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Original Article

Paediatrics Section

# Effect of Ionic Calcium and Vitamin D3 in Lumbar Spine Bone Mineral Density of Paediatric Epileptic Patients on Antiepileptic Drugs

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## ABSTRACT

**Introduction:** Epilepsy is one of the most common neurologic conditions occurring in persons under 21 years of age. Vitamin D deficiency is highly prevalent among children with epilepsy. Antiepileptic Drugs (AEDs) are associated with decreased Bone Mineral Density (BMD) as AEDs increase catabolism of 25-hydroxy vitamin D by induction of the hepatic P 450 enzyme system, which leads to relative hypocalcaemia, increased levels of parathyroid hormone (PTH) and subsequently low BMD.

**Aim:** To evaluate the association of ionic calcium and vitamin D3 in paediatric epileptic patients who were on AEDs with BMD.

**Materials and Methods:** This was an observational cross-sectional study carried out at Department of Paediatrics, SPMC, Bikaner, Rajasthan, India from December 2020 to November 2021. A total of 150 epileptic patients aged 5-15 years who were on AED therapy for more than six months and a comparable group of 130 age and gender matched healthy individuals participated in the present study. Serum vitamin D3, Alkaline Phosphatase (ALP), ionic calcium and phosphorous levels were assessed and compared between both the groups. Using OSTEOPRO DEXA BMD at the lumbar spine was calculated. Mann-Whitney U test and t-test were used to compare quantitative data, whereas Chi-square test was used to compare qualitative data in two groups. Non parametric tests (Spearman's correlation) were used to explore the correlation between the two variables. The p-value <0.05 was considered to be statistically significant.

**Results:** The mean age of study group and control group were 9.94±2.61 years and 10.09±2.53 years, respectively. Mean serum ionic calcium (1.09±0.13 mmol/L) was significantly lower in study group as compared to controls (1.15±0.13 mmol/L) with p-value <0.001. Mean serum phosphorous and serum ALP levels were not significantly different in study and control group. The mean vitamin D3 level (16.70±5.35 ng/mL) was lower in children receiving AEDs as compared to controls (19.08±5.39 ng/mL) with p-value <0.001. Serum levels of ionic calcium and vitamin D3 were found to be significantly lower in groups with polytherapy and enzyme inducer group of AEDs (p<0.05), whereas only statistically significant difference in vitamin D3 was found in subjects with more than two years of AED therapy. The mean Lumbar Spine Bone Mineral Apparent Density (LSBMAD) of the study and control group were 0.47±0.14 g/cm$^2$ and 0.61±0.12 g/cm$^2$ respectively.

**Conclusion:** Epileptic children receiving multiple drugs for longer duration showed more decline in calcium and serum 25-Hydroxy vitamin D compared to those with single drug for shorter duration.


**Keywords:** Bone mineralisation, Epilepsy, Hypocalcaemia, Neurological condition, Seizures

## INTRODUCTION

Epilepsy occurs under the age of 21 years and is most common neurological condition. Onset of the seizures from early childhood have a profound long-term impact in growth and development [1]. Vitamin D exists as serum 25-Hydroxy vitamin D in circulation, which is the marker of vitamin D levels in the body [1]. Vitamin D plays a pivotal role in maintaining a balance between phosphorous and calcium levels as well as their metabolism. The structure of vitamin D is 9, 10 secosteroid and in human body two types are dominantly present vitamin D3 and D2. Vitamin D deficiency can cause reduced bone mineralisation and bone fracture [2]. Vitamin D is essential for the proper maintenance and development of bone. Serum 25-Hydroxy vitamin D concentration status and reduced levels are seen in both adults and children taking AEDs. The most active metabolite of vitamin D is 1,25 $(OH)_2$ D is the most active metabolite of vitamin D and it is found to be decreased in adults taking AEDs [3,4]. Parathyroid gland secretes PTH, which is directly involved in the regulation of calcium. When there is a decrease in serum calcium, PTH acts to increase bone breakdown or resorption. An increase in circulating PTH associated with AED therapy is also reported [5].

Decrease in biologically active forms of Vitamin D that results in hypocalcaemia and feedback hypersecretion of circulating PTH can be attributed to decreased absorption of calcium from the intestine. An increase in PTH leads to increased bone resorption and ultimately reduced BMD and increased fracture risk [6]. Therefore, along with inhibition of the cellular response to PTH, direct inhibition of calcium absorption from the intestine, inhibition of osteoblast cell growth, inhibition of calcitonin secretion and direct effects of AEDs on bone cells also plays a pivotal role in bone health [7]. The resultant hypocalcaemia can exacerbate seizures that are treated with higher doses of anticonvulsants, which sets up a vicious cycle [8]. It's not a routine practice of supplementing calcium and vitamin D3 in children receiving AED in Indian scenario. It is already known that AEDs are associated with bone loss and hypovitaminosis D in adults and elderly people, mainly by enzyme inducer group of AEDs like phenytoin phenobarbitone and carbamazepine [9,10]. The effect of AEDs in paediatric bone health data are meagre in literature as few depicts a need for supplementation of calcium and Vitamin D3 along with initiation of AEDs [11-14], whereas, others cannot establish a relation [15-17].

In the present study, the aim was to determine the association of ionic calcium and vitamin D3 with paediatric BMD at lumbar spine along with the impact of the variables of AED therapy on bone turnover markers in epileptic children aged 5-15 years belonging to north western Rajasthan, India.

## MATERIALS AND METHODS

This observational cross-sectional study was conducted in paediatric hospital in Sardar Patel Medical College, Bikaner, Rajasthan, India, from December 2020-November 2021 with the ethical approval from Institutional Ethical Committee (IEC) vide No : 3711/ 10/11/2020.

**Inclusion criteria:** Children aged between 5-15 years having epilepsy were included in the study. Epilepsy was defined as having atleast two unprovoked seizures more than 24 hours apart and who were are on AED for longer than six months duration [18].

**Exclusion criteria:** Children with diseases primarily involving bone metabolism such as rickets and hypoparathyroidism or familial history of bone metabolism disorder like renal failure, liver diseases and those who were on chronic treatment with drugs other than anticonvulsants were excluded from the study.

**Sample size calculation:** The prevalence of children having reduced BMD with use of antiepileptics ranges from 20-85% from previous studies [19,20]. Taking an average prevalence of 40% for the present study, the sample size was calculated to be 150, using the formula:

$$n=\frac{z^2\ p\times q}{d^2}$$

n=sample size, p=prevalence, q=(1-p), z=critical value (95% confidence interval z=1.96)

d=precision of study (max. Allowable error 20% of prevalence (i.e. 40%)=0.08

$$N=\frac{(1.96)^2\times 0.4\times 0.6}{(0.08)^2}$$

$$=144\ (\text{approx.}150)$$

The study involved 150 epileptic children and 130 age and gender-matched healthy controls. Considering the age and patient's gender, the controls were recruited through an age/gender stratified randomly selected sampling method from local schools. All the parents or guardians, both in case and control groups signed a written informed consent and assent.

### Study Procedure

A trained technician took 5 mL venous blood from anterior cubital vein under aseptic precaution. Ionic calcium, phosphorous, Serum 25-Hydroxy vitamin D (25 OHD) and ALP were measured in both study and control groups. Normal serum ALP levels are significantly higher in children with reference ranges from 210-810 IU/L compared to adult range of 20-140 IU/L [21]. Ionic calcium normal value ranges from 1.10-1.40 mmol/L and serum phosphorous normal value ranges between 4-7 mg/dL in children. Hypocalcaemia considered with values less than 1.10 mmol/L. According to the latest global consensus, recommendations on prevention and management of nutritional rickets, 25 OHD serum level higher than 50 nmol/L (20 ng/mL) was considered as vitamin D sufficient, and less than 20 ng/mL is considered as vitamin D deficient [22,23].

Child's lumbar spine (LV1-LV4) was examined in supine position with their lower limbs partially raised to reduce lumbar lordosis, to be straight and centered with the last rib pair and upper sacrum visualised. The Regions Of Interest (ROI) that is L1-L4 vertebral segments are generated automatically using OSTEOPRO software. Using bone densitometer OSTEOPRO DEXA by BM TECH, BMD was evaluated of lumbar spine. To reduce the effect of growth and bone size on bone mineral density, the authors calculated the bone density per unit volume [24,25].

Hence, Bone Mineral Apparent Density (BMAD) in lumbar area was calculated through the following formula:

$$\text{Lumbar BMAD}=\frac{\text{Bone Mineral Content of L2-L4}}{\text{Bone area}^{1.5}}$$

## STATISTICAL ANALYSIS

The collected data were coded, tabulated and statistically analysed using Statistical Package for the Social Sciences (SPSS) software version 26.0. Descriptive statistics for numerical data by mean, standard deviation and minimum and maximum of the range. Mann-Whitney U test and t-test were used to compare quantitative data whereas Chi-square test was used to compare qualitative data, in two groups. Non parametric tests (Spearman's correlation) were used to explore the correlation between the two variables, as atleast one of the variables was not normally distributed. The p-value <0.05 was considered to be statistically significant.

## RESULTS

In present study, the mean age of study group and control group were 9.94±2.61 years and 10.09±2.53 years, respectively with 40 (26.7%) of cases in the 9-11 year age group followed by 36 (24%) in 11-13 year age group. Among cases, 95 (63.3%) were males and 55 (36.7%) were females, whereas, 83 out of 130 (63.8%) were males and 47 (36.2%) were females in controls. The mean LSBMAD of the study and control group were 0.47±0.14 (g/cm²) and 0.61±0.12 (g/cm²), respectively [Table/Fig-1].

| Age (years) | Lumbar spine bone mineral apparent density (g/cm²) | | | | |
|---|---|---|---|---|---|
| | Mean±SD | | | | p-value |
| | Cases | N=150 | Control | N=130 | |
| ≥5-≤7 | 0.52±0.07 | 18 | 0.54±0.05 | 16 | 0.132[2] |
| 7-≤9 | 0.50±0.10 | 27 | 0.57±0.04 | 15 | 0.222[1] |
| 9-≤11*** | 0.46±0.08 | 40 | 0.61±0.09 | 42 | 0.003[1] |
| 11-≤13*** | 0.48±0.07 | 36 | 0.64±0.09 | 35 | 0.003[2] |
| 13-≤15*** | 0.44±0.05 | 29 | 0.69±0.08 | 22 | <0.001[1] |

**[Table/Fig-1]:** Mean lumbar spine bone mineral apparent density (LSBMAD) according to age group in study and control subjects.
***Significant at p<0.05, 1: Wilcoxon's Mann-Whitney U Test, 2: t-test

The mean serum phosphorous values in the study and control group were 4.40±0.85 mg/dL and 4.43±0.89 mg/dL, respectively, whereas the mean ALP was 356.16±160.98 U/L in study group and 347.46±144.25 U/L in control group [Table/Fig-2].

| Parameters | Group | | p-value |
|---|---|---|---|
| | Study group (n=150) | Control (n=130) | |
| Serum 25 OHD (ng/mL)*** | 16.70±5.35 | 19.08±5.39 | <0.001[1] |
| ALP (U/L) | 356.16±160.98 | 347.46±144.25 | 0.697[1] |
| S phosphorous (mg/dL) | 4.40±0.85 | 4.43±0.89 | 0.914[1] |
| Ionic calcium (mmol/L)*** | 1.09±0.13 | 1.15±0.13 | <0.001[1] |

**[Table/Fig-2]:** Comparison between study groups and controls regarding the laboratory findings.
***Significant at p<0.05, 1: Wilcoxon's Mann-Whitney U Test

Children with Vitamin D3 deficiency 118 (78.7%) were significantly more in those receiving antiepileptic therapy as compared to healthy controls 86 (66.2%) with p=0.032 [Table/Fig-3].

| Vitamin D3*** | Group | | p-value |
|---|---|---|---|
| | Study (n=150) | Control (n=130) | |
| <20 ng/mL | 118 (78.7%) | 86 (66.2%) | 0.032[1] |
| ≥20 ng/mL | 32 (21.3%) | 44 (33.8%) | |

**[Table/Fig-3]:** Comparison between patients and controls regarding the vitamin D3 deficiency.
***Significant at p<0.05, 1: Chi-square Test

Children with hypocalcaemia 95 (63.3%) were significantly more in those receiving AEDs as compared to healthy controls 58 (44.6%) with p=0.014 [Table/Fig-4].

Out of 150 patients, 93 (62.0%) were receiving monotherapy and the rest 57 (38.0%) were on polytherapy. Only 18 patients (12%)

were on enzyme-inducer group of drugs phenytoin, carbamazepine and clobazam in the present study [Table/Fig-5].

| Ionic calcium*** | Group | | p-value |
|---|---|---|---|
| | Study (n=150) | Control (n=130) | |
| <1.10 mmol/L | 95 (63.3%) | 58 (44.6%) | 0.014[1] |
| ≥1.10 mmol/L | 55 (36.7%) | 72 (55.4%) | |

**[Table/Fig-4]:** Comparison between patients and controls regarding the hypocalcaemia.
***Significant at p<0.05, 1: Chi-square test

| Therapy | n (%) |
|---|---|
| Monotherapy | 93 (62.0) |
| Polytherapy | 57 (38.0) |
| Sodium valproate | 145 (96.7) |
| Phenytoin | 16 (10.7) |
| Levetiracetam | 54 (36.0) |
| Carbamazepine | 5 (3.3) |
| Clobazam | 1 (0.7) |
| Enzyme inducers | 18 (12.0) |
| Mean duration of AEDs (months) (m±SD) | 18.63±10.55 |

**[Table/Fig-5]:** Distribution of cases according to AED therapy.

About 87 out of 150 subjects (58%) were on AEDs for less than two years and around 42% of subjects took antiepileptic therapy for more than two years.

There was a positive correlation between vitamin D3 (ng/mL) and LSBMAD (g/cm²), and this correlation was weakly positive statistically significant (rho=0.19, p=0.021). For every one unit increase in vitamin D3 (ng/mL), the LSBMAD (g/cm²) increases by 0.02. Ionic calcium also had a positive correlation with LSBMAD (g/cm²), and this correlation was statistically significant (rho=0.16, p=0.044) [Table/Fig-6]. Whereas, even though, there was a positive correlation of ionic calcium and vitamin D3 with LSBMAD in the control group, it was not statistically significant [Table/Fig-7].

| Parameters | Lumbar spine bone mineral apparent density (g/cm²) | p-value |
|---|---|---|
| Vitamin D3 (ng/mL)*** | Correlation coefficient (rho)=0.19 | 0.021[1] |
| ALP (U/L) | Correlation coefficient (rho)=-0.08 | 0.311[1] |
| S phosphorous (mg/dL) | Correlation coefficient (rho)=0.09 | 0.300[1] |
| Ionic calcium*** | Correlation coefficient (rho)=0.16 | 0.044[1] |

**[Table/Fig-6]:** Association between lumbar spine bone mineral apparent density (g/cm²) and parameters in study group.
***Significant at p<0.05, 1: Spearman's correlation

| Parameters | Lumbar spine bone mineral apparent density (g/cm²) | p-value |
|---|---|---|
| Vitamin D3 (ng/mL) | Correlation coefficient (rho)=0 | 0.983[1] |
| ALP (U/L) | Correlation coefficient (rho)=-0.02 | 0.826[1] |
| S phosphorous (mg/dL) | Correlation coefficient (rho)=-0.04 | 0.677[1] |
| Ionic calcium | Correlation coefficient (rho)=0.03 | 0.720[1] |

**[Table/Fig-7]:** Association between lumbar spine bone mineral apparent density (g/cm²) and parameters in control group.

Serum levels of Ionic calcium and Vitamin D3 were found to be significantly lower in epileptic children who were on multiple drugs and enzyme-inducer group of AEDs (p<0.05) [Table/Fig-8,9].

| Variables | Monotherapy (n=93) | Polytherapy (n=57) | p-value |
|---|---|---|---|
| Ionic calcium*** | 1.12±0.13 | 1.05±0.12 | 0.001[1] |
| Vitamin D3 (ng/mL)*** | 17.17±5.25 | 15.92±5.47 | 0.047[1] |
| ALP (U/L) | 389.12±135.98 | 467.46±124.25 | 0.327[1] |
| S phosphorous (mg/dL) | 4.70±0.55 | 5.23±0.91 | 0.621[1] |

**[Table/Fig-8]:** Comparison between monotherapy and polytherapy on calcium and vitamin D3 in study group
***Significant at p<0.05, 1: Wilcoxon's Mann-Whitney U Test

| Parameters | Enzyme inducer n=18 | Non enzyme inducer n=132 | p-value |
|---|---|---|---|
| Vitamin D3 (ng/mL)*** | 13.59±4.26 | 17.12±5.36 | 0.002[1] |
| Ionic calcium*** | 1.02±0.10 | 1.10±0.13 | 0.004[1] |
| ALP (U/L) | 426.16±101.38 | 392.46±112.45 | 0.082[1] |
| S phosphorous (mg/dL) | 4.40±0.85 | 4.43±0.89 | 0.244[1] |

**[Table/Fig-9]:** Comparisons between enzyme inducers and non enzyme inducers on calcium and vitamin D3 in study group.
***Significant at p<0.05, 1: Wilcoxon's mann-whitney U Test

Statistically significant difference in vitamin D3 was found in those who took AEDs for more than two years (p-value=0.04), whereas, difference in Ionic calcium was not found to be statistically significant with p-value=0.09* [Table/Fig-10].

| Parameters | Duration of therapy (years) (n=150) | | |
|---|---|---|---|
| | <2 years n=87 | ≥2 years n=63 | p-value |
| Vitamin D3 (ng/mL) *** | 1.2±0.11 | 1.0±0.16 | 0.04[1] |
| Ionic calcium | 0.5±0.5 | 0.5±0.6 | 0.09 |
| ALP (U/L)*** | 426.16±101.38 | 552.46±142.45 | 0.04[1] |
| S phosphorous (mg/dL) | 4.05±0.64 | 4.43±0.29 | 0.07 |

**[Table/Fig-10]:** Bone turnover markers in patients on the basis of duration of antiepileptic therapy.
***Significant at p<0.05, 1: Wilcoxon's mann-whitney U test

## DISCUSSION

The present singe centre cross-sectional study depicts around 118 (78.7%) with hypovitaminosis D and 95 (63.3%) with hypocalcaemia in the study group and 86 (66.2%) and 58 (44.6%) with hypovitaminosis D and hypocalcaemia in control group.

Osman NMM et al., in a study on 60 epileptic children with ongoing and 60 healthy controls had a mean age of 9.03±2.02 years in the study group. They also found out that ALP level was significantly higher in patients than in controls while there was no significant difference between patients and controls regarding serum calcium and phosphorous [26]. There was no statistically significant difference between mean ALP and serum phosphorous levels among study and control group in present study whereas Paticheep S et al., [16] in a study of 30 epileptic children with AEDs for atleast six months and 30 healthy children stated that ALP level was significantly higher in patients than in controls and there was no significant difference between patients and controls regarding serum calcium and phosphorous [16]. In contrast to this study, Vestergaard P reported that there were signs of vitamin D deficiency and elevated ALP, elevated PTH, and radiological signs of osteomalacia, while there was no significant decrease in serum calcium levels [12].

Serin HM et al., reported that the differences between phosphorous, PTH, calcium and vitamin D levels of the patients were not statistically significant while ALP was statistically significant [17]. The AEDs affect both calcium homeostasis and phosphate concentration in the body which are essential components of bone metabolism. Hypocalcaemia and hypophosphatemia were commonly seen in patients receiving AEDs [27].

Children with vitamin D3 deficiency (78.7%) were significantly more in those receiving AEDs as compared to healthy controls (66.2%) with p=0.032. The mean vitamin D3 level (16.70±5.35 ng/mL) was lower in children receiving antiepileptic therapy as compared to controls (19.08±5.39 ng/mL) with p-value <0.001. This was similar to study done by Farhat G et al., that showed mean vitamin D3 levels were lower for the enzyme-inducing AEDs (18±11 ng/mL) compared with non enzyme inducing AEDs (22±18 ng/mL) [13].

Vitamin D3 and ionic calcium had a statistically significant positive correlation with BMD with each unit increase in vitamin D3 (ng/mL)

and ionic calcium increases the LSBMAD (g/cm²) by 0.02 and 0.19 units, respectively. This was in contrast, to study done by Farhat G et al., who reported that BMD was reduced in a study group of 29 children receiving AEDs and that the reduction was not correlated with vitamin D levels [13]. Sreedharan M et al., reported hypvitaminosis D in ambulant children who were on valproate monotherapy for more than six months [28]. Another study by Ameena T and Zaher T [29] revealed higher prevalence of vitamin D3 insufficiency in epileptic children on valproic acid and need for supplementation before initiation of AEDs which was in line with the study done by Napakjira L and Nabang C [14].

### Limitation(s)

Being a single centre hospital-based observational study was the main limitation of present study. Daily intake of calcium, duration of sunlight exposure, physical activity and Tanner staging of puberty were not considered. The effect of individual drugs, due to small sample size and dosage of drugs were not incorporated into the present study. There was no follow-up done in any of the cases.

## CONCLUSION(S)

In India, it's not a routine practice of supplementing vitamin D3 and calcium in children with epilepsy. Epileptic children receiving multiple drugs for longer duration showed more decline in calcium and serum 25-Hydroxy vitamin D compared to those with single drug for shorter duration. Thus, the present study emphasises the importance of supplementation of calcium and vitamin D, in children who were on AEDs and also, on judicious selection of AEDs.

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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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