

# Derangements in bone mineral parameters and bone mineral density in south Indian subjects on antiepileptic medications

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## Abstract

**Background:** Although there are reports describing the association of alternations of bone and mineral metabolism in epileptic patients with long-term anticonvulsant therapy, there are only limited Indian studies which have looked at this aspect. **Objectives:** This study was done to compare the prevalence of changes in bone mineral parameters and bone mineral density (BMD) in ambulant individuals on long-term anticonvulsant therapy with age- and body mass index (BMI)-matched healthy controls. **Materials and Methods:** There were 55 men (on medications for more than 6 months) and age- and BMI-matched 53 controls. Drug history, dietary calcium intake (DCI), and duration of sunlight exposure were recorded. Bone mineral parameters and BMD were measured. **Results:** The control group had a significantly higher daily DCI with mean  $\pm$  SD of  $396 \pm 91$  mg versus  $326 \pm 101$  mg ( $P = 0.007$ ) and more sunlight exposure of  $234 \pm 81$  vs  $167 \pm 69$  min ( $P = 0.05$ ). BMD at the femoral neck was significantly lower in cases ( $0.783 \pm 0.105$  g/cm<sup>2</sup>) when compared to controls ( $0.819 \pm 0.114$  g/cm<sup>2</sup>). Majority of the patients (61%) had low femoral neck BMD ( $P = 0.04$ ). There was no significant difference in the proportion of subjects with vitamin D deficiency ( $<20$  ng/mL) between cases ( $n = 32$ ) and controls ( $n = 37$ ) ( $P = 0.234$ ). **Conclusions:** Vitamin D deficiency was seen in both the groups in equal proportions, highlighting the existence of a high prevalence of this problem in India. Low femoral neck BMD found in cases may stress the need for supplementing calcium and treating vitamin D deficiency in this specific group. However, the benefit of such intervention has to be studied in a larger proportion of epileptic patients.

## Key Words

Anticonvulsants, bone mineral density, epilepsy, vitamin D

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## Introduction

In India, the prevalence rate of epilepsy has been estimated to be 1%.<sup>[1]</sup> The urban-rural divide for this disease is alarming with studies done in Bengaluru suggesting that the prevalence may be twice as much in rural when compared to urban regions.<sup>[2]</sup> A substantial amount of healthcare needs of most of the rural population is met by hospitals in primary and secondary care

settings. Phenytoin and sodium valproate continue to be the major antiepileptic drugs (AEDs) being used in India.<sup>[3]</sup>

The adverse effects of long-term AEDs on bone and mineral metabolism was initially reported by Kruse in 1968, who observed radiological evidence of rickets and low serum calcium levels in 15% of a German pediatric outpatient population with epilepsy.<sup>[4]</sup> It has also been observed that these changes were seen as early as within 60 days of starting therapy.<sup>[5]</sup>

These findings of derangements in calcium and phosphate metabolism in patients with anticonvulsant therapy have been reported in epileptic populations throughout the world with prevalence rates ranging from 3 to 30%.<sup>[6-10]</sup> AEDs like phenytoin, carbamazepine, and sodium valproate induce hepatic oxidase activity through microsomal enzymes (p 450) in the liver.<sup>[11]</sup> This in turn increases the metabolism of vitamin

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D and thus can lead to hypocalcemia, hypophosphatemia, low vitamin D, and high parathyroid hormone (PTH) levels. The fracture risk in these patients is heightened much more by unsteadiness in gait, fall, and limited mobility. Biochemical changes described earlier are frequently seen in 30-40% of patients, in majority of these subjects the changes are either mild or subclinical in nature. The effect of AEDs on bone can also be modified by a number of factors like exposure to sunlight and poor dietary intake of calcium and vitamin D.<sup>[12]</sup> Fractures in these patients also place a considerable economic burden.<sup>[13]</sup>

However, there are no studies in this regard in the southern Indian population with regards to epilepsy. This is relevant in an Indian context, since a high prevalence of vitamin D deficiency has been reported widely in the normal and diseased population.<sup>[14-16]</sup>

The present study attempts to determine as to whether poor dietary calcium intake (DCI), decreased sunlight exposure, hypocalcemia, hypophosphatemia, low vitamin D, and low bone mineral density (BMD) occur with greater frequency in males who are on long-term anticonvulsant therapy.

## Materials and Methods

### Design: A prospective cross-sectional study

Fifty-five ambulant male patients with epilepsy between 20 and 50 years of age, who were on at least one of the enzyme inducing anticonvulsants (phenytoin, phenobarbitone, or carbamazepine) for more than 6 months, attending the epilepsy clinic of the neurology department, were selected for the study. Fifty-three healthy subjects, matched for age and body mass index (BMI) were recruited from the community health database of the institution, as controls. Subjects with concomitant hepatic or renal diseases, malabsorption, and on other medications like corticosteroids, which could potentially affect the vitamin D and calcium metabolism were excluded.

A detailed clinical history, type of seizure, pattern of medications like type and duration of AEDs, and a physical assessment was conducted in all subjects. The daily intake of calcium was estimated by using semiquantitative food frequency questionnaire (FFQ). Daily exposure to sunlight was estimated based on the duration of exposure to sunlight, amount of clothing, and extent of body surface area exposed to sunlight as detailed in an earlier study.<sup>[14]</sup> Physical assessment included evaluation for any specific features of osteomalacia, such as fractures or proximal muscle weakness. Informed consent was obtained from the all subjects and the study was approved by the institutional review board (IRB number 6203 dated 17/04/2009).

An overnight fasting blood sample was obtained for estimation of serum calcium, phosphate, albumin, alkaline phosphatase, creatinine, 25-hydroxyvitamin D (25(OH)D), and intact PTH. A radioimmunoassay (DiaSorin, Stillwater, Minnesota) was used for determination of vitamin D levels. The analytical sensitivity of this assay, when defined as the lowest quantity that differentiated from the zero standard ( $N = 20$ ) has been shown to be 1.5 ng/mL. The intra-assay coefficient of variation was

5.5% at a vitamin D level of 15.6 ng/mL and 9.3% at a vitamin D level of 52.5 ng/mL. Vitamin D deficiency has been defined by most experts as a vitamin D level of less than 20 ng/mL (50 nmol/L) and a level of 30 ng/mL or greater has been considered to indicate sufficient vitamin D and values between 20 and 30 ng/dL have been considered as indicative of vitamin D insufficiency. Intact PTH was measured by chemiluminescence method using Immulite analyzer 2000 (normal - 8-50 pg/mL). Other biochemical parameters were measured in a fully automated and computerized microanalyzer (Hitachi model 911; Boehringer Mannheim, Mannheim, Germany). The intra- and inter-assay coefficients of variation for these analyses were 1-5%.

BMD was assessed by using the Hologic DXA machine (QDR 4500; Hologic Inc, Waltham, Massachusetts) at the lumbar spine (L1-L4) and the femoral neck. The reference population consisted of normal Caucasian subjects from the manufacturer's database. The reference population (manufacturer's database) was Caucasian in origin for defining Z-scores. A Z-score less than two standard deviations (SDs) below the mean of the reference population was described as a low BMD.<sup>[17]</sup> The precision was 2% at both measured sites (spine and neck of femur).

### Sample size calculation

In an earlier study, vitamin D status was estimated in a group of ambulatory patients receiving anticonvulsants therapy and the mean difference of vitamin D level was found to be 6.2 ng/mL when compared between cases and controls. Vitamin D levels (mean  $\pm$  SD) in cases was  $28.2 \pm 10.3$  and  $34.4 \pm 12.7$  ng/mL in controls.<sup>[11]</sup> In order to detect a difference of 6.2 ng/mL with a 95% confidence and a power of 80%, a case-control study with 52 patients on AEDs for more than 6 months and 52 healthy individuals were to be selected.

### Statistical analysis

An analysis was done using the Statistical Package for Social Sciences (SPSS) version 17 software package. An independent sample *t*-test was used to compare the means of two continuous variables if the distribution was normal, and nonparametric tests were used otherwise. A correlation between two continuous, parametric variables was done using Pearson's correlation. Chi-square tests and Fisher's exact test were used where indicated.

## Results

A total of 55 ambulant epileptic men and 53 age- and BMI-matched controls were studied. Baseline demography, biochemical profile, and BMD of both the groups are shown in [Table 1]. The mean age (SD) in cases was 27.7 (7.9) and 29.6 (7.7) years in controls.

Of the 55 epileptic patients, 35 were diagnosed to have idiopathic epilepsy. Thirteen had partial onset seizure leading onto secondary generalization and seven presented with the features of temporal lobe epilepsy or focal seizures. Thirty-one (56.4%) were on monotherapy (23 on phenytoin, six on carbamazepine, and two on phenobarbitone) and 24 (43.6%) were on a combination (polytherapy) of more than one drug. The median duration of treatment was 15 months.

The control group had a significantly higher DCI ( $396 \pm 91$  vs  $326 \pm 101$  mg;  $P = 0.007$ ) and sunlight exposure ( $234 \pm 81$  vs  $167 \pm 69$  min;  $P = 0.05$ ). The mean serum phosphate level in cases was 3.8 mg/dL, which was significantly lower ( $P = 0.028$ ) when compared to those seen in controls (4.3 mg/dL); however, hypophosphatemia (<2.5 mg%) was detected only in one patient in the study group but none in the control group. The mean (SD) vitamin D level in the study subjects was  $19 \pm 7.5$  and  $17 \pm 7.2$  ng/mL in controls ( $P = 0.113$ ). Vitamin D deficiency (<20 ng/mL) was found in 32 (58.1%) cases and 37 (69.8%) controls ( $P = 0.234$ ).

The BMD at the femoral neck was significantly lower ( $P = 0.041$ ) in cases ( $0.783 \pm 0.105$  g/cm<sup>2</sup>) when compared to controls ( $0.819 \pm 0.114$  g/cm<sup>2</sup>) and significantly more proportion of patients had low femoral neck BMD ( $P = 0.04$ ). There was however, no difference in the proportion of patients having low BMD among cases and controls at spine [Table 2].

The correlations between BMD and various parameters were assessed in both cases and controls. BMI had a significant positive correlation with BMD at the spine and femoral neck in both cases and controls (spine  $r = 0.5$ ,  $P = 0.0001$ ; femoral neck  $r = 0.4$ ,  $P = 0.006$  in cases; spine  $r = 0.5$ ,  $P = 0.001$ ; and femoral neck  $r = 0.4$ ,  $P = 0.006$  in controls) and there were no correlations between other parameters and BMD.

A negative correlation was seen between PTH and vitamin D among cases and controls, which was significant among cases alone ( $r = -0.4$ ,  $P = 0.005$ ). A positive correlation found between duration of sunlight exposure and 25(OH)D level was significant only among cases ( $r = 0.3$ ,  $P = 0.013$ ).

**Table 1: Baseline characteristics of cases and controls**

Characteristic	Cases (N = 55)	Controls (N = 53)	P-value
	Mean (SD)	Mean (SD)	
Age (years)	27.7 (7.9)	29.6 (7.5)	0.11
BMI (kg/m <sup>2</sup> )	21.41 (4)	22.1 (3.8)	0.35
Sunlight exposure (min/day)	167 (69)	234 (81)	0.05
Dietary calcium mg/day	326 (101)	396 (148)	0.007
BMD - spine g/cm <sup>2</sup>	0.912 (0.108)	0.936 (0.122)	0.284
BMD - femoral neck (g/cm <sup>2</sup> )	0.783 (0.105)	0.819 (0.114)	0.041
Corrected calcium (mg/dL)	8.4 (0.3)	8.5 (0.3)	0.90
Phosphate (mg/dL)	3.8 (0.6)	4.3 (0.6)	0.028
Albumin (g/dL)	4.5 (0.2)	4.5 (0.3)	0.632
Creatinine (mg/dL)	0.8 (0.1)	0.9 (0.4)	0.144
Alkaline phosphatase (U/L)	86 (21)	101 (69)	0.140
25-hydroxy vitamin D (ng/mL)	19 (7.5)	17 (7.2)	0.113
Parathyroid hormone	57 (34)	49 (34)	0.074

BMD = Bone mineral density, BMI = Bone mineral density, SD = Standard deviation

**Table 2: Proportion of subjects with low bone mineral density in either group**

Characteristics	Cases (55) N (%)	Controls (53) N (%)	Significance, P-value
Lumbar spine	39 (70)	32 (60)	0.31
Neck of femur	34 (61)	22 (41)	0.04

## Discussion

This is the first such study to the best of our knowledge from southern India which looked into the changes in bone metabolic parameters and bone density in patients who were on antiepileptic therapy. Subjects who were on antiepileptic medications had a trend towards a low calcium intake, sunlight exposure, serum phosphate, and femoral neck BMD. The number of subjects with vitamin D deficiency was the same between cases and controls.

### Dietary calcium intake

DCI was lower than the recommended daily allowance in both the groups. There was a significantly lower intake of dietary calcium in patients on anticonvulsant therapy. Several other studies from various parts of India have documented a similar trend towards a low calcium intake in healthy subjects<sup>[18]</sup>. Harinarayan *et al.*, in a study conducted in a rural Indian population had found that the DCI was lower than the recommended daily allowance.<sup>[19]</sup> Moreover, calcium deficiency appears to be worsened by dietary factors like high phytate content in the south Indian diet which also contribute to a reduction in calcium absorption.<sup>[19]</sup> In the setting of nutritional calcium deficiency, PTH levels are raised in an attempt to convert 25(OH)D to 1,25-dihydroxyvitamin D to increase the calcium absorption. However, in patients with low 25(OH)D at baseline, the resultant secondary hyperparathyroidism only results in more bone resorption.

### Low serum phosphate

The lower serum phosphate level observed in our subjects with epilepsy has also been demonstrated in other studies.<sup>[20-22]</sup> However, there was no difference in the proportion of patients having hypophosphatemia between cases and controls.

Previous studies have shown that anywhere from 25 to 50% differently-abled children<sup>[20]</sup> or children on antiepileptic medications<sup>[22]</sup> had hypophosphatemia.

Hypophosphatemia may be secondary to vitamin D deficiency and also due to the direct effect of antiepileptic drugs on renal tubules in those on long-term treatment.<sup>[23,24]</sup> However, many subjects on chronic anticonvulsant therapy may not develop significant hypophosphatemia. This has been documented in earlier studies. Kruse *et al.*, noted a higher tubular transportation rate of phosphate despite secondary hyperparathyroidism in patients on anticonvulsant therapy.<sup>[25]</sup> They described a normal rise in urinary cyclic adenosine monophosphate (AMP) excretion without concomitant increase in the excretion of phosphate in the urine after the infusion of parathyroid extract in children on phenytoin and phenobarbitone treatment, resembling pseudohyperparathyroidism type II.

### Vitamin D levels

Vitamin D deficiency is quite common in India subcontinent.<sup>[14,19]</sup> Several studies from different parts of India in various subgroup of population including health volunteers, pregnant women, school children, hospital staff, and even army personnel show very high prevalence of vitamin D deficiency.<sup>[16]</sup> Our study showed low vitamin D in both cases and controls and the difference between these two groups was not significant.

Arya *et al.*, studied healthy volunteers from north India. The mean 25(OH)D in these volunteers was 12.3 ng/mL. Only one-third was vitamin D sufficient with a cutoff > 15 ng/mL.<sup>[26]</sup> Other studies have subsequently shown that healthy individuals, pregnant women, doctors, and nurses have extremely low vitamin D levels as opposed to depigmented women who have high normal levels.<sup>[27]</sup> There is a greater magnitude of normal vitamin D levels in those from rural compared to urban areas; however, the difference is relatively small.<sup>[19]</sup>

The proposed reasons for high prevalence of vitamin D deficiency among Indian population include skin pigmentation, clothing pattern, a lower, duration of sunlight exposure, genetic factors, and vegetarian diet.<sup>[14,15,19]</sup> Enzyme inducing properties of AEDs like phenytoin, carbamazepine, and phenobarbitone would have further contributed to the preexisting problem. Rapid vitamin D catabolism has been defined as the principal mechanism responsible vitamin D deficiency and osteomalacia in those patients.<sup>[12]</sup>

The duration of sunlight exposure had a positive correlation with vitamin D only in cases. The lack of correlation in controls is probably due to many factors including reporting bias and skin pigmentation.<sup>[14]</sup> Other studies have demonstrated significant correlation between sunlight exposure and vitamin D levels.<sup>[28]</sup>

Our study has shown higher PTH level among subjects with AEDS which is probably due to a combination of many factors such as vitamin D deficiency and poor DCI. Elevated PTH levels could be detrimental to bone in epileptic patients as it can increase the rate of bone resorption. Sahota *et al.*, have described a blunted response of PTH in nearly two-thirds of vitamin D deficient individuals in whom secondary hyperparathyroidism was not seen. This may explain the lack of a significant correlation between vitamin D and PTH in the control group.<sup>[29]</sup>

#### Bone mineral density

BMD was lower in patients on anticonvulsants and was significantly lower ( $P = 0.041$ ) at the neck of femur. Kulak *et al.*, studied BMD in a group of patients from Brazil on AEDs and 63.5% of patients had a T-score of less than -1.0 in at least in one site.<sup>[11]</sup> Farhat *et al.*, noticed similar changes in patients who were on anticonvulsant therapy for more than 6 months duration.<sup>[30]</sup> A progressive decline in femoral neck BMD has been reported over a period of 1 year, in subjects on anticonvulsant therapy.<sup>[31]</sup>

Patients using AEDs for more than 2 years and particularly those taking enzyme-inducing AEDs and those older than 40 years, have significantly lower BMD at relevant fracture risk sites.<sup>[32]</sup>

Amongst the various correlations, only BMI correlated with BMD (both at femoral neck and spine) in both cases and controls, which is a well-established occurrence.<sup>[14,33]</sup>

There have been reports of an increased incidence and risk of fractures in patients on chronic antiepileptic medications.<sup>[34,35]</sup> This would mean that the low BMD could also translate into

clinical outcomes like fractures and demand urgent attention and regular supplementation with vitamin D and calcium which is not a current clinical practice in India, to avoid fractures.<sup>[36]</sup>

#### Limitations

Vitamin D deficiency is more prevalent in the Indian population, and hence the small sample size failed to demonstrate any effect of antiepileptic medications on vitamin D. A larger sample would have brought out the differences more clearly. In addition, dichotomy observed with regards to changes in BMD between spine and femoral neck could not be further evaluated by bone histomorphometry for ethical reasons as it is an invasive procedure warranting bone biopsy from different sites.

#### Conclusions

In the present study, many of the patients (58.1%) on AEDs had low vitamin D levels. Simultaneously, these patients were found to have low DCI, inadequate exposure to sunlight and low BMD at the femur. This suggests that patients on antiepileptic medication are more prone to develop low BMD and this may stress the need for supplementing calcium and treating vitamin D deficiency in this specific group. However, the benefit of such intervention has to be studied in a larger cohort of epileptic patients.

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