Health Organization was the assumed average maintenance dose per day for a drug used for its main indication in adults [17]. The total exposure in dual therapy was calculated as the sum of the PDD/DDD for each of the AEDs used at any point of time.

### 2.5. Generation of AED(s)

AEDs belong to the first-generation were considered as "older AEDs" and AEDs belonging to second and third generation were considered as "newer AEDs".First-generation AEDs refer to those drugs in use or approved for use by the US FDA before 1993; second-generation AEDs are those approved between 1993 and 2007; and the most recent AEDs, approved after 2008, are referred to as third-generation AEDs [18].

### 2.6. Statistical analysis

The data was analysed with the help of SPSS Statistics for Windows Statistics version 21.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to summarize the demographic and clinical data. For quantitative variables and categorical variables, student *t*-test and Chi-square test, were used respectively to assess statistical significance. Pearson's test was used to assess correlation between various parameters and bone health.A *p*-value of < 0.05 was considered statistically significant. With regard to relative risk, a 95% confidence interval (CI) > 1 was considered statistically significant.

## 3. Results

### 3.1. Demographic profile of patients and controls

A total of 51patients with epilepsy satisfying the inclusion criteria were evaluated during the study period. The mean age of the cohort was 32 ± 13 years (range 19–70 years). There were 34 males (66%) and 17 females (34%). No significant age difference (p = .43) was noted between males (mean 34 ± 16 years, range 20–67 years) and females (mean 30 ± 17 years, range 18–70 years). The mean body mass index was 18.7 ± 11.1 (range 15–38) and CSES was 24.1 ± 8.9 (range 11–50). Vegetarian diet was consumed by seven patients (14%) and the rest 44 consumed a mixed diet (86%). 51 controls having no significant difference with regards to the above mentioned parameters were included for comparison, see Table 1 for details.

### 3.2. Comparison of bone health between patients and controls

We found that 37 (72.5%) patients had normal BMD,11 (21.5%) had osteopenia and 3(5.9%) patients had osteoporosis.

On comparing the biochemical and radiological markers of bone health between patients and controls (Table 1), serum vitamin D3 levels (15.99 ± 10.55 versus19.9 ± 9.50, p = .03), calcitonin levels (3.1 ± 2.7 versus6.9 ± 1.8, p < .001);T-score (−0.75 ± 1.22 versus0.004 ± 1.0, p ≤ .001)and Z-score (−0.38 ± 1.08 versus 0.002 ± 0.81, p = .04) in femur neck were found to be significantly lower in patients compared to age and gender matched controls (Fig. 1).

**Table 1**
Comparison of demographic profile, baseline characteristics and bone health between patients and controls.

| Clinical parameter | Patients | Controls | p Value[a] |
|---|---|---|---|
| Age in years (mean ± SD) | 19–70 (32 ± 13) | 18–62 (29 ± 12) | 0.23 |
| Gender, n (%) | | | 0.27[b] |
|   Male | 34 (66.6) | 31 (61) | |
|   Female | 17 (33.3) | 20 (39) | |
| Age of males (mean ± SD) | 20–67 (34 ± 16) | 18–68 (31 ± 13) | 0.41 |
| Age of females (mean ± SD) | 18–70 (30 ± 17) | 18–69 (29 ± 14) | 0.85 |
| CSES[d] | 11–50 (24.1 ± 8.9) | 13–50 (25.8 ± 9.5) | 0.36 |
| BMI | 15–38 (18.7 ± 11.1) | 16–42 (19.2 ± 8.9) | 0.80 |
| Diet, n (%) | | | 0.27[b] |
|   Vegetarian | 7 (14) | 5 (10) | |
|   Mixed | 44 (86) | 46 (90) | |
| Serum calcium | 9.4 ± 0.64 | 9.6 ± 0.40 | 0.06 |
| Serum phosphorous | 3.80 ± 0.67 | 3.6 ± 0.68 | 0.14 |
| Serum ALP | 89.74 ± 59.1 | 87.5 ± 21.43 | 0.63 |
| Serum PTH | 51.20 ± 22.70 | 46.8 ± 15.28 | 0.24 |
| Serum Vitamin D3 | 15.99 ± 10.55 | 19.9 ± 9.5 | 0.03 |
| Serum calcitonin | 3.1 ± 2.7 | 6.9 ± 1.8 | < 0.001 |
| Serum TSH | 2.89 ± 1.89 | 3.1 ± 1.7 | 0.56 |
| Femur T-score[c] | −0.75 ± 1.22 | 0.004 ± 1.0 | < 0.001 |
| Femur Z-score[c] | −0.38 ± 1.08 | 0.002 ± 0.81 | 0.04 |

AP-anteroposterior, CSES-composite score for socioeconomic status, n-number, PTH-parathyroid hormone,ALP-alkaline phosphatase,TSH-thyroid stimulating hormone, SD- standard deviation, TSH-thyroid stimulating hormone.

[a] Student t-test.
[b] Chi square test.
[c] See Section 2.3 for definition.
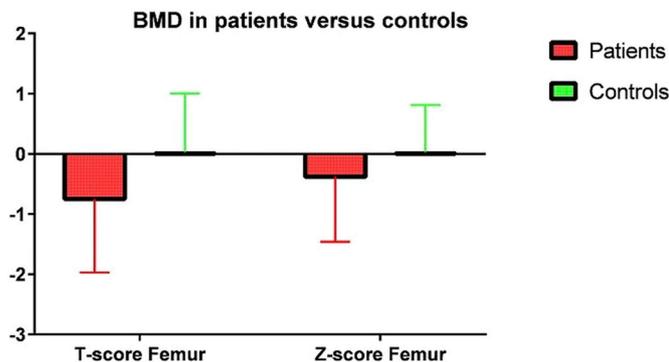[d] See Section…. for details.



**Fig. 1.** Mean T-score (−0.75 ± 1.22 versus0.004 ± 1.0, p < .001)and Z-score at femur neck (−0.38 ± 1.08 versus 0.002 ± 0.81, p < .001) were found to be significantly lower in patients compared to controls.

Rest of the biochemical and radiological parameters did not significantly differ between these two groups.

### 3.3. Clinical profile of patients and AEDs used as mono and polytherapy

The mean age of onset and duration of epilepsy were 16 ± 11 (range 0–63) and 15 ± 9 (range 2–38) years respectively. The mean seizure frequency was 4–7 per month (range 0–30). The mean developmental quotient was 98.43 ± 11.2. The type of epilepsy was focal in 27 patients (53%), generalised in nine (18%) and combined - generalised plus focal onset in 15 patients (29%).

Nine (18%) patients were on monotherapy and 42 (82%) on polytherapy. Valproate, n = 7(78%) was the most commonly used drug as monotherapy; while regimens including combinations of clobazam, n = 34 (68.6%), oxcarbazepine, n = 21 (43.1%) and valproate,

**Table 2**
Clinical profile of patients with epilepsy and AEDs used.

| | |
|---|---|
| Age of onset in years, (mean ± SD) | 0–63 (16 ± 11) |
| Duration in years, (mean ± SD) | 2–38 (15 ± 9) |
| Seizure frequency/month (mean ± SD) | 0–30 (4–7) |
| Developmental quotient | 98.43 ± 11.2 |
| Type of epilepsy | |
|   Focal | 27 (53) |
|   Generalised | 9 (18) |
|   Combined | 15 (29) |

| AEDs used | Enzymatic effect | Monotherapy n = 9 (18%) | Polytherapy n = 42(82%) |
|---|---|---|---|
| Newer n = 42 (84%) | | | |
|   Clobazam | Neutral | | 34 |
|   Lacosamide | Neutral | | 3 |
|   Levetiracetam | Neutral | 1 | 7 |
|   Lamotrigine | Neutral | 1 | 4 |
|   Oxcarbazepine | Inducer | | 21 |
|   Peramapanel | Inducer | | 2 |
|   Rufinamide | Inhibitor | | 1 |
|   Zonisamide | Inhibitor | | 3 |
| Older n = 33 (65%) | | | |
|   Carbamazpine | Inducer | | 7 |
|   Clonazepam | Neutral | | 1 |
|   Phenobarbitone | Inducer | | 3 |
|   Phenytoin | Inducer | | 6 |
|   Valproate | Inhibitor | 7 | 17 |

n-number, SD- standard deviation.

n = 17(33.3%)were the most frequently used polytherapy.

42 (84%) patients were on newer AEDs and 33 (65%) were on older AEDs. Among these in the monotherapy group, two patients (22%) were on newer AEDs and seven (78%) on older AEDs; where as in the polytherapy group, two (4.8%) were on older AEDs, 16 (38.1%) on newer AEDs and 24 (57.1%) on a combination of newer and older AEDs.

32 (62.7%) of people were on enzyme inducer AEDs,25 (49%) on enzyme inhibitor AEDs, 40 (78.4%) on enzyme neutral AEDs.Among these in the monotherapy group, two patients (22%) were on enzyme neutral AEDs and seven (78%) were on older AEDs; where as in the polytherapy group, 18 (42.8%) were on a combination of enzyme inducer plus inhibitor AEDs, 14 (33.3%) on enzyme inducer plus neutral AEDs and 10 (23.8%) on enzyme inhibitor plus neutral AEDs.Details about older and newer enzyme inducer, inhibitor or neutral AEDs used as mono and polytherapy are summarised in Table 2.

### 3.4. Correlation between BMD and biochemical markers of bone health

No significant correlation was noted between any of the biochemical markers analysed in patients and the femur T and Z-scores

**Table 3**
Correlation between BMD and i) onset and duration of epilepsy, AED exposure and developmental status; ii) metabolic markers of bone health.

| AED | Femur T-Score | | Femur Z-Score | |
|---|---|---|---|---|
| | r² | p value | r² | p value |
| Age of onset of epilepsy | −0.04 | 0.81 | 0.74 | 0.01 |
| Duration of epilepsy | −0.25 | 0.11 | −0.35 | 0.27 |
| Developmental quotient | −0.04 | 0.78 | 0.41 | 0.01 |
| Seizure frequency | 0.12 | 0.44 | 0.27 | 0.40 |
| Cumulative drug dosage | −0.26 | 0.04 | −0.37 | 0.12 |
| Vitamin D3 | −0.06 | 0.69 | 0.32 | 0.32 |
| Calcitonin | 0.10 | 0.55 | 0.15 | 0.65 |
| PTH | −0.11 | 0.49 | 0.01 | 0.99 |
| ALP | 0.01 | 0.93 | −0.46 | 0.13 |

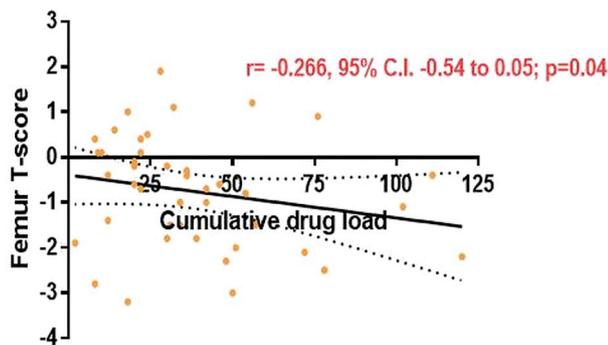r²-Pearson correlation, ALP-alkaline phosphatase, PTH-parathormone.

**Fig. 2.** Correlation between cumulative drug load and femur T-score. Pearson correlation showing significant negative correlation ($r = -0.0266$, 95% C.I. $-0.54$ to $0.05$; $p = .04$) between cumulative drug load and femur T-score.

(Table 3).

### 3.5. Correlation between BMD and age of onset and duration of epilepsy, developmental status and AED exposure

A significant positive correlation was noted between femur Z-score and higher age of onset of epilepsy ($r^2 = 0.74$, $p = .01$) and developmental quotient ($r^2 = 0.41$, $p = .01$). No significant correlation was noted between the seizure frequency or duration of epilepsy and BMD (Table 3).

Taking into consideration the AED exposure in terms of cumulative drug dosage a significant negative correlation (Fig. 2) was noted between cumulative drug load and femur T-score of patients with epilepsy ($r^2 = -0.27$, $p = .04$). There was no significant correlation noted between AED dosage and BMD ($r^2 = 0.03$, $p = .44$).

### 3.6. Comparison of bone health and AED dosage between patients on various AED sub-groups

The overall mean dosage for enzyme inducer AEDs (PDD/DDD ratio: $1.12 \pm 0.53$), was significantly higher than for enzyme inhibitor AEDs ($0.68 \pm 0.44$, $p < .001$); albeit there being no significant dosage between these two groups when used as monotherapy ($1 \pm 0$ for inducers versus $0.68 \pm 0.44$ for inhibitors, $p = .36$). The biochemical and radiological markers of bone health showed no statistical significant difference between these two groups (Table 4).

Comparing patients who were exclusively on older or newer AEDs and mono or polytherapy; no significant difference was noted with regards to mean dosage or metabolic or radiological markers of bone health, except for serum alkaline phosphatase being higher in the polytherapy group ($93.21 \pm 70.37$) compared to monotherapy ($55.33 \pm 21.63$, $p = .006$).

### 3.7. Relative risk of low BMD for AEDs and effect of drug dosage on BMD

Relative risk for low BMD was nearly twice in patients on polytherapy (RR = 1.37, CI = 0.69–2.74) compared to monotherapy (RR = 0.73, CI = 0.37–1.45). Among the various AEDs used; clobazam (RR = 1.51, CI = 0.82–2.78), oxcarbazepine (RR = 1.33, CI = 0.68–2.59), phenobarbitone (RR = 1.31, CI = 0.26–6.7), and levetiracetam (RR = 1.18, CI = 0.45–3.06) had overall higher relative risk for low BMD when used either as mono or polytherapy (Table 5). In the monotherapy group, valproate had a high relative risk (RR = 3.5, CI = 1.09–11.29). In the polytherapy group; clobazam (RR = 1.31, CI = 0.58–2.95), valproate (RR = 1.25, CI = 0.57–2.72), phenobarbitone (RR = 1.23, CI = 0.24–6.37) and oxcarbazepine (RR = 1.13, CI = 0.54–2.34) had higher relative risk for low BMD.

**Table 4**
Comparison of AED dosage and influence of bone health based on status of enzyme, generation and number of AEDs.

| Variable | Enzymatic effect-overall | | | Enzymatic effect-monotherapy | | | Older AEDs (mean ± SD) N = 9 | Newer AEDs (mean ± SD) N = 18 | p value[a] | Monotherapy (mean ± SD) N = 9 | Polytherapy (mean ± SD) N = 42 | p value[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Enzyme inducers (mean ± SD) N = 32 | Enzyme inhibitors (mean ± SD) N = 25 | p value[a] | Enzyme inducers (mean ± SD) N = 2 | Enzyme inhibitors (mean ± SD) N = 7 | p value[a] | | | | | | |
| Total dosage (PDD/DDD)[b] | 1.12 ± 0.53 | 0.68 ± 0.44 | < 0.001 | 1 ± 0 | 0.68 ± 0.44 | 0.36 | 0.56 ± 0.73 | 1.83 ± 0.79 | 0.42 | 0.44 ± 0.53 | 2.21 ± 1.22 | 0.42 |
| Serum calcitonin | 2.67 ± 1.84 | 3.62 ± 3.47 | 0.09 | 3.5 ± 0.71 | 2 ± 1.26 | 0.11 | 2.25 ± 1.28 | 2.94 ± 1.66 | 0.28 | 2.38 ± 1.30 | 3.24 ± 2.87 | 0.18 |
| Serum PTH | 54.03 ± 26.18 | 46.9 ± 15.70 | 0.12 | 56 ± 1.41 | 48.29 ± 16.36 | 0.55 | 46.33 ± 17.36 | 51 ± 22.66 | 0.59 | 50.00 ± 14.58 | 51.45 ± 24.21 | 0.81 |
| Serum Vitamin D3 | 15.09 ± 7.64 | 16.41 ± 12.85 | 0.32 | 11 ± 8.49 | 17.71 ± 21.12 | 0.69 | 20.67 ± 19.24 | 13.06 ± 6.72 | 0.14 | 16.22 ± 18.77 | 15.34 ± 8.18 | 0.89 |
| Serum ALP | 91 ± 36.5 | 90 ± 36.67 | 0.47 | 75 ± 9.99 | 49.71 ± 21.01 | 0.16 | 64.78 ± 43.75 | 83.39 ± 29.58 | 0.21 | 55.33 ± 21.63 | 93.21 ± 70.37 | 0.006 |
| T-score femur[b] | −0.74 ± 1.33 | −0.84 ± 1.25 | 0.39 | −1.45 ± 0.64 | −0.58 ± 1.36 | 0.43 | −0.86 ± 1.44 | −0.36 ± 1.09 | 0.32 | −0.74 ± 1.25 | −0.8 ± 1.24 | 0.89 |
| Z-score femur[b] | −0.37 ± 0.83 | −0.48 ± 1.55 | 0.73 | −0.34 ± 0.89 | −0.38 ± 1.08 | 0.96 | −0.43 ± 0.69 | −0.2 ± 0.66 | 0.68 | −0.36 ± 1.05 | −0.38 ± 1.08 | 0.96 |

ALP-alkaline phosphatase, PDD-prescribed daily dose, DDD-daily defined dose, PTH-parathyroid hormone, SD-standard deviation.
[a] Student t-test.
[b] See Section 2.3 for definition.

**Table 5**
Comparison of relative risk of low BMD for individual AEDs.

| AED | Overall[a] | | Monotherapy | | Polytherapy | |
|-----|------|------|------|------|------|------|
| | RR | C.I. | RR | C.I. | RR | C.I. |
| Clobazam | 1.51 | 0.82–2.78 | | | 1.31 | 0.58–2.95 |
| Oxcarbazepine | 1.33 | 0.68–2.59 | | | 1.13 | 0.54–2.34 |
| Phenobarbitone | 1.31 | 0.26–6.70 | | | 1.23 | 0.24–6.37 |
| Levetiracetam | 1.18 | 0.45–3.06 | | | 0.93 | 0.36–2.41 |
| Carbamazepine | 0.96 | 0.43–2.16 | | | 0.89 | 0.38–2.01 |
| Valproate | 0.89 | 0.47–1.66 | 3.5 | 1.09–11.29 | 1.25 | 0.57–2.72 |
| Lamotrigine | 0.85 | 0.30–2.40 | | | 0.79 | 0.28–2.27 |
| Phenytoin | 0.844 | 0.35–2.06 | | | 0.778 | 0.32–1.91 |
| Lacosamide | 0.625 | 0.26–1.48 | | | 0.577 | 0.24–1.41 |
| Zonisamide | 0.625 | 0.26–1.48 | | | 0.58 | 0.24–1.41 |

[a] 95% confidence interval ( > 1 is statistically significant), C.I.-confidence interval, RR-relative risk.

## 4. Discussion

One of the important co-morbidities associated with epilepsy but is often neglected by the treating Physician or Neurologist, is the effect of chronic anti-epileptic drug usage on bone health. The potential effects of AEDs on bone metabolism are less well known which is illustrated by a survey of 624 neurologists which showed that only 28% were aware that AEDs are associated with reduced bone mass. Prophylactic calcium and vitamin D supplements for their epilepsy patients were prescribed only by 9% of pediatric and 7% of adult neurologists among them [19].

Our study included a heterogeneous cohort of persons with epilepsy exposed to AED mono/polytherapy having diverse mechanisms of action. The main highlights of our study are: i) BMD is lower in patients having chronic exposure to AEDs compared to age and gender matched controls; ii) BMD is negatively correlated with cumulative drug load; independent of AED dosage, generation or enzymatic effect; iii) high risk group includes people having early age of onset of epilepsy, developmental delay and use of polytherapy in general and with certain AEDs like clobazam, levetiracetam, oxcarbazepine, phenobarbitone and valproate. Higher relative risk for low bone density in patients on polytherapy than monotherapy, has been previously reported in few previous studies [16,20,21].The observations from our study, in comparison with previous reports are summarised in Table 6.

The pathogenesis of AED associated bone abnormalities have shown that enzyme inducing AEDs cause Vitamin D deficiency by mechanism of hepatic CYP450 system induction; thereby increasing Vitamin D catabolism into its polar inactive metabolites with subsequent hypocalcemia and resultant PTH hypersecretion. This leads to accelerated bone resorption and increased fracture risk [9,10,22]. Majority of published literature support supplementing Vitamin D for patients exposed to enzyme inducer AEDs but the effect on bone metabolism for other classes of AEDs like enzyme inhibitors and enzyme neutral AEDs is unclear and conflicting [11,12,23,24].

We did not find any significant difference in the bone health between patients exposed to enzyme inducer versus inhibitor AEDs; despite the higher overall dosage of enzyme inducer AEDs compared to inhibitors. This indicates that; i) a complex pharmacokinetic interaction between AEDs as well as pharmacodynamic effects of AED polytherapy on bone metabolism, affects bone health irrespective of the drug dosage and ii) low BMD may be by virtue of other mechanisms other than the effect on CYP-450 enzyme metabolism alone. The available literature suggests that this could be related to direct effects of AEDs on bone cells, direct inhibition of calcium absorption from the intestine, inhibition of osteoblast cell growth, and inhibition of calcitonin secretion [22,25].

A retrospective cohort study on 560 patients observed that patients on newer, non-enzyme inducing anticonvulsants had less osteoporosis at the lumbar spine, femoral neck, and hip suggesting that newer anticonvulsant medications are not associated with lower BMD [26]. We analysed the safety profile of newer AEDs with regards to bone health in great detail, since world-over people are using newer AEDs more with the seemingly clichéd belief that these are superior as far as adverse effects are considered. We found no significant difference between BMD in patients exposed exclusively to newer versus older AEDs; and the risk for low BMD was higher for certain newer AEDs such as clobazam, oxcarbazepine and levetiracetam as well as older AEDs like phenobarbitone and valproate. A higher incidence of lower BMD in patients treated with newer AEDs such as levetiracetam, oxcarbazepine, lamotrigine, topiramate and clonazepam has been previously reported various studies [20,27,28]; but there are no previous reports pertaining to the effect clobazam on bone health, apart from precautionary warnings stating clobazam may affect bone growth when given to children under 12 years of age [29]; this needs to be followed up in large scale studies.

We found that mean T score was significantly lower when cumulative drug load extends beyond 25 years.In tertiary care epilepsy referral centres like ours, that cater to a large number patients with refractory epilepsy, with the mean duration of epilepsy being nearly 15 years and majority of patients are on two or more AEDs, the cumulative drug dose would be > 25 in nearly all patients, predisposing them for risk of low BMD and fractures. It is also observed that anticonvulsants can be withdrawn in 10% of patients who are seizure free for 2 years, the remaining vast majority need to continue long-term AEDs. Our data and previous literature reports [30–33], underscore the importance of mandatory screening for bone density in all patients with refractory epilepsy and recommend screening in patients who need to continue AEDs beyond two years for seizure control.

Our study had certain limitations: i) small sample size, the power of the study was 0.441 and a larger sample size of 120 patients is needed to re-affirm statistical significance;but this is a pilot study in this regard ii) lack of serum AED concentrations of AEDs iii) limited exposure to monotherapy and some of the newer AEDs iv) follow-up data on BMD is contemplated as a separate paper and hence details pertaining to this have not been included in the present paper (All patients detected to be

**Table 6**
Comparison of present study with similar studies on effect of enzyme inducers versus inhibitors, newer versus older AEDs and mono versus polytherapy on bone health.

| Study | Country/Study design | Population | Significant findings |
|-------|---------------------|-----------|---------------------|
| Fuleihan et al. [30] | Lebanon/cohort | 137 adults/88 children | Age, polypharmacy, therapy duration, EIAEDs significantly affect BMD |
| Beniczky et al. [21] | Denmark/cohort | 168 adults | LEV, OXC as monotherapy significantly affect BMD |
| Osman et al. [20] | Egypt/case- control | 60 cases/60 controls | Older AEDs and polytherapy cause significant effect on BMD |
| El-haggar et al. [27] | Egypt/case-control | 48 cases/30 controls | LEV monotherapies and polytherapy showed harmful effects on bone but LTG did not. |
| Current study, 2018 | India/prospective case-control | 51 cases/51 controls | Earlier age of onset of epilepsy, developmental delay, use of polytherapy, higher CDD and usage of drugs such as CLB, OXC, LEV, PB and VPA carry high risk for low BMD. Bone health ⟷ between EIAEDs and EInbAEDs; or between newer and older AEDs |

⟷-no significant change, BMD-bone mineral density, CBZ-carbamazepine, CDD-cumulative drug dosage, CLB-clobazam, EIAED-enzyme inducing antiepileptic drugs, EInbAEDs–enzyme inhibiting antiepileptic drugs, LEV-levetiracetam, PB-phenobarbitone, LTG-lamotrigine, OXC-Oxacarbazepine, VPA-valproate.

having low BMD or Vitamin D deficiency were administered calcium 500 mg/day plus Vitamin D supplementation 60,000 units once a week for 8 weeks and advised to repeat Vitamin D levels every 3 months and a DEXA scan every 6 months on follow-up). v) lack of correlation between biochemical parameters and BMD can be attributed largely by small sample size and other factors such as diverse age, gender, epilepsy type and duration and AED effect.

In our study, calcium and vitamin D supplements were not routinely administered for any patients. A recent meta-analysis with this regard, found that Vitamin D supplementation appears to have a positive effect on bone turnover markers, particularly alkaline phosphatase [34].Multi-centric studies recruiting more patients are warranted to formulate guidelines to ensure optimal maintenance of bone health in persons with epilepsy who are destined to use them as mono or polytherapy for a longer duration of time and to ascertain the role of high dose vitamin D supplementation (> 1800 IU) to manage the adverse effect of AEDs on bone health in adults with epilepsy.

## 5. Conclusions

Bone health in epilepsy is adversely affected by chronic exposure to AEDs; irrespective of the enzymatic effect or generation of AEDs. Complex pharmacodynamic mechanisms of AEDs as well as pharmacokinetic interactions between various AED polytherapies affects bone health. In addition to old generation AEDs, newer AEDs also cause decline in bone health, this needs to be considered seriously in this era when more and more of them are being used with a broad understanding that the adverse effect profile is far less and tolerable for these newer drugs.

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## References

[1] Epilepsy Fact Sheet, World Health Organisation, Available at http://www.who.int/mental_health/neurology/epilepsy/en/, (2012) (accessed February 17 2019).

[2] N.E. Bharucha, Epidemiology of epilepsy in India, Epilepsia 44 (2003) 9–11.

[3] N.E. Bharucha, Epidemiology and treatment gap of epilepsy in India, Ann. Indian Acad. Neurol. 15 (4) (2012) 352.

[4] Y. Zhang, Y. Zheng, J. Zhu, J. Zhang, Z. Zheng, Effects of antiepileptic drugs on bone mineral density and bone metabolism in children: a meta-analysis, J. Zhejiang Univ. Sci. B 16 (7) (2015) 611–621.

[5] P. Souverein, D. Webb, H. Petri, J. Weil, T. Van Staa, T. Egberts, Incidence of fractures among epilepsy patients: a population-based retrospective cohort study in the general practice research database, Epilepsia. 46 (2) (2005) 304–310.

[6] S. Karceski, Seizure medications and their side effects, Neurology 69 (22) (2007) E27–E29.

[7] A. Verrotti, G. Coppola, P. Parisi, A. Mohn, F. Chiarelli, Bone and calcium metabolism and antiepileptic drugs, Clin. Neurol. Neurosurg. 112 (1) (2010) 1–10.

[8] C. Meier, M. Kraenzlin, Antiepileptics and bone health, Ther. Adv. Musculoskelet. Dis. 3 (5) (2011) 235–243.

[9] C. Dent, A. Richens, D. Rowe, T. Stamp, Osteomalacia with long-term anticonvulsant therapy in epilepsy, BMJ 4 (5727) (1970) 69–72.

[10] S. Chung, C. Ahn, Effects of anti-epileptic drug therapy on bone mineral density in ambulatory epileptic children, Brain and Development 16 (5) (1994) 382–385.

[11] N. Oner, M. Kaya, S. Karasalihoglu, H. Karaca, C. Celtik, F. Tutunculer, Bone mineral metabolism changes in epileptic children receiving valproic acid, J. Paediatr. Child Health 40 (8) (2004) 470–473.

[12] S. Petty, L. Paton, T. O'Brien, J. Makovey, B. Erbas, P. Sambrook, et al., Effect of antiepileptic medication on bone mineral measures, Neurology 65 (9) (2005) 1358–1365.

[13] K. Nakken, E. Taubøll, Bone loss associated with use of antiepileptic drugs, Expert Opin. Drug Saf. 9 (4) (2010) 561–571.

[14] I.E. Scheffer, S. Berkovic, G. Capovilla, M.B. Connolly, J. French, L. Guilhoto, et al., ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology, Epilepsia 58 (4) (2017) 512–521.

[15] World Health Organization, Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis: Report of a WHO Study Group [meeting held in Rome from 22 to 25 June 1992], Available at http://www.who.int/iris/handle/10665/39142, (1994) (accessed February 17 2019).

[16] S. Singla, S. Kaushal, S. Arora, G. Singh, Bone health in patients with epilepsy: a community-based pilot nested case–control study, Ann. Indian Acad. Neurol. 20 (2017) 367–371.

[17] WHO Collaborating Centre for Drug Statistics Methodology (WHOCC), Definition and General Considerations, Available at: http://www.whocc.no/ddd/definition_and_general_considera (accessed February 17 2019).

[18] L.A. Rudzinski, N.J. Vélez-Ruiz, E.R. Gedzelman, E.A. Mauricio, J.J. Shih, I. Karakis, New antiepileptic drugs: focus on ezogabine, clobazam, and perampanel, J. Investig. Med. 64 (2016) 1087–1101.

[19] C. Valmadrid, C. Voorhees, B. Litt, C. Schneyer, Practice patterns of neurologists regarding bone and mineral effects of antiepileptic drug therapy, Arch. Neurol. 58 (9) (2001) 1369.

[20] N. Osman, R. Abdel Aziz, G. Soliman, A. Gamal Mohamed, Bone mineral density evaluation of epileptic children on anti-epileptic medications, Egypt. J. Radiol. Nucl. Med. 48 (4) (2017) 1083–1090.

[21] S.A. Beniczky, J. Viken, L.T. Jensen, N.B. Andersen, Bone mineral density in adult patients treated with various antiepileptic drugs, Seizure 21 (2012) 471–472.

[22] L. Fitzpatrick, Pathophysiology of bone loss in patients receiving anticonvulsant therapy, Epilepsy Behav. 5 (2004) 3–15.

[23] J.R. Chaudhuri, K.R. Mridula, C. Rathnakishore, B. Balaraju, V.S. Bandaru, Association of 25-Hydroxyvitamin D deficiency in pediatric epileptic patients, Iran. J. Child Neurol. 11 (2) (2017) 48–56.

[24] B. Menon, C. Harinarayan, The effect of anti epileptic drug therapy on serum 25-hydroxyvitamin D and parameters of calcium and bone metabolism—a longitudinal study, Seizure 19 (3) (2010) 153–158.

[25] R. Lee, K. Lyles, C. Colón-Emeric, A review of the effect of anticonvulsant medications on bone mineral density and fracture risk, Am. J. Geriatr. Pharmacother. 8 (1) (2010) 34–46.

[26] R. Lee, K. Lyles, R. Sloane, C. Colón-Emeric, The association of newer anticonvulsant medications and bone mineral density, Endocr. Pract. (2012) 14:1–22.

[27] S.M. El-Haggar, T.M. Mostafa, H.M.S. Allah, G.H. Akef, Levetiracetam and lamotrigine effects as mono- and polytherapy on bone mineral density in epileptic patients, ArqNeuropsiquiatr 76 (7) (2018) 452–458.

[28] H. Salimipour, S. Kazerooni, M. Seyedabadi, I. Nabipour, R. Nemati, D. Iranpour, et al., Antiepileptic treatment is associated with bone loss: difference in drug type and region of interest, J. Nucl. Med. Technol. 41 (3) (2013) 208–211.

[29] What Should I Know Regarding Pregnancy, Nursing and Administering Clobazam Film to Children or the Elderly? Available at http://www.webmd.com/drugs/2/drug-158673-1981/clobazam-oral/clobazam-film-oral/details/list-precautions (accessed June 12 2019).

[30] G. El-Hajj Fuleihan, L. Dib, B. Yamout, R. Sawaya, M. Mikati, Predictors of bone density in ambulatory patients on antiepileptic drugs, Bone 43 (1) (2008) 149–155.

[31] P. Souverein, D. Webb, J. Weil, T. Van Staa, A. Egberts, Use of antiepileptic drugs and risk of fractures: case-control study among patients with epilepsy, Neurology 66 (9) (2006) 1318–1324.

[32] P. Vestergaard, L. Rejnmark, L. Mosekilde, Fracture risk associated with use of antiepileptic drugs, Epilepsia 45 (11) (2004) 1330–1337.

[33] R. Sheth, N. Binkley, B. Hermann, Progressive bone deficit in epilepsy, Neurology 70 (3) (2007) 170–176.

[34] H. Fernandez, H.T. Mohammed, T. Patel, Vitamin D supplementation for bone health in adults with epilepsy: a systematic review, Epilepsia 59 (2018) 885–896.