INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

PAGE 46
2019 Nov; 26(1): 1-128
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

CORRELATION BETWEEN VITAMIN D AND CALCIUM LEVELS IN CHILDREN WITH NEWLY DIAGNOSED EPILEPSY AND AFTER SIX MONTHS OF ANTIEPILEPTIC THERAPY

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ABSTRACT

Children with epilepsy should take long-term anti-epileptic drugs. Long-term use of antiepileptic drugs can reduce vitamin D levels leading to low blood calcium levels. This study aimed to analyze the correlation between vitamin D and calcium levels in children with newly diagnosed epilepsy children and ≥ 6 months of therapy. This was an analytical observational study with cross-sectional research design. The vitamin D levels were measured using the Vidas instrument from bioMerieux with ELFA (enzyme-linked fluorescent assay) method. Samples were collected during June-August 2018 from Inpatient and Outpatient Clinics. The samples were divided into newly diagnosed epilepsy group and after six months therapy group. Each group was measured for vitamin D and serum calcium levels. The correlation between the two parameters was analyzed using independent T-test. From the 19 samples of newly diagnosed epilepsy, there were 57.9% low vitamin D and 10.5% low calcium levels. From the 20 subjects with 6 months therapy, 70% were low vitamin D and 25% were low calcium levels. There was a relationship between vitamin D and calcium levels in patients with newly diagnosed epilepsy and after ≥ 6 months of therapy. Low vitamin D and low calcium levels were predominantly found in the antiepileptic therapy group than the newly diagnosed epilepsy. Low vitamin D levels were possibly caused by the long-term use of antiepileptic drugs that affected serum calcium levels. This study showed a significant relationship between vitamin D and serum calcium levels in patients with newly diagnosed epilepsy and after six months of therapy.

Key words: Vitamin D, calcium, epilepsy

INTRODUCTION

Epilepsy is a neurological disorder that frequently occurs at the children's age. Epilepsy patients must take long-term anti-epileptic drugs. It is assumed that the use of anti-epileptic drugs can reduce vitamin D and serum calcium levels. Research on vitamin D influence to various clinical manifestations due to vitamin D deficiency has been widely carried out. However, research on vitamin D and calcium status in children with epilepsy are still limited.[1] Some of the studies that have been conducted provided varied results. Most of the studies focused on the adverse effects of antiepileptic drugs on vitamin D and bone metabolism.

There were contradictory results of research on vitamin D levels in children with epilepsy. A study by Wirrell showed lower vitamin D levels in the group treated with oxcarbazepine and carbamazepine compared to the control group.[2] A study by found in children with early diagnosed epilepsy compared to the normal group.[3] Other studies showed contradictory results suggesting that long-term administration of anti-epileptic drugs gave no effect to vitamin D levels and serum calcium levels.[4]

This study aimed to analyze the correlation between vitamin D and calcium levels in newly diagnosed epileptic children and after ≥ 6 months of therapy.

METHODS

This was an analytical observational study with cross-sectional research design. The vitamin D levels were measured using the Vidas instrument from BioMerieux with the Enzyme-Linked Fluorescent Assay (ELFA) method. Samples were collected during June-August 2018 from Inpatient and Outpatient Clinics in the Dr. Soetomo Hospital, Surabaya. The

Mintzer stated that lower vitamin D level were group and after six months therapy group. Each group was measured for vitamin D and serum calcium levels. The correlation between the two parameters was analyzed using independent T-test.

The study was approved by the Medical Ethics Committee of Dr. Soetomo Hospital Surabaya, Indonesia (0484/KEPK/VIII/2018).

RESULTS AND DISCUSSION

Of the 19 subjects with newly diagnosed epilepsy, 57.9% showed low vitamin D and 10.5% showed low calcium. Of the 20 subjects after six months of therapy, 70% showed low vitamin D and 25% showed low calcium levels (Table 1).

Some organizations in the world classify vitamin D levels as deficiencies (<20 ng/mL), insufficient (20-29 ng/mL), and sufficient (30-100 ng/mL). However, this study classified vitamin D levels as low (<30 ng/mL) and sufficient (30-100 ng/mL). In the newly diagnosed epilepsy group, there were 57.9% of subjects with low vitamin D and the rest with sufficient vitamin D levels. There were 70% of subjects in the ≥6 months group showed low vitamin D levels and the rest showed sufficient vitamin D levels. The results of vitamin D measurement in both groups were statistically analyzed using independent T-test. The results of statistical analysis showed no significant differences of vitamin D levels between the newly diagnosed epilepsy group and epilepsy patients with ≥ 6 months of antiepileptic samples were divided into newly diagnosed epilepsy therapy (p=0.125). Interpretation of vitamin D levels can be seen in Table 2.

Low vitamin D levels were found in the ≥6 months anti-epilepsy therapy group compared to the newly diagnosed group. Two mechanisms are thought to cause low vitamin D in epilepsy patients with > 6 months of treatment. The first mechanism is the induction of the active vitamin D in patients receiving anti-epileptic therapy by cytochrome P450 enzyme in the liver. P450 cytochrome converts active vitamin D into an inactive form in the liver microsomes. The second mechanism activation of the Pregnane X Receptor (PXR) and Steroid Xenobiotic Receptor (SXR).[5]

Early activation of vitamin D occurs in the liver. The forms of vitamins D2 and D3 will be hydroxylated by CYP27A to form 25 (OH) D. Anti-epileptic drugs bind and activate SXR forming a complex that binds PXR which activates the 24-hydroxylase enzyme through interaction with the Vitamin D Response Element (VDRE). This 24-hydroxylase enzyme mediates the loss of the 25-hydroxyl group from 25-hydroxyvitamin D and 1, 25-hydroxyvitamin D. This causes vitamin D to become inactive.[5]

Low levels of vitamin D were also found in the newly diagnosed group of epilepsy who had never received anti-epileptic therapy before. It was in accordance with the research by Mintzer *et al*. which stated that low vitamin D levels were estimated to occur in more than 1 billion people in the world. This was influenced by the daily habits of each individual,

Table 1. Characteristics of the research subjects

	Newly Diagnosed	≥ 6 month of Therapy
Gender		
Males	10 (52.6%)	15 (75.0%)
Females	9 (47.4%)	5 (25.0%)
Range of age		
< 5 yo	12 (63.3%)	9 (45.0%)
5-<10 yo	4 (21.1%)	8 (40.0%)
≥ 10 yo	3 (15.8%)	3 (15.0%)
Vitamin D serum levels (ng/mL)		
Range	15.60 – 54.70	7.80 – 47.60
Calcium serum levels (mg/dL)		
Range	8.20-9.80	8.00-9.90

Table 2. Interpretation of vitamin D serum levels

Vitamin D level (ng/mL)	Diagnosed Epilepsy		P
	New	≥ 6 Months	
Low (<30)	11 (57.9%)	14 (70.0%)	
Sufficient (30-100)	8 (42.1%)	6 (30.0%)	
Mean±SD	30.96±9.33	25.49±12.14	0.125

Table 3. Interpretation of serum calcium levels

Calcium Level (mg/dL)	Diagnosed Epilepsy		P
	New	≥ 6 Months	
< 8.5	2 (10.5%)	5 (25.0%)	
8.5-10.1	17 (89.5%)	15 (75.0%)	
Mean±SD	9.05±0.44	8.88±0.56	0.308

such as: spending more time indoors to watch television and computers, inadequate access to play in open areas outside the house, the use of skin creams containing sunscreen, lack of sun exposure, and lack of food intake of vitamin D sources. The decrease of vitamin D levels in children with newly diagnosed epilepsy varies greatly.[3]

Serum calcium levels were grouped into 2 categories: low calcium (<8.5 mg/dL) and normal calcium levels (8.5-10.1 mg/dL). This study showed low serum calcium levels in 10.5% of the new diagnosis of epilepsy group and 25% of the ≥ 6 months antiepileptic therapy group. The results of serum calcium measurement in both groups were statistically analyzed using independent T-test. The results of the statistical analysis showed no significant differences of serum calcium levels between the newly diagnosed epilepsy group and group of epilepsy patients with ≥ 6 months of anti-epileptic therapy. Interpretation of serum calcium levels can be seen in Table 3.

Some factors are underlining the low calcium levels in epilepsy patients. The antiepileptic drug is correlated with the concentration change of bone phosphate metabolism that will result in the alteration of calcium levels in the serum. Normal calcium levels are produced from various interrelated processes, such as calcium absorption in the intestine, calcium extraction from bone, and calcium regulation by the kidneys. Vitamin D plays an important role in all these processes. Hypovitaminosis D interferes with intestinal calcium absorption, leading to secondary hyperparathyroidism and causing bone loss. Maximum calcium absorption occurs when vitamin D is in the range of 30-40 ng/mL, equivalent to vitamin D levels required to maintain parathyroid hormone balance.[3,6]

Some of the results of this study yielded low vitamin D levels and normal serum calcium levels. Normal calcium, in this case, was caused by the body uptake of calcium deposits from bones to maintain normal calcium levels in the blood. Normal calcium levels in this study supported by the study of Daglar *et al*, which stated that the vitamin D cut-off value of <10 ng/mL was able to significantly cause hypocalcemia.[7] This was supported by the fact that Indonesia's geographical location is in the equatorial area with abundant sunlight. This was probably the reason why vitamin D deficiency was not found among newly diagnosed epilepsy patients in this study. Insufficient vitamin D levels (20-29 ng/mL) were reported instead.

This study found a correlation between the results of vitamin D and serum calcium measurement in both groups. The results of statistical analysis using independent T-test showed a significant correlation between vitamin D levels and serum calcium levels in the newly diagnosed epilepsy group and group with ≥ 6 months anti-epileptic therapy. There was a correlation between vitamin D and serum calcium levels with r = 0.676 and p <0.0001. Distribution of vitamin D and serum calcium levels can be seen in Figure 1.

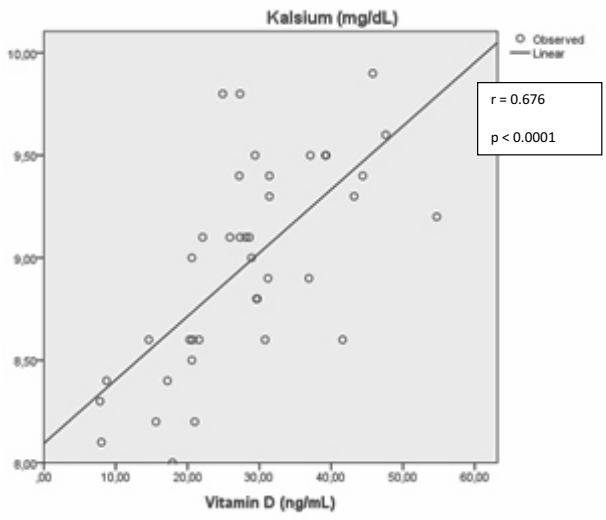

Figure 1. Distribution of vitamin D and serum calcium levels

Low vitamin D levels were found in the group with ≥ 6 months of anti-epileptic therapy. Low serum calcium levels were similarly more prevalent in the group of epilepsy patients with ≥ 6 months anti-epileptic therapy than the newly diagnosed epilepsy group. The results of this study were in line with the results of Mintzer *et al*. which showed lower

vitamin D levels in the long term anti-epileptic therapy group compared to the non-therapy group.[3] Fong *et al*. observed 22% vitamin D deficiency and 41% insufficient vitamin D levels with low blood calcium levels in a population of epileptic children who received long-term anti-epileptic therapy in Australia.[8] Study by Nicolaidou showed that carbamazepine and sodium valproate caused hypovitaminosis D in children, despite no difference of serum calcium levels found in the treatment group compared to the control group.[6] This study was not in accordance with a study by Smith *et al*. which showed no significant correlation between calcium and vitamin D levels.[9]

The limitations of this study were no initial vitamin D and calcium levels measurement before therapy in the control for newly diagnosed epilepsy group and group of ≥ 6 months anti-epileptic therapy. Therefore, it was not confirmed whether there was a decrease of serum calcium levels in patients with normal calcium levels. Cohort design was not used in this study to prospectively examine vitamin D and serum calcium levels in both groups.

CONCLUSION AND SUGGESTION

This study showed that there was a significant correlation between vitamin D levels and serum calcium levels in children with newly diagnosed epilepsy and ≥ 6 months of antiepileptic therapy.

Prospective cohort studies should be conducted in similar groups with vitamin D and calcium levels from the results of this study as a baseline.

CONFLICT OF INTEREST

The author declared no conflict of interest regarding the manuscript.

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