Section: Paediatrics

Original Research Article

STUDY OF VITAMIN D DEFICIENCY IN CHILDREN UNDER 12 YEARS OLD ON ANTIEPILEPTIC DRUG TREATMENT

Vasanth Jeyaram[1], S.Zamir Ahmed[2], M. Mohammed Shakeel[3], Rahul Jayaseelan[1], B. Mythili[4]

[1]*Assistant Professor, Department of Paediatrics, Institute of Child Health and Hospital for Children, Madras Medical College, Tamilnadu, India*
[2]*Assistant Professor, Department of Paediatrics, Thanjavur medical college, Tamilnadu, India*
[3]*Senior Resident, Department of Paediatrics, Institute of Child Health and Hospital for Children, Madras Medical College, Tamilnadu, India*
[4]*Professor, Department of Paediatrics, Dhanalakshmi Srinivasan medical college, Tamilnadu, India*

Received *: 02/04/2025*
Received in revised form *: 17/05/2025*
Accepted *: 04/06/2025*

Corresponding Author:
Dr. Rahul Jayaseelan,
Assistant Professor, Department of Paediatrics, Institute of Child Health and Hospital for Children, Madras Medical College, Tamilnadu, India
Email: vasyjeva.2.dr@gmail.com

DOI: 10.70034/ijmedph.2025.2.369

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (2); 2051-2055

ABSTRACT

Background: Epilepsy is a common chronic neurological disorder that often requires the prolonged use of antiepileptic drugs (AEDs). Certain enzyme-inducing AEDs, such as phenytoin and carbamazepine, can disrupt vitamin D metabolism, increasing the risk of vitamin D deficiency and related bone disorders, particularly in the paediatric populations. Aim: To assess the association between AED use and serum 25-hydroxyvitamin D levels in paediatric epilepsy patients.

Materials and Methods: A case-control study was conducted over 18 months at a tertiary care hospital involving 142 children aged ≤12 years. The study included 71 children with epilepsy on AED therapy for at least six months and 71 age-matched healthy controls without a history of seizures. Serum levels of 25-hydroxyvitamin D, calcium, phosphorus, and alkaline phosphatase were measured. Subgroup analyses were performed between the monotherapy and polytherapy.

Results: The control group had a male predominance (85%), whereas females predominated in the case group (61%). Children on AEDs had significantly lower serum vitamin D3 levels (18.49 ± 6.48 ng/mL) than controls (22.18 ± 6.98 ng/mL; $p = 0.001$) and significantly higher alkaline phosphatase levels ($p = 0.047$). No significant differences were observed in calcium and phosphorus levels between the monotherapy and polytherapy subgroups. A positive correlation was observed between vitamin D3 and calcium ($r = 0.279$, $p = 0.018$).

Conclusion: AED therapy is associated with reduced serum vitamin D levels in children, indicating the need for routine monitoring and potential supplementation to prevent deficiency-related complications.

Keywords: Epilepsy, Antiepileptic drugs, Vitamin D deficiency, Paediatric, Bone metabolism, Serum 25-hydroxyvitamin D.

INTRODUCTION

Epilepsy, a disease of the nervous system that affects all ages, is the most prevalent non-communicable disease worldwide.[1] It is a chronic condition with recurrent seizures triggered from within the brain, which occur in the absence of a metabolic-toxic disease.[2] The prevalence of epilepsy ranges from 4 to 10 per 1000 population.[3] Antiepileptic drugs (AEDs) are used to prevent the recurrence of seizures. The AEDs commonly used are carbamazepine (CBZ), Phenytoin, Phenobarbitone (PB), sodium valproate, clobazam, and levetiracetam.[4] At a given time, approximately 1% of the population is on long-term and sometimes lifelong therapy with AEDs and is therefore exposed to the potential undesirable metabolic side effects of these drugs. The side effects involve changes in homocysteine, lipoproteins, and vitamin D metabolism.[5]

As multiple health outcomes depend on adequate vitamin D status, the effects of AEDs on vitamin D homeostasis in children are of considerable value. Vitamin D is essential for proper bone growth and development in children. The type, dosage, and duration of AED treatment influence the extent of drug-induced osteopathy.[6] Phenytoin, phenobarbital, and carbamazepine have been investigated for their influence on vitamin D metabolism. The most common theory is that AEDs induce cytochrome P450 enzymes in the liver and cause increased conversion of vitamin D to inactive metabolites.

Inactive vitamin D results in decreased absorption of calcium in the intestines, leading to hypocalcaemia, an increase in parathyroid hormone in circulation, and an increase in bone turnover.[7] This, in turn, causes mineral resorption from the bone to maintain calcium within the normal range for vital functions.[8] These biochemical alterations may increase the risk of developing rickets, typically emerging within three months of initiating antiepileptic monotherapy. Childhood epilepsy is under-resourced and under-treated, with a large treatment gap in India.[9] This concern is particularly relevant in India, where nutritional deficiencies are prevalent and epilepsy treatment often involves long-term monotherapy or polytherapy. Therefore, this study aimed to investigate the association between serum 25-hydroxyvitamin D levels and its deficiency in children with epilepsy.

MATERIALS AND METHODS

This case-control study was conducted on 142 paediatric patients admitted to the Paediatric Intensive Care Unit (PICU), paediatric ward, or outpatient department at Mahatma Gandhi Government Memorial Hospital attached to K.A.P. Viswanatham Government Medical College Hospital, Tiruchirapalli, for 18 months, from February 2018 to July 2019. The study was approved by the Institutional Ethics Committee (I.E.C.No.19/2018) and informed consent was obtained before initiation of the study.

Inclusion criteria

This study included paediatric patients ≤ 12 years of age who were admitted for the treatment of epilepsy and were on AED treatment for a minimum of 6 months.

Exclusion criteria

Paediatric patients on AEDs, taking vitamin D supplements, suffering from other systemic diseases or neurological deficits while taking vitamin D, with metabolic bone disease, renal and hepatic impairments, endocrine disorders, or those already on vitamin D supplements, and children with epilepsy who had been seizure-free and off medication for three or more years were excluded.

Methods

Paediatric patients were categorised as the control group (n=71) which included healthy participants without any history of seizures, rickets, or other bone-related disorders. The case or study group (n=71) included paediatric patients with epilepsy who were on AEDs. The patients were assessed for their vitamin D levels, and peripheral venous blood (2 mL) was collected. The patients' charts were systematically reviewed, and vitamin D levels and risk factors were evaluated. The levels of calcium, phosphorus, and alkaline phosphatase and the date of blood sampling were recorded. Children's age and gender, body mass index, underlying disease, type of anticonvulsant, and duration of anticonvulsant use were also recorded.

Statistical analysis

Data were presented as mean, standard deviation, frequency and percentage. Continuous variables were compared using the independent sample t-test. The correlation between continuous variables was assessed using Pearson's correlation test. Significance was defined as $p < 0.05$ using a two-tailed test. Data analysis was performed using IBM SPSS version 20.0.

RESULTS

Patients in the control group had a higher mean age (7.44±3.45 years) than those in the case group (6.23±3.14 years), showing a significant difference (p=0.03). Similarly, the mean weight was higher in the control group (21.61±14.24 kg) than in the case group (17.13±7.12 kg), with a significant difference (p=0.019). There were no significant differences in height and BMI between the groups. Male children were significantly more prevalent in the control group (85%) than in the case group (39%), whereas female children predominated in the case group (61%) compared to the control group (15%), and the difference was significant ($p < 0.001$) [Table 1].

Table 1: Comparison of demographics between the groups.

		Mean ± S.D		P value
		Control	Case	
Age		7.44±3.45	6.23±3.14	0.03
Height (in cm)		112.06±26.07	106.28±20.46	0.144
Weight (kg)		21.61±14.24	17.13±7.12	0.019
BMI		14.92±2.46	14.79±3.01	0.781
Gender (%)	Male	60(85%)	28(39%)	<0.001
	Female	11(15%)	43(61%)	

There was no significant difference in the mean serum calcium and phosphorus levels between the two groups (p>0.05). The mean alkaline phosphatase levels were significantly higher in the case group (163.88±68.58 U/L) than in the control group (142.54±58.02 U/L) (p=0.047). Serum vitamin D3 levels were significantly lower in the case group (18.49±6.48 ng/mL) than in the control group (22.18±6.98 ng/mL) (p=0.001) [Table 2].

Table 2: Comparison of biochemical parameters between the groups

	Mean ± S.D.		P value
	Control	Case	
Serum calcium	8.59±0.55	8.42±0.51	0.053
Serum phosphorus	3.85±0.40	3.94±0.31	0.121
Alkaline phosphatase	142.54±58.02	163.88±68.58	0.047
Serum vitamin D3	22.18±6.98	18.49±6.48	0.001

No significant differences were observed between children receiving monotherapy and those receiving polytherapy in terms of serum calcium (8.44 ± 0.53 vs. 8.40 ± 0.50 mg/dL; p = 0.732), serum phosphorus (3.98 ± 0.30 vs. 3.91 ± 0.32 mg/dL; p = 0.311), alkaline phosphatase (171.03 ± 74.85 vs. 156.53 ± 61.69 U/L; p = 0.377), or serum vitamin D3 levels (19.01 ± 6.54 vs. 17.96 ± 6.46 ng/mL; p = 0.499) [Table 3].

Table 3: Comparison of biochemical parameters between monotherapy and polytherapy

	Mean ± S.D.		P value
	Monotherapy	Polytherapy	
Serum calcium	8.44±0.53	8.40±0.50	0.732
Serum phosphorus	3.98±0.30	3.91±0.32	0.311
Alkaline phosphatase	171.03±74.85	156.53±61.69	0.377
Serum vitamin D3	19.01±6.54	17.96±6.46	0.499

Serum vitamin D3 levels were significantly positively correlated with serum calcium levels (r = 0.279, p=0.018). However, no significant correlations were observed between serum vitamin D3 and serum phosphorus (r = -0.131, p=0.276), alkaline phosphatase (r = -0.087, p=0.472), or the duration of anticonvulsant therapy (r = 0.083, p=0.492) [Table 4 and Figures 1–4].

Table 4: Correlation of vitamin D3 with other biochemical parameters and duration of anticonvulsant therapy

	Vitamin D3	
	r value	P value
Serum calcium	0.279	0.018
Serum phosphorus	-0.131	0.276
Alkaline phosphatase	-0.087	0.472
Duration of anticonvulsant	0.083	0.492

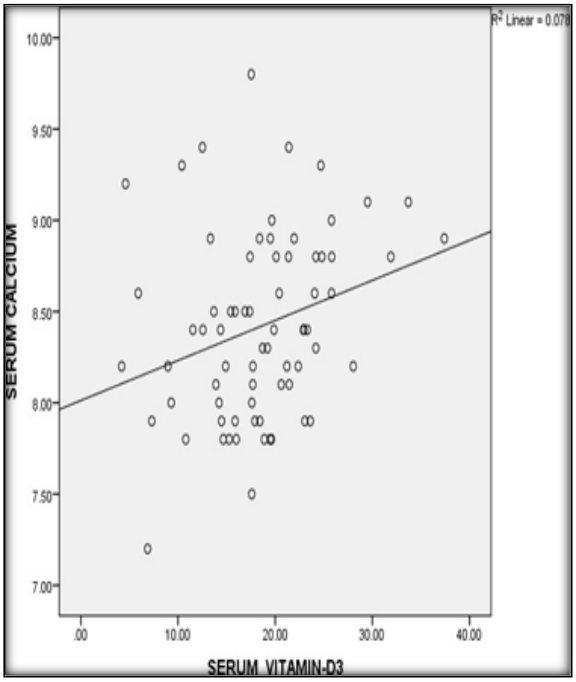

Figure 1: Correlation between calcium and vitamin D3

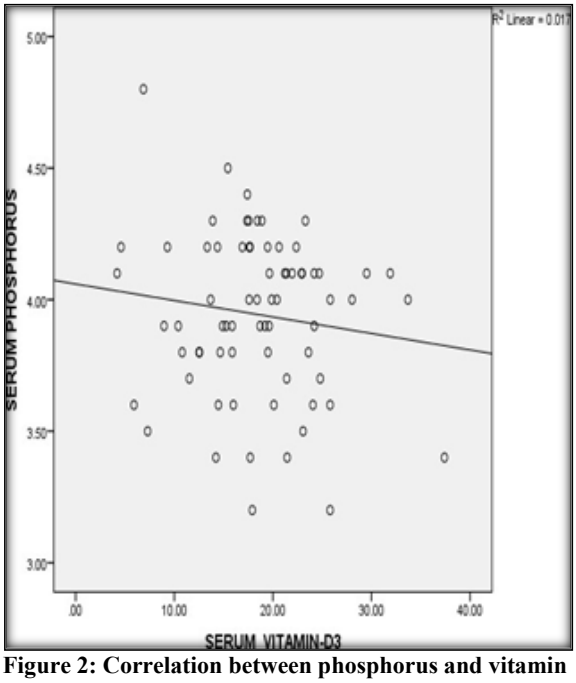

Figure 2: Correlation between phosphorus and vitamin D3

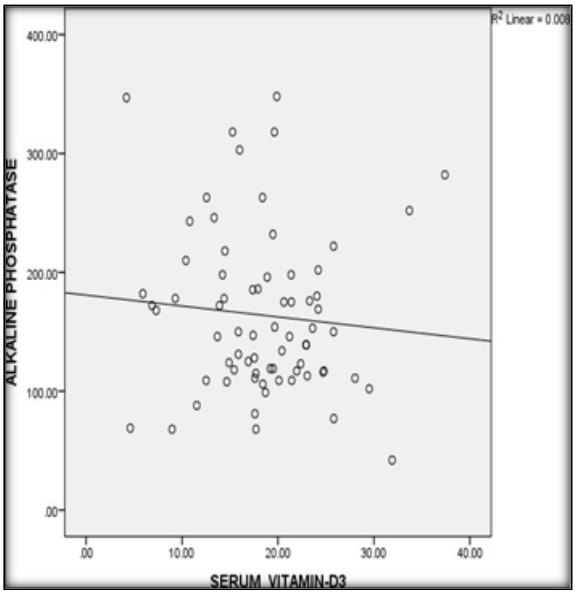

Figure 3: Correlation between alkaline phosphatase and vitamin D3

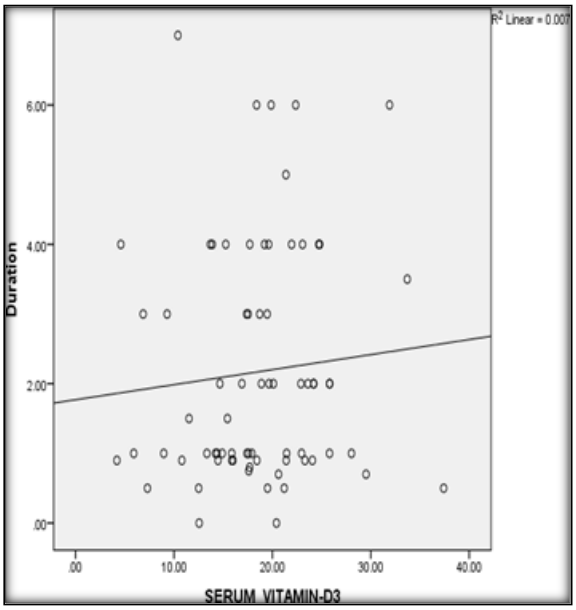

Figure 4: Correlation between the duration of anticonvulsant therapy and vitamin D3

DISCUSSION

This study aimed to assess the impact of antiepileptic drug therapy on serum 25-hydroxyvitamin D levels in children aged ≤ 12 years. There was no difference in 25(OH)D3 levels according to sex, seizure type, or between patients receiving mono- and polytherapy. Patients in the control group had a significantly higher mean age and weight than those in the case group.

The mean alkaline phosphatase levels were significantly higher in the case group than those in the control group. Serum vitamin D3 levels were significantly lower in the case group than in the control group. Serum vitamin D3 showed a significant positive correlation with serum calcium, and there was no significant correlation between serum vitamin D3 and serum phosphorus, alkaline phosphatase, or duration of anticonvulsant therapy.

Fong et al. found that Indian ethnicity, immobility and polytherapy with AEDs were significant risk factors for low vitamin D levels in children with epilepsy.[10] Seth et al. found that 83% of non-ambulant children with cerebral palsy on AEDs were vitamin D deficient.[11] Sreedharan et al. found that significant risk of vitamin D deficiency in ambulant children with epilepsy on monotherapy with CBZ or VPA.[12] Nivedita Patil et al. found that the risk of vitamin D deficiency increased, as the duration of AED usage increased.[13]

A prospective case-controlled study by Chaudhary et al. reported similar findings, as the prevalence of 25-hydroxyvitamin D deficiency was significantly higher among cases (45%) than among controls (24%). The mean alkaline phosphatase level was significantly higher, and the mean serum calcium level was significantly lower (8.3±1.5) in the cases. In contrast, they found a significant association with a longer duration of AED use ($p<0.0001$).[14] A Prospective cohort study with cross-sectional comparison by He et al. reported that there was a significant decrease in 25(OH)D3 in epileptic children compared to controls.[15]

Similarly, Rafiq et al. reported that 32.4% of children on AEDs had vitamin D deficiency (≤20 ηg/dL) vs. 5.9% in controls ($p=0.006$).[16] Abd El-Gaffar et al. also reported that 53.3% of children on AEDs had vitamin D deficiency vs. 2.2% in controls.[17] A prospective case-control study by Saket et al. found a mean age of 5.72±2.9 years (cases) and 5.64±2.9 years (controls), with male predominance observed in the control group. The mean Ca and P were comparable across the groups ($p > 0.05$); however, the mean vitamin D3 level was lower in the case group compared to the control group with a significant difference ($p=0.040$).[18]

These results highlight a consistent reduction in vitamin D levels among children receiving antiepileptic therapy, regardless of the regimen, reinforcing the need for routine monitoring in clinical practice.

Limitations

The relatively small sample size limits generalisability, and 25(OH)D3 levels were not measured before the use of anticonvulsants. Serum parathyroid hormone, urine calcium, and urine phosphate levels were not measured. We also do not routinely screen children with epilepsy using dual-energy X-ray absorptiometry scans to evaluate bone mineral density, which means we cannot comment on the potential impact of our children's low vitamin D levels on their bone mineralisation.

CONCLUSION

Our study showed that serum (25[OH]D) levels were significantly lower in patients with epilepsy than in healthy controls. The possibility of vitamin D

deficiency in children taking anticonvulsants should be considered in clinical practice. Increased attention from both paediatric neurologists and primary care physicians to vitamin D status and bone health among children with epilepsy is warranted. Routine screening for vitamin D levels and consideration of prophylactic supplementation may benefit the long-term management of paediatric epilepsy. Further examination of the impact of vitamin D supplementation on bone health in this population is needed.

REFERENCES

1. Andhi N, Tulasi A, Ranjith Reddy V, Pooja Rao CS. An observational study: To assess the therapeutic outcome and prevalence of neurological psychological and cognitive effects in patients taking antiepileptic medication. EPRA Int J Multidiscip Res 2022:13–23. https://doi.org/10.36713/epra10112.
2. Saxena S, Singh S, Sankaraneni R, Makhija K. Epilepsy. Family Medicine, Cham: Springer International Publishing; 2022, p. 889–904. Doi: 10.1007/978-3-030-54441-6_71
3. Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts ACG. Use of antiepileptic drugs and risk of fractures: case-control study among patients with epilepsy. Neurology 2006; 66:1318–24. https://doi.org/10.1212/01.wnl.0000210503.89488.88.
4. Reddy DS. Clinical pharmacology of current antiepileptic drugs. PCI- Approved-IJPSN 2014; 7:2305–19. https://doi.org/10.37285/ijpsn.2014.7.1.1.
5. Hamed SA, Nabeshima T. The high atherosclerotic risk among epileptics: the atheroprotective role of multivitamins. J Pharmacol Sci 2005; 98:340–53. https://doi.org/10.1254/jphs.crj05003x.
6. Bartl R. Antiepileptic drug-induced osteopathy. Subtypes, pathogenesis, prevention, early diagnosis and treatment. Dtsch Med Wochenschr 2007; 132:1475–9. https://doi.org/10.1055/s-2007-982057.
7. Meier C, Kraenzlin ME. Antiepileptics and bone health. Ther Adv Musculoskelet Dis 2011; 3:235–43. https://doi.org/10.1177/1759720X11410769.
8. Arora E, Singh H, Gupta YK. Impact of antiepileptic drugs on bone health: Need for monitoring, treatment, and prevention strategies. J Family Med Prim Care 2016; 5:248–53. https://doi.org/10.4103/2249-4863.192338.
9. Keni RR, Thomas SV. Bridging the gap in epilepsy treatment in A resource-limited setting. Ann Indian Acad Neurol 2020; 23:427. https://doi.org/10.4103/aian.AIAN_608_19.
10. Fong CY, Kong AN, Noordin M, Poh BK, Ong LC, Ng CC. Determinants of low bone mineral density in children with epilepsy. Eur J Paediatr Neurol 2018; 22:155–63. https://doi.org/10.1016/j.ejpn.2017.10.007.
11. Seth A, Aneja S, Singh R, Majumdar R, Sharma N, Gopinath M. Effect of impaired ambulation and antiepileptic drug intake on vitamin D status of children with cerebral palsy. Paediatr Int Child Health 2017; 37:193–8. https://doi.org/10.1080/20469047.2016.1266116.
12. Sreedharan M, Devadathan K, Mohammed Kunju PA, Sasidharan B, Pillai JP, Vasumathy Amma MA, et al. Vitamin D deficiency in ambulant children on carbamazepine or Sodium valproate monotherapy. Indian Pediatr 2018; 55:307–10. https://pubmed.ncbi.nlm.nih.gov/29428922/
13. Patil NI, Rai SH. Study of vitamin D levels in epileptic children in age group of 2-16 years. Asian J Pharm Clin Res 2015; 8:242–3. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=7ca969afeb8432a6f5de7b6f4e696ce77da06f1f.
14. Chaudhuri JR, Mridula KR, Rathnakishore C, Balaraju B, Bandaru VS. Association of 25-hydroxyvitamin D deficiency in pediatric epileptic patients. Iran J Child Neurol 2017; 11:48–56. https://pubmed.ncbi.nlm.nih.gov/28698728/.
15. He X, Jiang P, Zhu W, Xue Y, Li H, Dang R, et al. Effect of antiepileptic therapy on serum 25(OH)D3 and 24,25(OH)2D3 levels in epileptic children. Ann Nutr Metab 2016; 68:119–27. https://doi.org/10.1159/000443535.
16. Rafiq M, Bano S, Tariq P. Effects of antiepileptic drug therapy on 25oh vitamin D levels. Pak J Physiol 2015; 11:24–6. https://doi.org/10.69656/pjp.v11i4.412.
17. Abd El-Gaffar H, Ali H, El-Awady H. Evaluation of serum vitamin D level in epileptic children on anticonvulsant drug therapy. Fayoum Univ Med J 2023; 12:63–71. https://doi.org/10.21608/fumj.2023.336854.
18. Saket S, Varasteh N, Halimi Asl AA, Saneifard H. How antiepileptics may change the serum level of vitamin D, calcium, and phosphorus in children with epilepsy. Iran J Child Neurol 2021; 15:19–27. https://doi.org/10.22037/ijcn.v15i1.25952.