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Correlation of Vitamin D Level and Bone Mineral Density in Epilepsy Children Who Received Oral Antiepileptic Drug

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Abstract

BACKGROUND: Vitamin D plays an essential role in achieving adequate bone mineralization. Antiepileptic drug (AED) will cause a change in calcium serum levels and bone mineral density (BMD) through increase catabolism of Vitamin D in the liver, as well as having a direct effect on the bone.

AIM: The aimed of this study was to know the correlation of Vitamin D [25(OH)D] level and BMD in epilepsy children who received oral AED.

METHODS: This cross-sectional study was conducted from May to September 2016. Subjects were collected using consecutive sampling in 1−11-year-old epilepsy children who went to the pediatric Neurology and Endocrinology outpatient clinic at Sanglah Hospital. Age, sex, body weight, body height, type and number of AED used, and duration of treatment were recorded. Measurement of 25(OH)D level and BMD was performed. Pearson test was used to analyze the strength of correlation based on normality test result.

RESULTS: Thirty subjects were collected, male (19/63.33%), mean age was 7.22 years, mean treatment duration was 1.71 years. Type of AED was inducer AED (18/60%) and non-inducer AED (12/40%). Mean Vitamin D level was 27.19 ng/mL and mean BMD was 0.78 g/cm^2. Partial correlation test of Vitamin D level with BMD after controlling age found r = 0.118 with p = 0.54.

CONCLUSION: There was weak correlation between Vitamin D level and BMD in epilepsy children who received oral AED, but the correlation analysis was not sufficient to prove the relationship.

Introduction

The prevalence of epilepsy in the world is 10 per 1.000 people, with incidence 50 per 100.000 people per years [1]. Epilepsy is closely related to the incidence of fractures. Some of them are caused directly due to seizure, a fall, or without seizures before. Patients with epilepsy receiving long-term antiepileptic drug (AED) treatment. Antiepileptic drug treatment was identified as a risk factor for decreasing in bone density and impaired calcium metabolism [2]. Risk of fracture that occurs after a few years of taking AED is 2–6 times more likely to happen than the general population [3].

Antiepileptic drug is divided into two major groups, that is, AED which induces liver enzymes and AED which does not induce liver enzymes. The antiepileptic drug that induces the cytochrome P450 enzyme, such as carbamazepine (CBZ), phenytoin (PHT), and phenobarbital (PB), is estimated to increase catabolism of Vitamin D in the liver, resulting in decreased levels of 25-hydroxyvitamin D (25(OH)D) which helps absorption of calcium in intestines. Disruption of calcium absorption in intestine will cause hypocalcemia. It will trigger parathyroid hormone secretion which increases calcium resorption in the bone. This causes a decrease in bone calcium which results in reduced bone density or osteopenia [4], [5]. Antiepileptic drug which does not induce liver enzymes such as valproic acid (VPA) works by giving immediate effect on bone growth through mechanisms of inhibiting the proliferation of chondrocyte cells in bones [6].

Vitamin D is an essential nutrient that maintains the homeostasis of calcium and phosphorous levels in the body for the proper development and maintenance of bone. Serum 25(OH)D concentration is the most commonly used index of Vitamin D status, reduced level is seen in both adults and children taking AED. The other side effects involve changes in in homocysteine and lipoproteins metabolism [7].

The association between 25(OH)D levels and BMD has been shown in several studies. One study in 2015 showed AED do adversely affect the bone mineral metabolism, as manifested by decreased Vitamin D levels in serum [8]. Other study showed with low serum Vitamin D, significant effects on total body bone mineral content and lumbar spine BMD were roughly equivalent to a 2.6% and 1.7% point greater change from baseline in the Vitamin D supplemented group [9]. The purpose of this study to prove the correlation of Vitamin D level and bone mineral density in epilepsy children who received oral AED.

Methods

This analytic cross-sectional study was conducted on May–September 2016. Inclusion criteria were epilepsy children 1–11 years of age, who went to the pediatric Neurology and Endocrinology outpatient clinic at Sanglah Hospital Denpasar-Bali, get first-line antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, ad valproic acid) for more than 6 consecutive months, and parents agree to participate and sign the informed consent. Exclusion criteria were patients who got severe cerebral palsy, puberty, liver disease, gastrointestinal disease, autoimmune disease, malignancy, bone disease, hormonal disorders, long-term corticosteroid treatment, Vitamin D supplementation, and calcium during treatment. Ethical clearance was approved by the Commissions of Ethics of the Medical School Udayana University, Sanglah Hospital, Denpasar-Bali.

Subjects were consecutively enrolled until completion of the required sample size. Age, sex, body weight, body height, type and number of AED used, and duration of treatment were recorded. Body weight and height measurement are measured using scale ZT-120® standard type; body weight with precision of 0.5 kg and height with precision 0.5 cm. Those scales were last calibrated in May 2016. The duration of treatment AED is the interval from the first treatment given until the time of the study. Serum of 25(OH) D level measurements was performed according to enzyme-linked immunosorbent assay (ELISA) with the unit ng/mL in Prodia Laboratory, Denpasar. Vitamin D3 deficiency was defined as serum level of 25(OH) D less than 20 ng/mL, Vitamin D insufficiency was defined as serum level of 25(OH)D range from 20 to 32 ng/mL, and Vitamin D sufficient was defined as serum level of 25(OH)D range from 33 to 80 ng/mL [10]. Bone density was determined using dual-energy X-ray absorptiometry (DXA) by GE Healthcare en CORE 2007 in Wing Amerta Sanglah Hospital, Denpasar. Results for BMD were expressed as absolute values (g/cm^2). According to the WHO criteria, normal bone density was considered when the Z score was >−1.0, osteopenia was considered when the Z score was between −2.5 and −1.0, and osteoporosis was considered when the Z score was <−2.5 [11]. All measurements were recorded on questionnaire and then collected by researcher for analysis.

Statistical analysis

Statistical analysis in this study using computer statistics SPSS 23 software. Characteristics of data shown in table and narrative form. The data distribution was analyzed with Kolmogorov–Smirnov test because the sample size was 30 and considered normal if p >0.05. Pearson test is used if the data are normally distributed, and if the data are not normally distributed, then Spearman test will be done.

Table 1: Characteristics of subjects

Characteristics of subjects	n=30
Gender, n (%)	
Male	19 (63.33)
Female	11 (36.67)
Age (years), mean (SD)	7.22 (3.5)
Body weight (kg), mean (SD)	24.7 (11.99)
Body height (cm), median (minimum–maximum)	121 (77–168)
Type of AED, n (%)	
Inducer AED	18 (60)
Non-inducer AED	12 (40)
Number of AED, n (%)	
Monotherapy	26 (86.67)
Polytherapy	4 (13.33)
Duration of AED (year), median (minimum–maximum)	1.71 (0.5–11)
Serum 25(OH) D level (ng/mL), mean (SD)	27.19 (7.27)
BMD (g/cm^2), mean (SD)	0.78 (0.1)

SD: Standard deviation, AED: Antiepileptic drug, BMD: Bone mineral density.

Results

This study was conducted from May to September 2016, there were 30 children that met the inclusion and exclusion criteria. The mean age of subjects was 7.2 years (SD 5.9–8.5) and mean treatment duration was 1.7 years (0.5–11). There were 18 children (60%) who used inducer AED and 12 children (40%) who used non-inducer AED. The mean serum 25(OH)D level was 27.19 ng/mL, and mean BMD was 0.78 g/cm^2. The characteristics of subjects are described in Table 1. The normality test result for Vitamin D level and BMD was normal (Table 2).

Table 2: Normality test result

Variable	p
Vitamin D	0.114
BMD	0.185

BMD: Bone mineral density.

Pearson correlation test was used to analyze the correlation between Vitamin D level and BMD. We found negative correlation between Vitamin D level and BMD with r = −0.317, but statistically not significance with p more than 0.05 (p value = 0.088) (Table 3).

Table 3: Correlation between Vitamin D level and bone mineral density

Variable	Mean (SD)	r	p
Vitamin D	27.19 (7.27)	−0.317	0.088
BMD	0.78 (0.1)		

SD: Standard deviation.

Linier regression test was done to find the factor that can contribute correlation between Vitamin D level and BMD. Age was the only factor that statistically significant (Table 4).

Table 4: Linear regression test

Variable	B	95% CI	p
Vitamin D	0.002	−0.002–0.006	0.347
Age	0.024	0.013–0.034	< 0.001
Duration of AED	−0.01	−0.022–0.002	0.105
Type of AED	0.037	−0.02–0.094	0.19

AED: Antiepileptic drug, CI: Confidence interval.

Partial correlation test was done to find the correlation of Vitamin D level with BMD after controlling

age, with r=0.118, but statistically not significance with p more than 0.05 (p value = 0.54 (Table 5).

Table 5: Partial correlation test

Controlled variable	Variable	BMD	
		r	p
Age	Vitamin D	0.118	0.54

BMD: Bone mineral density.

Discussion

It is well established that Vitamin D plays an essential role in achieving adequate bone mineralization. Vitamin D status is best measured by the serum 25(OH) D concentration which accounts for both endogenous and exogenous sources of the vitamin [12], [13]. Antiepileptic drug associated osteopathy which includes decreased BMD, increased fracture risk, and overt osteomalacia, but most of the data available are from adults [14]. Children and adolescent treated with antiepileptic drug are known to have problems with bone mineral density and have 2–6 times higher risk of fracture than healthy controls [15].

Vitamin D level decreases with age. A previous study examining adults between the ages of 20 and 96 years indicated that 25(OH)D concentration decreases as age increases. A study by Pohan *et al.* (2015) showed that epileptic children who took long-term anticonvulsant therapy have lower mean 25(OH)D level and higher prevalence of Vitamin D insufficiency than the non-epileptic control group [16].

Our study had evaluated 30 children with epilepsy and received oral AED. The mean level of 25(OH)D was 27.18 ng/mL. There were 3 patients (10%) with Vitamin D deficiency, 17 patients (56.7%) with Vitamin D insufficiency, and 10 patients (33.3%) with normal Vitamin D level. There were 2 patients (9%) exhibited osteoporosis (Z score ≤-2.5), 11 patients (50%) exhibited osteopenia (Z score between -2.5 and -1.0), and 9 patients (40.9%) had normal bone density. In this study, the mean BMD is 0.78 g/cm^2.

The previous studies on 71 children with osteogenesis imperfecta (OI) failed to find a relationship between serum 25(OH)D concentrations and histomorphometry measures of bone microstructure and mineralization in iliac bone biopsy samples [17]. However, there was positive correlation between serum 25(OH)D concentration and lumbar spine BMD in a larger retrospective study on 282 children and adolescents with OI types I, III, and IV [18].

Our study found that there was no correlation between Vitamin D level and BMD. In bivariate analysis with Pearson test, there was negative correlation between Vitamin D level and BMD. This result was not in accordance with the theory which states that low Vitamin D level can cause low BMD (positive correlation). Vitamin D helps the absorption of calcium in the intestine. Low level of Vitamin D level can cause hypocalcemia which can result calcium reabsorption from bone and decrease in BMD. The confounding factor that can contribute to the outcome needed to be controlled. Linier regression test found that age was the only confounding factor that statistically significant. Partial correlation test was done with controlling age as confounding factor, and there was weak positive correlation between Vitamin D level and BMD (r=0.118), but not statistically significant (p = 0.54).

This study had several limitations. First, we were unable to determine a causal relationship since the study had a cross-sectional design. Second, quality and quantity of sun exposure with mean daily intake of Vitamin D that can affect Vitamin D level were not measured. In this study, we found that age was the only statistically significant confounding factor that can affect the correlation between Vitamin D level and BMD. Further study by controlling age in the inclusion criteria is needed to find the correlation between Vitamin D level and BMD.

Conclusion

There was weak correlation between Vitamin D level and BMD in epilepsy children who received oral AED, but the correlation analysis was not sufficient to prove the relationship.

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