ORIGINAL ARTICLE

Prevalence and Risk Factors of Low Vitamin D Level in Adults with Epilepsy: A Cross-sectional Study at a Single Tertiary Neurological Center in Thailand

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Background: Epilepsy has a wide-ranging impact on the quality of life in patients of all age groups. Reduced levels of active vitamin D contribute to various bone diseases and may influence seizure control. Nevertheless, the risk factors for low vitamin D levels in patients with epilepsy remain inconclusive and are not well-established. The limited number of studies in Thailand may not be sufficient to provide guideline recommendations for screening vitamin D levels in adults with epilepsy.

Objective: To evaluate the prevalence and risk factors of low vitamin D levels in Thai adults with epilepsy taking long-term antiepileptic drugs. To provide supporting recommendations for screening vitamin D levels in patients with epilepsy for early diagnosis and appropriate vitamin supplementation.

Materials and Methods: The present study was a cross-sectional study conducted on 87 adults with epilepsy aged 18 to 76 years who were followed up at the Neurological Institute of Thailand between March and October 2023. Patients with comorbidities affecting vitamin D metabolism were excluded from the study. Baseline demographic data, epilepsy-related information, and anti-seizure medication information were analyzed. Blood tests for vitamin D for 25-hydroxyvitamin D [25(OH)D], calcium, phosphorus, and albumin were performed.

Results: The prevalence of low vitamin D levels was 85%, including deficiency at 37% and insufficiency at 48%, with the mean (±SD) of serum 25(OH)D being 21.9±7.60 ng/mL. Multivariate analyses revealed that female was significantly associated with low vitamin D levels, adjusted OR 4.97 (95% CI 1.23 to 20.05). There was no significant association among epilepsy-related information, anti-seizure medications, and low vitamin D levels.

Conclusion: The prevalence of low vitamin D levels in the present study was significantly higher than that observed in the previous studies, which is consistent with the findings of the recent studies in many countries. The authors strongly recommend screening for vitamin D levels in Thai adults with epilepsy, particularly in females. Early diagnosis and management of this condition are beneficial for patients with epilepsy and can help mitigate the various complications resulting from low vitamin D levels.

Keywords: Epilepsy; Low vitamin D level; Vitamin D deficiency; Vitamin D insufficiency; Antiseizure medications; Prevalence; Risk factors

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Epilepsy is recognized as one of the most significant chronic neurological diseases. The World Health Organization estimates that approximately 50 million individuals are affected worldwide, with an incidence rate ranging from 4 to 10 cases per 1,000 people[1]. In Thailand, the reported incidence is between 5.9 and 7.2 cases per 1,000 people, with an estimated 380,000 to 470,000 individuals suffering from epilepsy[2]. Epilepsy has a wide-ranging impact on the quality of life in patients of all age groups, as it may lead to disabilities due to developmental problems, accidents, or consequences of uncontrolled seizures[1]. Moreover, the multiple and long-term use of anti-seizure medications may affect the quality of life of patients. In addition to prevent seizures, certain medications also affect metabolism and the absorption of nutrients and minerals, subsequently contributing to the deficiency of these essential elements. Vitamin D is one of the most important minerals and has been explored in studies of anti-seizure medications and their metabolism[3-5].

Vitamin D plays an important role in calcium-phosphate homeostasis by facilitating the absorption of calcium and phosphate from the small intestine and renal tubules. Therefore, this process is essential

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for bone and muscle strength[3-5]. Previous studies have illustrated an association between antiseizure medications and low bone mineral density or an increased risk of bone fractures[6-8]. One of the most discussed theories involves enzyme-inducing antiepileptic drugs (EIAEDS), which induces cytochrome P450, leading to increased catabolism of 25-hydroxyvitamin D [25(OH)D] into inactive metabolites[3-5]. Low levels of active vitamin D, or hypovitaminosis D, subsequently increase parathyroid hormone levels, contribute to bone resorption and various bone diseases such as osteoporosis, osteomalacia, and pathologic bone fractures[9-11]. Studies revealed an increasing trend in osteoporotic bone fractures, leading to loss of functional disability, impaired quality of life, and increased mortality[12,13]. In addition to maintaining bone health, research has found that vitamin D plays a role in controlling seizures in epilepsy[14,15]. A study conducted in Hungary evaluated the effects of vitamin D replacement in 13 patients with pharmacologically resistant epilepsy and low vitamin D levels. After three months of vitamin D3 replacement, all patients achieved normal vitamin D levels, with a median seizure reduction of approximately 40%[16]. Thus, vitamin D offers benefits that require further monitoring and assessment.

The prevalence of low vitamin D levels in epilepsy patients ranges from 23% to 95.8% in adults and 23% to 92% in children, varies, and differs among countries, geographic areas, age groups, and ethnicities[13,17,18]. There is limited data and research in Thailand, but a study from Prince of Songkhla University in 2013 revealed that 3% had vitamin D deficiency and 20.3% had vitamin D insufficiency[17]. Another study that aimed to evaluate the association between antiseizure medications, vitamin D levels, and bone mass in children with epilepsy found that 23% of them had vitamin D deficiency[18].

Certain risk factors for low vitamin D levels in epilepsy are inconclusive and not well-established. Previous studies have found that the duration of antiepileptic drug use[19], female gender[20,21], duration of light exposure[20], EIAEDS[13,22,23], polytherapy[14,22], and smoking[23] may be associated with abnormal vitamin D levels in patients with epilepsy. However, there is no consensus regarding the factors that play essential roles in vitamin D deficiency in patients with epilepsy.

The present study objective was to evaluate the prevalence of and risk factors for low vitamin D levels in Thai adults with epilepsy taking long-term antiepileptic drugs. The present study aimed to provide supporting recommendations for screening vitamin D levels in patients with epilepsy. This proactive approach aimed to enable early diagnosis and appropriate vitamin supplementation to prevent bone diseases and their subsequent complications.

Materials and Methods

Patients and study design

The present study was a cross-sectional study evaluated the prevalence of low vitamin D levels, defined as vitamin D deficiency, in conjunction with vitamin D insufficiency. This retrospective cohort study was conducted to identify the risk factors associated with low vitamin D levels in adult patients with epilepsy.

The authors enrolled 100 patients with epilepsy aged 18 to 76 years followed-up at the outpatient department of the Neurological Institute of Thailand between March and October 2023. The patients were diagnosed with epilepsy based on the definition of the International League Against Epilepsy (ILAE) 2017 and were able to independently engage in daily life activities. The authors excluded patients with medical comorbidities that affected vitamin D metabolism, such as chronic liver disease, stage 4-5 chronic kidney disease, thyroid and parathyroid diseases, severe skin disease, or granulomatous disease. In addition, those taking medications that could affect vitamin D levels or bone mass, such as glucocorticoids, thiazides, and bisphosphonates, or those currently taking vitamin D or calcium were excluded. Informed consent was obtained from all the volunteers.

The present study was approved by the Institutional Review Board of Neurological Institute of Thailand (No. 66016).

Data collection and laboratory investigations

Baseline demographic data including gender, age, weight, height, body mass index (BMI), duration of light exposure, smoking status, and alcohol consumption were collected. Additionally, epilepsy-related information, including type and etiology of epilepsy, number of antiseizure medications, duration of taking antiseizure medications, and type of antiseizure medications categorized as EIAEDs and non-EIAEDs, were reviewed. Blood tests for vitamin D [25(OH)D], calcium, phosphorus, and albumin were performed.

Vitamin D levels were categorized as normal for 25(OH)D level of 30 ng/dL or more and low, consisting of vitamin D deficiency and insufficiency

for 25(OH)D level of less than 30 ng/dL.

Statistical analysis

The sample size was calculated based on the prevalence of low vitamin D in a previous study conducted in Malaysia, which reported a prevalence of 40%(20). A power of 80% (1-β) and significance level 0.05 (α) suggested the estimated number of samples was 93. In total, 100 patients were recruited, considering dropouts. The frequency and prevalence of low vitamin D levels were reported as percentages. Continuous data were reported as mean ± standard deviation (SD). Clinical variables were compared between patients with low vitamin D levels and normal vitamin D levels using Fisher's exact test and independent t-test for categorical and continuous data. Variables which were significant in univariate analysis ($p<0.1$) were included in a multiple logistic regression model to assess the adjusted association of variables that appeared to be risk factors for low vitamin D levels. The cutoff for statistical significance was set at p-value less than 0.05. All data were entered into the Stata, version 13.1 (StataCorp LP, College Station, TX, USA) for analyses.

Results

Prevalence of low vitamin D levels in Thai adults with epilepsy

One hundred patients were recruited for the present study, 87 completed the required laboratory assessments, 13 patients were excluded due to incomplete clinical information.

Baseline demographic data associated with vitamin D status were categorized as usual, insufficient, or deficient (Table 1). In summary, the mean age was 39.1±13.9 years (range 18 to 78). Female participants comprised 60% of the sample with 52 subjects. The mean BMI indicated a normal weight across all groups. Approximately two-thirds of the patients had less than 60 minutes of sunlight exposure per day. Almost all recorded seizure types were focal, and structural epilepsy contributed to 57% of epilepsy etiologies, based on the current ILAE classification. Fifty-seven patients (65.5%) were taking EIAEDs and 30 (34.5%) were taking non-EIAEDs. The average length of time patients took antiseizure medications was 13.9±11 years. Surprisingly, the incidence of low vitamin D level was found to be as high as 85% (74 patients). The present study observed vitamin D deficiency and insufficiency in 37% (32 patients) and 48% (42 patients) of the participants, respectively. Only 15% of patients had normal vitamin D levels. The mean serum 25(OH)D was 21.9±7.60 ng/mL.

Risk factors associated with low vitamin D level in Thai adults with epilepsy

In the univariate analysis of potential risk factors predicting low vitamin D levels, female gender was found to have a significant association (p=0.03). Other patient characteristics, such as epilepsy history and use of antiepileptic drugs, including the number, duration, and type of antiepileptic drugs, were not associated with serum vitamin D levels. The authors also found no differences in the biochemical laboratory investigations between the two groups (Table 2).

Multivariate logistic regression analyses adjusted for other factors, such as sunlight exposure duration and duration and type of antiepileptic drugs, revealed that the only statistically significant risk factor for low vitamin D levels in the present study was female gender (adjusted odds ratio [OR] 4.97, 95% confidence interval [CI] 1.23-20.05, p=0.02). Sunlight exposure of less than 60 minutes per day was observed more often in the low-vitamin D group, but the difference was not statistically significant (Table 3).

Discussion

The present study aimed to evaluate the prevalence and risk factors of epilepsy in adults taking long-term antiseizure medications who were followed-up at the outpatient department of a tertiary care center in Thailand. High prevalence of low vitamin D levels was found, reaching up to 85%, with vitamin D deficiency at 37% and insufficiency at 48%. The authors identified a statistically significant risk factor associated with low vitamin D levels, which is female gender (adjusted OR 4.97, p=0.02). The authors did not find a significant association between the type such as EIAEDs versus non-EIAED, number, or duration of antiepileptic drugs and low vitamin D levels. There was no difference in blood chemistry between the two groups.

The prevalence observed in the present study was significantly higher than that reported in a previous study in Thailand involving 123 adult patients with epilepsy between 2004 and 2006. In that study, vitamin D deficiency was reported in 3.3% and insufficiency in 20.3%[17]. Furthermore, the present study findings surpassed the prevalence observed in the general Thai population. According to the data from the Thai 4th National Health Examination

Table 1. Patient demographics and baseline characteristics associated with vitamin D status

Factors	Overall	Vitamin D status		
		Normal (≥ 30 ng/mL)	Insufficiency (20 to 29 ng/mL)	Deficiency (<20 ng/mL)
Number of patients	87	13	42	32
Sex; n (%)				
Female	52 (60.0)	4 (7.7)	19 (36.5)	29 (55.8)
Male	35 (40.0)	9 (25.7)	23 (65.7)	3 (8.6)
Age (years); mean±SD	39.1±13.9	43.7±12.6	40.6±14.2	35.4±13.4
BMI (kg/m^2); mean±SD	23.8±4.8	23.0±2.8	24.6±4.8	23.1±5.4
Sunlight exposure; n (%)				
<60 minutes/day	54 (62.0)	5 (9.3)	23 (42.6)	26 (48.1)
≥60 minutes/day	33 (38.0)	8 (24.2)	19 (57.6)	6 (18.1)
Smoking status; n (%)				
Non-smokers	79 (91.0)	12 (15.1)	38 (48.1)	29 (36.7)
Ex-smokers >1 year	3 (3.0)	-	2 (66.7)	1 (33.3)
Smokers within 1 year	5 (6.0)	1 (20.0)	2 (40.0)	2 (40.0)
Alcohol status; n (%)				
Non-alcohol	77 (88.0)	13 (16.8)	38 (49.3)	26 (33.8)
Ex-alcohol >1 year	5 (6.0)	-	2 (40.0)	3 (60.0)
Alcohol drink within 1 year	5 (6.0)	-	2 (40.0)	3 (60.0)
Seizure type; n (%)				
Focal seizure	83 (95.5)	13 (15.7)	41 (49.5)	29 (34.9)
Generalized seizure	4 (4.5)	-	1 (25.0)	3 (75.0)
Etiology; n (%)				
Structural	49 (57.0)	8 (16.3)	20 (40.8)	21 (42.9)
Genetic	1 (1.0)	-	1 (100)	-
Immune	1 (1.0)	1 (100)	-	-
Infectious	1 (1.0)	-	-	1 (100)
Unknown	35 (40.0)	4 (11.4)	21 (60.0)	10 (28.6)
Duration of AEDs (years); mean±SD	13.9±11.0	14.3±10.7	16.7±13.2	10.4 (7.0
Type of AEDs; n (%)				
EIAEDs	57 (65.5)	8 (14.0)	29 (50.9)	20 (35.1)
• Phenytoin	17 (19.5)	3 (17.6)	8 (47.1)	6 (35.3)
• Phenobarbital	18 (20.7)	3 (14.9)	9 (50.0)	6 (33.3)
• Carbamazepine	28 (32.2)	2 (7.1)	17 (60.7)	9 (32.1)
• Topiramate ≥200 mg	14 (16.1)	3 (21.4)	7 (50.0)	4 (28.6)
Non-EIAEDs	30 (34.5)	5 (16.7)	13 (43.3)	12 (40)
• Valproate	21 (24.1)	5 (23.8)	9 (42.9)	7 (33.3)
• Topiramate <200 mg	9 (10.3)	2 (22.2)	4 (44.4)	3 (33.3)
• Levetiracetam	58 (66.7)	11 (19.0)	28 (48.2)	19 (32.8)
• Other	37 (42.5)	8 (21.6)	12 (32.4)	17 (46.0)

BMI=body mass index; AEDs=antiepileptic drugs; EIAEDs=enzyme-inducing antiepileptic drugs; SD=standard deviation

Survey (NHESIV), conducted between August 2008 and March 2009, the prevalence of vitamin D deficiency and insufficiency in the healthy Thai population was 5.7% and 45.2%, respectively[24]. Therefore, the present study results are consistent with recent studies conducted in Saudi Arabia, India, and Türkiye, which reported a prevalence of low vitamin D levels in adults with epilepsy ranging from 86.8% to 95.8%[14,25].

Vitamin D in the human body is sourced from sunlight, food, and supplements, with two main types, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Most vitamin D3 is endogenously synthesized in the skin upon exposure to sunlight. It is also present in animal products, such as oily fish, liver, red meat, egg yolks, cheese, and butter.

Table 2. Factors associated with normal or low vitamin D levels in Thai epileptic patients

	Normal vitamin D level [25(OH)D ≥30 ng/mL]	Low vitamin D level [25(OH)D <30 ng/mL]	p-value
Number of patients	13	74	
Sex: female; n (%)	4 (7.7)	48 (92.3)	0.03*
Age (years); mean±SD	43.7±3.5	38.3±1.6	0.20
BMI (kg/m^2); mean±SD	23.0±0.8	24.0±0.6	0.51
Sunlight exposure; n (%)			0.07
<60 minutes/day	5 (9.3)	49 (90.7)	
Smoking status; n (%)			0.70
Non-smokers	12 (15.2)	67 (84.9)	
Ex-smokers >1 year	-	3 (100)	
Smokers within 1 year	1 (20.0)	4 (80.0)	
Alcohol status; n (%)			1.00
Non-alcohol	13 (16.9)	64 (83.1)	
Ex-alcohol >1 year	-	5 (100)	
Alcohol drink within 1 year	-	5 (100)	
Seizure type; n (%)			1.00
Focal seizure	13 (15.7)	70 (84.3)	
Generalized seizure	-	4 (100)	
Etiology; n (%)			0.30
Structural	8 (16.3)	41 (83.7)	
Genetic	-	1 (100)	
Immune	1 (100)	-	
Infectious	-	1 (100)	
Unknown	4 (11.4)	31 (88.6)	
Number of AEDs; n (%)			0.13
1 to 2 AEDs	4 (8.7)	42 (91.3)	
≥3 AEDs	9 (22.0)	32 (78.0)	
Duration of AEDs (years); mean±SD	14.3±3.0	13.9±1.3	0.87
Type of AEDs; n (%)			0.76
EIAEDs	8 (14.0)	49 (86.0)	
Non-EIAEDs	5 (16.7)	25 (83.3)	
Laboratory; mean±SD			
Calcium (mg/dL)	9.3 (0.1)	9.2 (0.1)	0.77
Phosphate (mg/dL)	3.2 (0.1)	3.4 (0.1)	0.25
Albumin (g/dL)	4.3 (0.1)	4.4 (0.1)	0.50

25(OH)D=25-hydroxyvitamin D; BMI=body mass index; AEDs=antiepileptic drugs; EIAEDs=enzyme-inducing antiepileptic drugs; SD=standard deviation
* Statistical significance, p<0.05

Table 3. Multivariate logistic regression model of risk factors for low vitamin D level

	Adjusted odds ratio	95% CI	p-value
Sex			
Female compared with male	4.97	1.23 to 20.05	0.02*
Sunlight exposure duration			
<60 minutes/day compared with ≥60 minutes/day	3.03	0.82 to 11.1	0.09
Duration of AEDs	0.99	0.93 to 1.05	0.67
Type of AEDs			
EIAEDs compared with non-EIAEDs	1.76	0.43 to 7.19	0.43

AEDs=antiepileptic drugs; EIAEDs=enzyme-inducing antiepileptic drugs; CI=confidence interval
* Statistical significance, p<0.05

In contrast, vitamin D2, or ergosterol, is derived from plant sources and presented in fortified foods, such as yeast, mushrooms, fortified milk, and cereals. After entering the circulation, both forms of vitamin D are metabolized to 25(OH)D in the liver. This compound is then metabolized in the kidneys to 1,25-dihydroxyvitamin D, the biologically active form of vitamin D in the human body[26,27]. Numerous factors affect serum vitamin D levels. First, geographic area, season, altitude, and air pollutants are all associated with sunlight reaching the Earth. Second, certain behaviors are associated with exposure to sunlight, such as sunscreen usage, clothing, occupation, and lifestyle. Finally, individual factors include skin color resulted from melanin, food intake, aging, and hepatic and renal functions[26,27]. The recent surge in low vitamin D levels may be due to multifactorial factors, including increasing indoor activities, such as office work, shopping in air-conditioned stores, or even indoor gymnasium use. Social preferences for fair skin tone led to the avoidance of sunlight exposure and increased sunscreen use, particularly among females. The increase in air pollutants has led to a decrease in UVB radiation reaching the ground. Furthermore, foods high in vitamin D may not be easily accessible or popular among Thai people. All these factors contribute to lower vitamin D levels despite Thailand being in a tropical zone with abundant sunlight exposure throughout the year.

The authors identified a statistically significant risk factor associated with low vitamin D levels, which is female gender (adjusted OR 4.97, p=0.02). This aligns with the findings of two studies in Malaysia that identified female gender as a significant risk factor for vitamin D deficiency[20,21]. Consequently, this pattern is consistent with observations in a normal Thai population, indicating that low serum 25(OH)D levels are associated with female gender[24]. However, previous studies did not find any association between gender and vitamin D levels[13,14,23,25]. Among the participants, 95% experienced focal seizures, and over half had seizures due to a structural cause, according to the ILAE 2017 classification. The present study found that the type and classification of epilepsy did not significantly affect vitamin D levels. Additionally, no association was found between the type such as EIAEDs versus non-EIAEDs, number, or duration of antiepileptic drugs and low vitamin D levels. Therefore, there was no significant difference in blood chemistry between the two groups. Subsequently, basic laboratory parameters, such as calcium or phosphate levels, did not show benefits in assessing vitamin D status in patients with epilepsy.

The effects of antiepileptic drugs on serum vitamin D levels are a subject of debate, and data from studies have yielded conflicting results. Research conducted in both adults and children with epilepsy has indicated that EIAEDs are significant risk factors for low vitamin D levels[5,13,22]. In contrast, Khoo et al.[21] found that EIAEDs did not affect vitamin D levels. However, the effects of several antiepileptic drugs remain unclear. Nagarjunakonda et al.[25] and Jésus et al.[28] found that the vitamin D level or the percentage of vitamin D deficiency was not significantly different between epilepsy patients with and without drug resistance, similar to the present study. Nevertheless, studies revealed that polytherapy is one of the risk factors for low vitamin D[14,20,23]. These conflicts may be attributed to differences in the study design, ethnicity, geographic location, or dietary habits among the study populations.

The present study had limitations. First, the data source for clinical information was a retrospective collection, therefore, it might not have captured all relevant information. Second, there was a lack of information regarding the previous type and duration of antiepileptic drug used, including drug adjustment before assessing vitamin D levels, dietary calcium, and intake of vitamin D-rich food. Third, certain data such as the duration of sunlight exposure rely on patient estimation, which introduces potential inaccuracies. Finally, this single-center population had a smaller sample size than initially calculated, potentially resulting in low statistical power. Suggestions for future studies to include multicenter studies with larger sample sizes. Collecting additional confounding factors, such as sunscreen use and adjustment for antiepileptic drugs, would be beneficial. Further analysis of clinical outcomes such as bone fractures could provide valuable information.

Conclusion

The present study evaluated the prevalence and risk factors of low vitamin D levels in adults with epilepsy in the outpatient department of a tertiary care center in Thailand. The prevalence of low vitamin D levels was significantly higher than that reported in the previous studies, which is consistent with relevance studies conducted in many countries. The authors strongly recommend screening for vitamin D levels in Thai adults with epilepsy, particularly in females. Managing vitamin D deficiency and insufficiency

through strategies such as increasing calcium- and vitamin D-rich food intake, participating in more outdoor activities with enhanced sunlight exposure, and appropriate use of vitamin supplements are beneficial for patients with epilepsy and can help mitigate various complications resulting from low vitamin D levels.

What is already known on this topic?

The prevalence of low vitamin D levels in patients with epilepsy ranges from 23% to 95.8% in adults and 23% to 92% in children and varies among countries, geographic areas, age groups, and ethnicities. However, the prevalence of and risk factors associated with low vitamin D levels in Thai patients with epilepsy remain unclear.

What does this study add?

The authors found a high prevalence of low vitamin D levels, reaching up to 85%, with vitamin D deficiency at 37% and insufficiency at 48%. Female patients had a high risk of vitamin D deficiency. The authors strongly recommend screening for or supplementing vitamin D levels in Thai adults with epilepsy, particularly female patients.

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Conflict of interest

The authors declare no conflict of interest.

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