

# Disturbed calcium-vitamin D metabolism in patients on anti-epileptic drugs

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## Abstract

**Introduction:** Epilepsy is a common chronic neurological disorder, usually requiring long term treatment with anti-epileptic drugs (AEDs). There is paucity in data in relation to the effect of AED on calcium metabolism in North India. In view of this the present study was undertaken to assess the effect of AED on calcium metabolism.

**Methods:** The present cross-sectional study included epileptic patients of both sex attending the neurology OPD & IPD clinics. Patients were divided into three groups: - group 1 included patients on monotherapy receiving 1 AED, group 2 on dual therapy receiving 2 AED and group 3 patients on polytherapy receiving >2 AED. Serum analysis of total calcium, phosphorus, alkaline phosphorus, ionised calcium & vitamin D levels were conducted. The data between the groups was analyzed by using 1 way analysis of variance (ANOVA).

**Results:** The study included 150 patients in which 50 patients each belonged to groups 1, 2 and 3 respectively. 60% patients were male. 86 patients had generalised epilepsy and 64 suffered from partial seizures. 42% of the patients were on AED treatment for >5 years. Serum levels of calcium and vitamin D were significantly decreased ( $p=0.000$  and  $p>0.05$  respectively) in the polytherapy group in comparison to the mono and dual therapy groups. On the other hand, alkaline phosphatase & phosphorus levels were significantly increased in the polytherapy group ( $p=0.000$ ).

**Conclusion:** Hypovitaminosis was commonly observed in the patients on AED, even at sub-therapeutic serum levels of the drug.

## Introduction

Epilepsy is a neurological disorder characterised by abnormal brain activity, causing seizures or periods of unusual behaviour, sensations and sometimes loss of awareness. The disease affects males and females of all races, ethnic background and ages. Transient symptoms can occur, such as loss of awareness or consciousness and disturbances of movement, sensation (including vision, hearing, and taste), mood, or mental function [1]. 70 million individuals are affected with epilepsy all over the world and nearly 12 million reside in India. The overall prevalence in India approximates 3 to 11.9 per 1000 population [2]. Anti epileptic drugs (AEDs) are the first choice of treatment for these individuals. However more than 50% of epileptics on AED develop bone abnormalities [3]. Cytochrome P-450 (CYP450) isoenzymes are induced by AEDs especially the classic AEDs such as benzodiazepines, carbamazepine, phenytoin, phenobarbital and valproic acid. The induction of these CYP-450 enzymes may lead to vitamin D deficiency, hypercalcemia, and increased risk of fractures, altered bone turnover which can lead to impaired bone mineral density [3]. Apart from AEDs, glucocorticoids, aromatase inhibitors, and anti-androgenic drugs are also associated with increased risk of osteoporosis [4]. If these drugs are used with AEDs, the risk of a decrease in bone density is highly increased. Recent studies have demonstrated that the awareness of neurologists regarding the effects of AEDs on bone density is low (28%). It has been reported that a small number of pediatric neurologists (9%) and adult neurologists (7%) prophylactically prescribe calcium and vitamin D together with AEDs [5]. The negative effects of AEDs on bone density

are complex, and their mechanism has not been fully understood. Both enzyme-inducing and non-inducing AEDs may cause abnormalities in bone metabolism [6,7]. There are very few studies in the Indian sub-continent evaluating vitamin D and calcium profile in epileptic patients with different treatment modalities. The aim of the present study was to therefore investigate the calcium metabolism in epilepsy patients who were on mono, dual and polytherapy anti-epileptic drug regime.

## Materials and methods

The present cross-sectional study included consented epileptic patients of both sex attending the epilepsy clinic, admitted to the neurology ward of GIPMER New Delhi. It was conducted between period of Jan to Dec 2017. Patients with co morbid illness such as gastrointestinal disease, chronic liver disease, kidney disease or those on calcium-vitamin D supplementation were excluded from the study. Patients were divided into three groups: - group 1 included patients on monotherapy receiving 1 AED, group 2 on dual therapy receiving 2 AED

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and group 3 patients on polytherapy receiving >2 AED. 4-5 ml of blood sample was collected in plain red vacutainer under aseptic conditions for analysing total calcium, phosphorus, alkaline phosphorus, ionised calcium, Vitamin D and Parathyroid hormone (PTH) levels. Fresh, clear, and nonhemolyzed samples were used. Routine tests were analyzed by Roche Cobas c501 autoanalyzer. The serum was separated and stored at -20°C until batch analysis for the estimation of 25(OH) hydroxyvitamin D (25(OH) D), PTH with Roche immunoassay autoanalyzer Cobas e411 using electrochemiluminescence technique. The minimum detection limit for PTH was 1 pg/ml (reporting reference interval 15-65 pg/ml) and for 25(OH) D was 5 ng/ml with the analytical measurement range of 3-70 ng/ml. The preferred level for 25(OH) D is recommended to be  $\geq 30$  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. Data was expressed as mean  $\pm$  standard deviation values. The data between the groups was analyzed by using 1-way analysis of variance (ANOVA). A p value of <0.05 was accepted as statistically significant.

## Results

The present cross-sectional study included 150 patients in which 50 patients each belonged to groups 1, 2 and 3 respectively. Patients in our study were associated with age group of 15-35 years with male:female ratio of 1.4:1. Mean age of onset of seizures in the study group was 19.18 $\pm$ 7.43 yrs. 86 patients had generalised epilepsy and 64 suffered from partial seizures. Table 1 shows 42% of the patients were on AED treatment with seizures duration for more than 5 years whereas the mean duration of seizures was highest in polytherapy group as 5.86 $\pm$ 2.31 years in Table 4. With reference to Table 2 showing biochemical measurements, calcium and phosphorus levels were found to be significantly decreased in patients on polytherapy in comparison to those on mono and dual therapy (p=0.000 respectively). Similarly, Vitamin D levels were found to be the lowest in patients on polytherapy (p=0.000). On the other hand, levels of Alkaline Phosphatase & PTH were found to be elevated in the polytherapy group (p=0.000) as shown in Table 2.

25 (OH) Vitamin D deficiency (< 20 ng/mL) was observed in 72% patients on monotherapy (n=36), in 86% patients on dual therapy (n=43) and 96% patients on polytherapy (n=48) as shown in Table 3. On correlating serum levels of Vitamin D with duration of seizures a negative correlation was observed in all patients though the correlation was found to be statistically significant in polytherapy group (p<0.05) as shown in Table 4.

## Discussion

Epilepsy is a major public health problem affecting majority of people worldwide. Treatment with AEDs is generally chronic, if not lifelong and may be associated with significant metabolic effects including decreased bone mass and increased fractures [8,9]. This

**Table 1.** Demographic characteristics of patient's according to the type of therapy

Demographic characteristics	Patients on mono therapy	Patients on dual therapy	Patients on poly therapy
Mean age	23.58 $\pm$ 8.5	23.6 $\pm$ 8.6	25.1 $\pm$ 11.7
Male/Female	25/25	32/18	31/19
Duration of seizure			
<5 yrs	36	35	18
5-10 yrs	14	11	30
>10 yrs	0	4	2
Mean age of onset	19.44 $\pm$ 6.8	18.88 $\pm$ 6.10	19.22 $\pm$ 10.9

**Table 2.** Laboratory characteristics of patient's according to the type of therapy. \*p=0.000

Parameters	Patients on mono therapy	Patients on dual therapy	Patients on poly therapy
S.Albumin	4.5 $\pm$ 0.26	4.42 $\pm$ 0.28	4.49 $\pm$ 0.23
S.Calcium	9.2 $\pm$ 0.42	8.9 $\pm$ 0.31	8.0 $\pm$ 0.22*
S.Phosphorus	4.46 $\pm$ 0.96	4.47 $\pm$ 0.68	4.26 $\pm$ 0.43*
Alkaline Phosphatase	109.3 $\pm$ 22.4	121.9 $\pm$ 13.3	149.2 $\pm$ 18.6*
I. Ca ++	1.04 $\pm$ 0.13	1.03 $\pm$ 0.12	1.02 $\pm$ 0.11
PTH	27.2 $\pm$ 40.0	48.53 $\pm$ 18.9	72.69 $\pm$ 6.93*
Vitamin D	16.81 $\pm$ 6.34	14.98 $\pm$ 4.79	10.66 $\pm$ 4.65*

**Table 3.** Vitamin D status of patient's according to the type of therapy

Drug therapy	No. (%) of patients with 25 (OH) vitamin D deficiency	No. (%) of patients with 25 (OH) vitamin D insufficiency	No. (%) of patients with 25 (OH) vitamin D sufficiency
Patients on mono therapy	36 (72)	13 (26)	1 (2)
Patients on dual therapy	43 (86)	7 (14)	0 (0)
Patients on poly therapy	48 (96)	2 (4)	0 (0)

**Table 4.** Correlation of vitamin D levels with duration of seizure in different therapy groups

Therapy	Mean duration of seizures	r value	p value
<b>Mono therapy</b>	3.85 $\pm$ 2.24	-0.167	0.246
<b>Dual therapy</b>	4.72 $\pm$ 3.47	- 0.155	0.282
<b>Poly therapy</b>	5.86 $\pm$ 2.31	- 0.299	<b>0.034</b>

is the first study to the best of our knowledge from northern India which looked into changes of bone metabolic parameters in patients who were on different regimens of antiepileptic drug therapy. Amongst users of AEDs, we observed significant hypocalcemia, hypoproteinemia, hyperparathyroidism, and increased levels of serum alkaline phosphatase in patients belonging to polytherapy group when compared to those on mono or dual therapy. Several theories have been proposed to explain the link between AEDs and bone disease. Hepatic induction of the cytochrome P450 enzyme system leading to increased catabolism of Vitamin D is the principal mechanism reported [10]. Other possible mechanisms include a direct effect on bone cells including impaired absorption of calcium and inhibition of response to PTH, hyperparathyroidism, and calcitonin deficiency [11]. AEDs that induce hepatic cytochrome P450 enzymes may cause increased conversion of Vitamin D to polar inactive metabolites in the liver microsomes and reduce levels of bio-available Vitamin D. Decreased biologically active Vitamin D leads to decreased absorption of calcium in the gut, resulting in hypocalcemia, and an increase in circulating PTH, which increases the mobilization of bone calcium stores and subsequent bone turnover. AEDs may interfere with intestinal absorption of calcium. Impaired absorption would lead to hypocalcemia and feedback hypersecretion of PTH. Markedly decreased calcium absorption was found in rats treated with phenytoin but not with phenobarbitone<sup>11</sup>. Hyperparathyroidism also has been suggested as a possible mechanism. Hyperparathyroidism can primarily activate bone resorption and through a coupling phenomenon and secondarily activate bone formation. A final postulated mechanism is calcitonin deficiency. Calcitonin is a hormone produced by the thyroid gland that inhibits osteoclast mediated bone resorption. Calcitonin deficiency may, therefore, accelerate bone turnover. This deficiency has been demonstrated both *in vitro* and *in vivo* [12,13]. 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 $\pm$ 1.3 to 17.2 $\pm$ 1.6 ng/ml (P<0.001) within 6 months of initiation

of AED therapy [14]. In another study by Krishnamurthy *et al.* It was observed 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 co-administration of calcium and 25(OH) D in recommended daily allowance dosage could be useful in limiting the changes in calcium and Vitamin D metabolism in patients on AEDs [15]. According to a study by Bartl *et al.* patients on long term treatment with AEDs have 2–3 fold risk of sustaining fractures. On an average, 50% of patients (ranging from 4% to 70% in different studies) have osteopathy. Bone loss has been noted with or even without evidence of Vitamin D deficiency among the enzyme-inducing drugs, especially phenytoin, phenobarbitone and carbamazepine [16].

We view the high prevalence of inadequate Vitamin D levels in epileptic patients as significant. Patients on polytherapy type of AED regimen are at a higher risk for low 25 (OH) D levels. Virtually all epileptic patients are at a risk for hypovitaminosis D. We could not screen our subjects with dual energy x-ray absorptiometry scans to evaluate bone mineral density. Therefore, we cannot comment on the impact of our patient's low Vitamin D levels on their bone mineralisation. However, we postulate that 25(OH) D levels are associated with abnormal bone metabolism and the risk for poor bone health and increased fracture risk.

## Conclusion

The present study emphasizes the need to create bone health awareness amongst epileptic patients and health care providers. Proper counselling regarding calcium and vitamin D intake, exposure to sunlight and physical activity is required. Further studies are needed to formulate clear guidelines on prophylactic Vitamin D supplementation needed for prevention and treatment of impaired bone metabolism in epilepsy.

## Conflicts of interest

None

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