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Original Research Article

Effect of antiepileptic drugs on bone metabolism in children using biochemical markers: a case control study

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ABSTRACT

Background: Most epileptic patients are diagnosed and treated in childhood and adolescence and this period is crucial in attaining peak bone mass. Few studies are conducted on children showing long term effects of AEDs on bone metabolism. So, the present study was conducted to evaluate correlation of long-term uses of AEDs with changes in bone metabolism using biochemical marker.
Methods: Total of 140 subjects divided into 70cases - Epileptic children aged 1 to 14 years who are on AEDs for at least 6months and 70 Controls- Children aged 1 to 14 years not on AEDs. Semi structured questionnaire was used to collect demographic data. Venous blood samples were collected and sent for laboratory investigations like Serum vitamin D, serum calcium, serum phosphorus, Parathyroid hormone and alkaline phosphatase levels.
Results: Mean age of study population in cases was 7.74±4.43 years and in controls was7.65±3.72 years. Mean vitamin-D, calcium, phosphorus decreases while PTH and ALP increases with duration of treatment in epileptic children with a statistically significant difference between them (P<0.05). Mean serum vitamin D level in cases and in controls was with no statistical significant difference between two groups. Mean serum calcium, phosphorus, parathormone and alkaline phosphatase levels in cases and controls all had a statistically significant mean difference between two groups. Serum vitamin-D, serum calcium, serum phosphorus was low in patients treated with enzyme inducing when compared to non-enzyme inducing drugs in epileptic children with a statistically significant difference between them (P<0.05). Serum vitamin-D, serum calcium, serum phosphorus was high in patients on monotherapy when compared polytherapy in epileptic children with a statistically significant difference between them (P<0.05).
Conclusions: Present study shows that children on AEDs for longer duration had low bone mineral parameters when compared to normal children. The study emphasizes that mineral levels need to be monitored in epileptic patients as they are at a higher risk of falling and bone fractures.

Keywords: Anti-epileptic drugs, Bone metabolism, Pediatric

INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent seizures and is defined as occurrence of two or more unprovoked seizures occurring >24 hours apart. Seizures may manifest as impairment or loss of consciousness, abnormal motor activity, behavioral abnormality, sensory disturbances or autonomic dysfunction.

Globally, an estimated 50 million with epilepsy, nearly 80% of whom live in low- and middle-income countries.[1] India contributes to one-sixth of global burden of epilepsy. Over 60% of epilepsy starts in childhood and prevalence rates range from 6-8per 1000population.[2]

The main stay in treatment of epilepsy is antiepileptic drugs (AEDs), often for a long duration. A large body of evidence indicates an association between AEDs and bone abnormalities ranging from decreased bone mineral metabolism to increased risk of fracture to an increased fracture risk mechanism being the AEDs act directly on bone cells that influence bone formation and resorption leading to osteoporosis and spontaneous bone fractures.[3-8] The drugs such as carbamazepine (CBZ), phenobarbitone (PB), phenytoin (DPH) and sodium valproate (VPA) which are commonly used to control seizure are known for inducing the activity of hepatic oxidase throughout the enzyme microsomal (P450). They influence the metabolism of minerals and bone by increasing vitamin D metabolism, that causes a deficiency of vitamin D (VDD).[9,10,11] This VDD inhibits intestinal calcium transport and absorption causing hypo calcemia.

For treating children, the most commonly used AED's are VPA, CBZ, DPH and PB either singly or as multiple therapy to control seizures. There are only few studies conducted to on children in relation to chronic use of AEDs with serum calcium, serum phosphorus, alkaline phosphatase (AP), parathormone (PTH) and 25-hydroxy vitamin D in our department. So, the present study was conducted to evaluate the correlation of long-term uses of AEDs with changes in bone metabolism using biochemical markers.

METHODS

It was single –center, case control study from Dec 2020 to May 2022, conducted at department of pediatrics, ESIC Medical College, Hyderabad. Approval was obtained from the institutional ethics committee. A written and informed consent was taken from parents of children who participated in the present study. sampling size in case data is on interval/ratio scale and mean is parameter of the study (reference Sharma et al). For the present study the sample size in each group was rounded to 70 in each group and the total sample size was 140 subjects.

Inclusion criteria

Group 1 cases

Epileptic children aged 1 to 14 years who are on AEDs for at least 6 months. Group 2: Controls- Children aged 1 to 14 years not on AEDs.

Exclusion criteria

Children with a history of medical disorders which likely affect bone metabolism (endocrinal, hepatic, renal, hematological and rheumatological diseases). Children on medications known to affect bone metabolism (Eg: steroids, diuretics, vitamin D and calcium supplements) and children with a known bone disorder or children recently bedridden for any reason like fractures or paralysis.

A semi structured questionnaire was used to collect demographic data regarding age, gender weight, BMI, comorbid conditions, nutritional status. Venous blood samples were collected and sent for laboratory investigations like Serum vitamin D levels, serum calcium, serum phosphorus, Parathyroid hormone and alkaline phosphatase levels.

Data collected was entered into MS-Excel 2013 spreadsheet. The collected data was analyzed using IBM statistical package for social sciences (IBM SPSS) version 23 software (trail version). Continuous variables were reported as mean±standard deviation (SD) while categorical variables were expressed as absolute values and percentages.

Microsoft Excel 2013 was used for generating charts and diagrams. 3. Chi-square test and paired t-test were applied to find the significant difference between two groups. 4). ANOVA test was applied to find the significant difference for more than two groups.5. P-value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the study population in cases was 7.74±4.43 yrs. and in controls was 7.6±3.72 years. In the case group 41.4% belongs to 1-5 years followed by 37.1% in 10- 14 years age group in the case group, 52.9% were male child and 47.1% were female child. In the control group 44.3% were male child and 55.7% were female child.

Table 1: Distribution of children between two groups according to gender.

Gender	Cases	Controls
Males	37 (52.9%)	31 (44.3%)
Females	33 (47.1%)	39 (55.7%)
Total	70 (100%)	70 (100%)

Table 2: Distribution of cases based on mean duration of treatment.

Duration	No. of cases	Percentage
<12 months	28	40
13-18 months	16	22.9
>18 months	26	37.1
Total	70	100

Mean duration of AEDs =15.6±5.9 months (6-27months)

Table 3: Distribution of cases based on enzyme inducing and non-enzyme inducing AEDs.

AEDs	No. of cases	Percentage
Enzyme inducing AEDs	43	61.4
Non enzyme inducing AEDs	27	38.6
Total	70	100

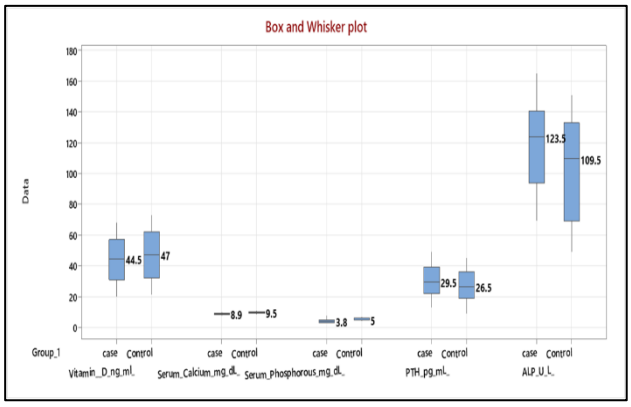

Figure 1: Boxes and whisker plots showing biomedical markers in cases/control.

The mean age of the study population in cases was 7.74±4.43 years and in control 7.65±3.72 years. In case group 29 (41.4%) belongs to 1-5 years, 15 (31.4%) belongs to 6-10years and 26 (37.2%) and in controls 24 (34.3%), 26 (37.1%), 20 (28.6%) belongs to 1-5, 6-10 and 11-14 years respectively. The mean duration of treatment with AEDs in cases group was 15.6±5.9 months. 40% of cases were under treatment for <12months, 22.9% cases were 13-18months and 37.1% were >18months.Out of 70 cases in the present study 61.4% were receiving enzyme inducing AEDs and 38.6% were receiving non enzyme inducing AEDs.

Vitamin D

The median vitamin D levels were lower among the cases as compared to the controls, suggesting that 50% of the cases had lower vitamin D levels than controls. Although the first quartiles (25%) were almost similar among cases and controls, the third quartile (75%) was higher among controls and the IQR was wider among controls as compared to cases, suggesting wider variation in vitamin D levels among the controls. No outliers noted

Serum calcium

The median, lower quartile and upper quartile of serum calcium levels were lower among cases as compared to controls. The box plots for serum calcium levels were very small for cases and controls, suggesting narrow range of levels in both groups i.e., all individuals in either group showed similar readings. However, the IQR was wider among controls as compared to cases, suggesting wider variation in serum Calcium levels among the controls. No outliers were seen.

Serum phosphorus

Serum Phosphorus levels, similar to serum Calcium levels, showed very short box plots i.e., IQRs, and the IQR ranges were slightly wider among cases. Median, first quartile and third quartile were lower among the cases, suggesting that overall, serum Phosphorus levels were lower among cases, as compared to controls.no outliers were seen.

Parathyroid hormone

Although the IQR was same in cases as well as controls, i.e., 17.25, median, first quartile and third quartile of PTH were higher among cases, suggesting possible positive association. No outliers were seen

Table 4: IQR depiction of biochemical markers in cases/controls.

Parameter	Cases				Controls			
	Q1	Q2 (Median)	Q3	IQR	Q1	Q2 (Median)	Q3	IQR
Vitamin -D (ng/ml)	31	44.5	57	26	32	47	62.25	30.25
Serum calcium (mg/dL)	8.3	8.9	9.2	0.9	9.1	9.5	10.3	1.2
Serum phosphorous (mg/dL)	2.9	3.8	4.9	2	5	5	6	1
PTH (pg/mL)	22	29.5	39.25	17.25	18.75	26.5	36	17.25
ALP(U/L)	93.25	123.5	140.5	46.75	69	109.5	132.75	63.75

Alkaline phosphatase

Similar to PTH, the median, first quartile and third quartile of ALP were higher among cases, but the IQR was wider among controls. No outliers noted. The mean vit-D level with duration of treatment ≤12 months, 13-18 months and18months was 58.3±4.3, 40.5±8.7 and 30.3±5.1 respectively. The mean vitamin D decreases with increase in duration of treatment with a statistically significant association between them.

The mean calcium level decreases with increase in duration of treatment with a statistically significant association between them. The mean serum calcium level

with duration of treatment ≤12 months, 13-18 months and >18 months was 9.3±0.2, 8.6±0.4 and 8.2±0.3 respectively. The PTH level increases with duration of treatment but there was no statistically significant association between them. The mean ALP level also increases with increase induration of treatment with a statistically significant association between them.

Table 6: Comparison of biochemical markers with mean duration of treatment with AEDs.

	Mean duration of treatment with AEDs			
	≤12 months	13-18 months	>18months	P-value (ANOVA)
Vitamin-D (ng/ml)	58.3±4.3	40.5±8.7	30.3±5.1	<0.001
Serum calcium (mg/dl)	9.3±0.2	8.6±0.4	8.2±0.3	<0.001
Serum phosphorus (mg /dl)	5.3±0.5	3.7±0.5	3.1±0.4	<0.001
PTH (pg/ml)	29.2±9.1	27.5±9.1	33.8±9.4	0.067
ALP (U/L)	90.4±13.6	128.4±14.8	146±2.3	<0.001

Table 7: Comparison of biochemical markers with cases and controls.

Biochemical markers	Cases		Controls		
	mean	SD	mean	SD	P value
Vitamin–D (ng/ml)	43.82	13.78	46.56	16.34	0.228
Serum calcium (mg/ml)	8.77	0.57	9.63	0.63	0.0001
Serum phosphorus (mg/ml)	4.13	1.09	5.47	1.08	0.0001
Parathormone (pg/ml)	30.54	9.48	27.01	10.34	0.001
Alkaline phosphatase (U/L)	119.7	28.2	103.6	33.3	0.0001

Table 8: Comparison of biochemical markers with type of AEDs.

Biochemical markers	Type of AEDs		
	Enzyme inducing	Non enzyme inducing	P value
Vitamin D (ng/ml)	37.7±11.8	53.6±10.8	<0.001
Serum calcium (mg/ml)	8.5±0.50	9.17±0.42	<0.001
Serum phosphorus (mg/ml)	3.6±0.9	4.9±0.9	<0.001
Parathormone (pg/ml)	33.04±9.6	26.5±7.9	0.005
Alkaline phosphatase (U/L)	132.6±23.5	99.2±22.5	<0.001

Table 9: Comparison of cases with mono/poly drug therapy of AEDs.

	Type of AEDs		
	Monotherapy	polytherapy	P-value
Vitamin-D(ng/ml)	45.6±12.6	30.6±11.5	<0.001
Serum calcium (mg/ml)	8.9±0.5	8.2±0.5	<0.001
Serum phosphorus (mg/ml)	4.3±1.1	3.3±10.4	<0.002
Parathormone(pg/ml)	29±9.2	33.5±10.4	0.238
Alkaline phosphatase(U/L)	114.4±26.2	145.4±23.8	0.003

DISCUSSION

A prospective case control study was carried out over a period of 18 months from December 2020 to May 2022 at Department of Paediatrics, ESIC Medical College, Hyderabad among Children between ages of 1 year to 14 years with an aim to assess the effect of Anti-Epileptic Drugs on bone metabolism using serum vitamin D, calcium, phosphorus, parathyroid hormone and alkaline phosphatase levels as biochemical markers.

The mean age of the study population in cases was 7.74±4.43 years and in controls was 7.65±3.72 years. In the case group 41.4% belongs to 1-5 years, 21.4% belongs to 6-10years followed by 37.1% in 11-14 years age group.[21] A similar study conducted by Borusiak et al had reported the mean age of children with seizures was 9.11±4.3 years. In the study by Razazizan et al.the mean age of the study group was 7.1±3.5 and in control group was 7.19±3.6 years.[22] Paticheep et al., had reported that the majority of the children in their study were around

five years.[24] Yaghini et al. had found no significant difference of age between two groups. Sidiartha et al.,[30] had reported that the mean age of the children with seizures was 8.5±1.9 years.[25]

In the case group, 52.9% were male child and 47.1% were female child. In the control group 44.3% were male child and 55.7% were female child. Studies conducted by Paticheep et al. Sidiartha et al and Yaghini et al had reported similar gender ratio in the study population.[24,25,30] However, Borusiak et al had reported that there was slight predominance of female child in seizure group.[21]

The mean duration of treatment with AEDs in cases group was 15.6±5.9 months. 40% of cases was under treatment for ≤12 months, 22.9% cases were 13-18 months and 37.1% cases was >18 months. Paticheep et al had reported that the mean duration of antiepileptic drug therapy was 23.04±16.33 months. In a study by Yaghini et al AEDs had been administered for a mean duration of 2.57years.[24,25] Sidiartha et al had found that the mean duration of children with epilepsy on AEDs in the study was 20.5 months.[30]

Out of 70 cases in the present study 61.4% were receiving enzyme inducing and 38.6% were receiving non-enzyme inducing AEDs. A similar study by Sidiartha et al., had reported that 60% were receiving enzyme inducing and 40% were receiving non-enzyme inducing. Borusiak et al had reported that majority of children with seizures were receiving non-enzyme inducing AEDs. Paticheep et al had reported that polypharmacy split of in their study antiepileptic drugs used was 56.7 percent on monotherapy and 43.3 percent on polytherapy. A similar study by Sidiartha et al had reported that 60% were on monotherapy.[21,24,30]

Serum vitamin D levels in cases vs controls

The mean serum vitamin D level in cases was 43.82±13.78 ng/ml and in controls was 46.56±16.34 ng/ml. There was no statistically significant mean difference between two groups ($p>0.05$). Similar to the study findings Singla et al., and Borusiak et al., had reported that the mean Vitamin-D level similar between cases and controls with no significant difference. Similar to the study findings Razazizan et al., had reported that mean serum vitamin D level in cases was 26.52±10.75 ng/mL and in controls was 30.09±10.4 ng/ml with no statistically significant mean difference between them.[21,22,28] Paticheep et al., and Yaghiniet al., had also reported no statistically significant differences in serum 25-hydroxyvitamin D level between the epileptic and control groups. However, in the study by Rauchenzauner et al, the proportion of children with vitamin D insufficiency was higher in the epilepsy group compared with the control group (32% vs 15%).[21,25] A meta-analysis conducted by Zhang et al., had reported a significant reduction in vitamin-D level among children who are under treatment with AEDs. However, we found a decrease in trend of vit D levels in children using AEDs for longer duration >12 months with statistical significance p value0.001.

Serum calcium levels in cases vs controls

The mean serum calcium level in cases was 8.77±0.57 mg/dl and in controls was 9.63± 0.69 mg/dl. There was a statistically significant mean difference between two groups with low serum calcium in cases when compared to controls ($p<0.05$). Similar to the study findings Singla et al., had reported that the mean calcium level in cases was 9.3±0.5 and in controls was 9.7±0.4 with a significant difference between them.[28] Borusiak et al., had reported that the mean concentrations of calcium were found to be significantly lower ($p<0.01$) among the cases was low when compared with controls. Hasannen et al., had also reported that mean serum calcium level in cases was 8±2mg/dl and in controls was 8.6±1.2 mg/dl with a statistical significant mean difference between two groups which was similar to the study findings.[21] However, Razazizan et al., had reported that mean serum calcium level in cases was 9.91±0.67 mg/dl and in controls was 10.08±3.3 mg/dl with no statistical significant mean difference between them.[22] Paticheep et al and Yaghini et al, had also reported no statistically significant differences in serum calcium level between the epileptic and control groups.[24,25] A meta-analysis conducted by Zhang et al., had reported no significant changes in serum calcium level among children who are under treatment with AEDs when compared to control group.[26]

Serum phosphorus levels in cases vs controls

The mean serum phosphorus level in cases was 4.13±1.09 mg/dL and in controls was5.47±1.08 mg/dl. There was a statistically significant mean difference between two groups with low serum phosphorus in cases when compared to controls ($p<0.05$). Similar to the study findings Borusiak et al., had also found low mean phosphorus level in cases when compared to controls with a statistical significant difference.[21] Hasannen et al., had also reported that mean serum phosphorus levels in cases was 4.5±1.1 mg/dl and in controls was 5.3±0.7 mg/dl with a statistical significant mean difference between two groups which was similar to the study findings.[29] In contrast to the study findings Singla et al,[13] had reported that the mean phosphorus level in cases was 3.4±0.5 and in controls was 3.5±0.7 with no significant difference between them. Paticheep et al., and Yaghini et al., had also reported no statistically significant differences in serum phosphorus level between the epileptic and control groups.[24,25] A meta-analysis conducted by Zhang et al., had reported no significant changes in serum phosphoruslevel among children who are under treatment with AEDs when compared to control group.[26]

Serum PTH levels in cases vs controls

The mean PTH level in cases was 30.54±9.48 pg/ml and in controls was 27.01±10.34 pg/ml with a statistical significant mean difference between two groups with high PTH in cases when compared to controls ($p<0.05$).Similar to the study findings Hasannen et al., had also reported that mean PTH level in cases was 43.6±29.1 pg/dl and in controls was 29.6±7.4 pg/dl with a statistical significant mean difference between two groups.[29] In contrast to the study findings Singla S et al., Paticheep et al, and Yaghini et al, had reported that the mean PTH level in cases and controls were similar with no significant difference between them.[24,25,28] A meta-analysis conducted by Zhang et al., reported no significant changes in PTH level among children who are under treatment with AEDs when compared to control group. Borusiak et al., had also found low PTH level in cases when compared to controls with a statistically significant difference.[21,26]

Serum ALP levels in cases vs controls

The mean ALP level in cases was 119.7±28.2 U/l and in controls was 103.6±33.3U/l. There was a statistical significant mean difference between two groups with high ALP incases when compared to controls ($p<0.05$).A meta-analysis conducted by Zhang et al, had also reported a significant increase in serum ALP level among children who are under treatment with AEDs when compared to control group.[26] Similar to the study findings Razazizan et al, Hasannen et al, and Yaghini et al, had reported that mean ALP level in cases was high when compared to controls with a significant mean difference between them.[22,26,29] However, in contrast to the study findings Paticheep et al, had reported that the mean ALP level in cases and controls were similar with no significant difference between them.[24]

Duration of treatment

The mean vitamin-D level with duration of treatment ≤12 months, 13–18 months and >18 months was 58.3±4.3, 40.5±8.7 and 30.3±5.1 ng/ml respectively. The mean vitamin-D decreases with increase in duration of treatment with a statistically significant association between them. The mean calcium level decreases with increase in duration of treatment with a statistically significant association between them. The mean Serum Calcium level with duration of treatment ≤12 months, 13–18 months and >18 months was 9.3±0.2, 8.6±0.4 and 8.2±0.3 mg/dl respectively. The mean serum phosphorus decreases with increase in duration of treatment with a statistically significant association between them. The mean PTH and ALP level increase with increase in duration of treatment with a statistically significant association between them. Similar to the study findings Hasannen et al., had found that the lowest serum calcium, phosphorus, and ALP were for patients receiving antiepileptic drugs for more months.[29] Sidiartha et al., had also reported a negative correlation between serum calcium with duration of treatment with AEDs However, Borusiak et al., did not detect any correlation between length of therapy and laboratory values. Razazizan et al., had also reported that calcium levels, alkaline phosphatase and 25-hydroxy vitamin D in patients were irrelevant with duration of treatment.[21,22,30]

Enzyme inducing AEDs vs non-enzyme inducing AEDs

The mean vitamin-D level in Enzyme inducing AEDs was 37.7±11.8 ng/ml and in non-enzyme inducing AEDs was 53.6±10.8 ng/ml. Akin et al., found no differences of vitamin-D levels while comparing children taking valproic acid and children on carbamazepine for at least 1 year.[19] The mean calcium level was low in Enzyme inducing AEDs when compared to non-enzyme inducing AEDs with a statistically significant difference between them. The mean calcium level in enzyme inducing AEDs was 8.52±0.50 mg/dl and in non-enzyme inducing AEDs was 9.17±0.42 mg/dl. Borusiak et al, had reported that mean calcium concentrations for patients treated with oxcarbazepine was low whereas patients treated with lamotrigine had concentrations within normal limits.[21] The mean Serum phosphorus level in Enzyme inducing AEDs was 3.6±0.9 mg/dl and in non-enzyme inducing AEDs was 4.9±0.9 mg/dl. The mean PTH level in Enzyme inducing AEDs were 33.04±9.6 pg/ml and in non-enzyme inducing AEDs were 26.5±7.9 pg/ml. The mean ALP level in Enzyme inducing AEDs was 132.6±23.5 U/l and in non-enzyme inducing AEDs was 99.2±22.5U/l Similar to the study findings Yaghini et al., had found that patients receiving enzyme-inducing AEDs had significantly lower biochemical bone markers when compared to those receiving non-enzyme inducing AEDs.[25] However, Borusiak et al, had found that there was no statistical significant difference between patients on different antiepileptic drugs medication for any of the bone markers.[21] Razazizan et al, had also reported that calcium levels, alkaline phosphatase and 25-hydroxy vitamin D in patients were irrelevant with drug type.[22]

Monotherapy vs multidrug therapy

The mean Vitamin-D level in children with monotherapy was 45.6±12.6 ng/ml and in children with multidrug therapy was 30.6±11.5 ng/ml with a statistically significant difference between them. The mean calcium level in children with monotherapy was 8.9±0.5 mg/dl and in children with multidrug therapy was 8.2±0.5 mg/dl with a statistically significant difference between them. The mean Serum phosphorus level in children with monotherapy was 4.3±1.1 mg/dl and in children with multidrug therapy was 3.3±0.9 mg/dl with a statistically significant difference between them. The mean PTH level in children with monotherapy was 29±9.5 and in children with multidrug therapy was 33.5±10.4 pg/ml. The mean ALP level in children with monotherapy was 114.4±26.2 U/l and in children with multidrug therapy was 145.4±23.8 U/l with a statistically significant difference

between them. Similar to the study findings Hasannen et al., had found that the lowest serum calcium, phosphorus, and ALP were for patients receiving polytherapy when compared to children receiving monotherapy.[29] In the study by Rauchenzauner et al., they found that AE monotherapy does not lead to Vitamin D deficiency in otherwise healthy children treated with non-enzyme inducing AEDs or minimal enzyme-inducing AEDs.[33]

Limitations

This study trial takes a heterogenous group of study participants as control group within the hospital settings which may not represent typical of albeit reasonable exclusion criteria were applied. selection of control group with wide range of age that has weak generizability is another drawback. Other limitations for this study could be small sample size and a smaller number of children included with longer duration of AED therapy more than 2 years.

CONCLUSION

The present study shows that children on longer duration of AEDs had low bone mineral parameters when compared to the normal children. Similarly, children on multiple AEDs and on enzyme inducing AEDs also had low bone mineral parameters as compared to those on monotherapy and non-enzyme inducing AEDs respectively. The study emphasizes the need for routine monitoring of bone mineral levels in all children on AEDs for longer duration as they are at a higher risk of falling and bone fractures. Altered bone mineral status can have remarkable effect on growing children which may ultimately affect their growth potential.

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