■ Original article

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Epileptic Disorders

# Vitamin D deficiency in a Portuguese epilepsy cohort: who is at risk and how to treat*

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**ABSTRACT**

***Objective.*** The epilepsy-related risk factors for vitamin D deficiency, particularly the use of enzyme-inducing antiepileptic drugs (EIAEDs), and how to treat vitamin D deficiency in patients with epilepsy remain unclear. Our aims were to explore risk factors and the influence of EAIEDs in vitamin D status and to determine the efficacy of a daily dose of oral cholecalciferol (vitamin D3) in epileptic patients with vitamin D deficiency.

***Methods.*** Clinical data were collected and 25-hydroxyvitamin D (25(OH)D) serum levels were measured. All patients with vitamin D deficiency (25(OH)D ≤20 ng/mL) or insufficiency (25(OH)D from 21-29 ng/mL) were treated with 6,670 IU/day cholecalciferol for eight weeks and 25(OH)D was then remeasured. Descriptive and inferential statistics were employed.

***Results.*** A total of 92 patients (44.6% males), with mean age of 41.0±14.8 years, were included. Measurements of 25(OH)D revealed that 79.3% patients had abnormal levels: 56.5% were vitamin D deficient and 22.8% were vitamin D insufficient. The statistically significant risk factors for vitamin D deficiency identified were: number of AEDs, treatment with EIAEDs, low sun exposure, high body mass index (BMI) and a high frequency of epileptic seizures. After treatment, 25(OH)D mean level increased by 98.99% (regardless of EIAED use or being overweight).

***Significance.*** In our sample, more than half of the adults with epilepsy showed 25(OH)D deficiency. Patients on EIAEDs had lower 25(OH)D levels. A daily dose of 6,670 IU cholecalciferol successfully led to the correction of 25(OH)D levels. A higher dose in obese patients or in patients taking EIAEDs may not be warranted and this should be considered in future guidelines for routine vitamin D deficiency treatment.

**Key words:** enzyme-inducing antiepileptic drugs; sun exposure; obesity; seizures; cholecalciferol treatment

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Vitamin D is a fat-soluble prohormone [1] and its impact on human health has been extensively studied in the last few years [2]. Despite its importance, it is estimated that one billion people worldwide are vitamin D insufficient or deficient [3]. In relation to epilepsy, most studies have reported that vitamin D deficiency is more prevalent in epileptic patients treated with antiepileptic drugs (AEDs), especially those related to cytochrome P450 induction (EIAEDs) [4]. These drugs have the ability to induce the cytochrome P450 enzymes, which are responsible for vitamin D catabolism and consequently convert vitamin D into inactive metabolites. The resulting hypovitaminosis leads to hypocalcaemia

and to an increase in parathyroid hormone levels, which increases bone turnover with higher susceptibility of osteopenia and bone fractures [5,6]. Furthermore, there are also other major factors related to vitamin D status that have to be taken into account, namely insufficient exposure to sun, geographical factors, skin pigmentation, inadequate diet, underlying diseases such as malabsorption syndromes, liver and kidney chronic diseases and alcohol abuse [7], body mass index superior to 30 kg/m$^2$, aging and pregnancy [8-9].

Although vitamin D deficiency is probably not the only contributing factor to the increased fracture risk, it is an easily modifiable one [10]. While the association between certain AEDs and bone density abnormalities has long been recognized, there is a paucity of evidence supporting optimal treatment. Supplementation with vitamin D would seem logical, and several authors have concluded that epileptic patients taking AEDs, mainly EIAEDs, should receive higher doses of vitamin D to achieve the appropriate 25-OHD level and to minimize the effects of AEDs on bone turnover [11-13]. The Endocrine Society Guidelines recommend that all adults with vitamin D deficiency should be treated with 6,000 IU of cholecalciferol (vitamin D3) daily to achieve a blood level of 25(OH)D above 30 ng/ml and a two or three-fold higher dose to correct vitamin D deficiency in obese patients, patients with malabsorption syndromes, and in patients on medication affecting vitamin D metabolism, such as AEDs [3]. However, there remains a lack of consensus both on efficacy, as well as on optimal vitamin D dosing in the supplementation of patients receiving EIAEDs or non-enzyme-inducing antiepileptic drugs (NEIAEDs) [14].

Therefore, our aims were to:

- screen for vitamin D deficiency and insufficiency among epileptic patients;
- identify the risk factors associated with vitamin D deficiency;
- explore the relationship between EIAEDs and vitamin D status;
- and determine whether treatment with 6,670 IU oral cholecalciferol daily leads to the correction of vitamin D serum level.

## Methods

On this longitudinal prospective study, a total of 92 consecutive epileptic patients were recruited from the Epilepsy Reference Center of the department of Neurology of Coimbra University and Hospital Centre. The inclusion criteria were: age above 18 years, good compliance to AED treatment and a reliable seizure record at least from three months prior to the study. The exclusion criteria were: pregnancy, changes to the AED schedule within the three months prior to the study, intake of vitamin D supplementation or medication interfering with vitamin D metabolism six months prior to the study, history of hypercalcemia, nephrolithiasis, parathyroid disease or gastric surgery. Clinical and demographic data were collected through a questionnaire completed by the patients during consultation as well as from clinical files. Potential risk factors influencing vitamin D status were assessed, which included: comorbidities, other medication, vitamin supplements, diet, physical activity (hours per week), toxic habits (alcohol, tobacco, substance use), sun exposure (hours per week from 10 a.m. to 3 p.m.) and season of the year when measurements were made (winter, spring, summer or autumn). Epilepsy type and aetiology were considered according to the International League Against Epilepsy (ILAE) classification [15]. Epilepsy was considered refractory when two tolerated and appropriately chosen AED schedules failed to achieve seizure freedom [16]. AED drugs were classified according to their ability to induce the hepatic cytochrome P450 enzymes [17]: EIAEDs (phenytoin, phenobarbital, carbamazepine, eslicarbazepine acetate, primidone, oxcarbazepine and topiramate >200 mg/day) and NEIAEDs (valproate, lamotrigine, gabapentin, levetiracetam, clobazam, pregabalin, zonisamide, lacosamide, perampanel, topiramate ≤200 mg/day and benzodiazepines).

Vitamin D status was defined accordingly to the Endocrine Society Guidelines: deficiency as a 25(OH)D level below or equal to 20 ng/mL and vitamin D insufficiency as a 25(OH)D level in the range of 21-29 ng/mL [3]. All vitamin D levels were obtained from the same laboratory using the same assay (Liaison, Diassorin®). From September 2017 to April 2018, serum levels of 25(OH)D were routinely obtained as part of our standard clinical care for patients with epilepsy. In addition, the following assessments were performed in the first analysis: complete blood count, renal functions, serum antiepileptic drug levels, and calcium, magnesium, phosphate and parathyroid hormone (PTH) levels. Vitamin D status was evaluated by determining 25(OH)D serum levels, in accordance with the Endocrine Society Guidelines [3]. All patients with 25(OH) D <30 ng/mL were treated with 6,670 IU/day of oral cholecalciferol for eight weeks (which corresponds to 10 drops/day). After that period, a second venous blood sample was taken to evaluate vitamin D status.

To evaluate the efficacy of vitamin D treatment, from the 92 initial patients, only 52 (56.5%) were considered. Of these, 19 (20.7%) patients had normal vitamin D levels and consequently were not treated nor reassessed and 21 (22.8%) patients were also excluded due to the following reasons: a second measurement was

not made in 14 (66.7%), six (28.5%) were excluded due to lack of compliance taking the daily cholecalciferol supplementation, and the second 25(OH)D measurement was performed with different equipment due to technical problems in one (4.8%).
The study was approved by the local Ethics Committee, and patients gave written informed consent to participate in the study.

### Statistical methods

Descriptive statistics of the sample were carried out using Excel. Relative frequencies, means and standard deviations (SD) were included, depending on the nature of the variables employed. To further illustrate some possible bivariate relationships between variables, graphical representations of the results such as pie charts, histograms as well as box-and-whisker charts were obtained using SPSS and Excel. In order to assess which of the independent variables considered (demographic, anthropometric, epilepsy-related features, comorbidities and lifestyle habits described above) have an impact on the dependent variable serum 25(OH) level, a multivariate analysis with generalized linear models was performed. For that purpose, the most suitable approach for a combination of continuous, ordinal and categorical variables was employed, through the development of a generalized linear model, obtained using the SAS Enterprise Guide statistical software. A pairwise comparison of means was also performed to compare 25(OH) serum levels before and after cholecalciferol supplementation.

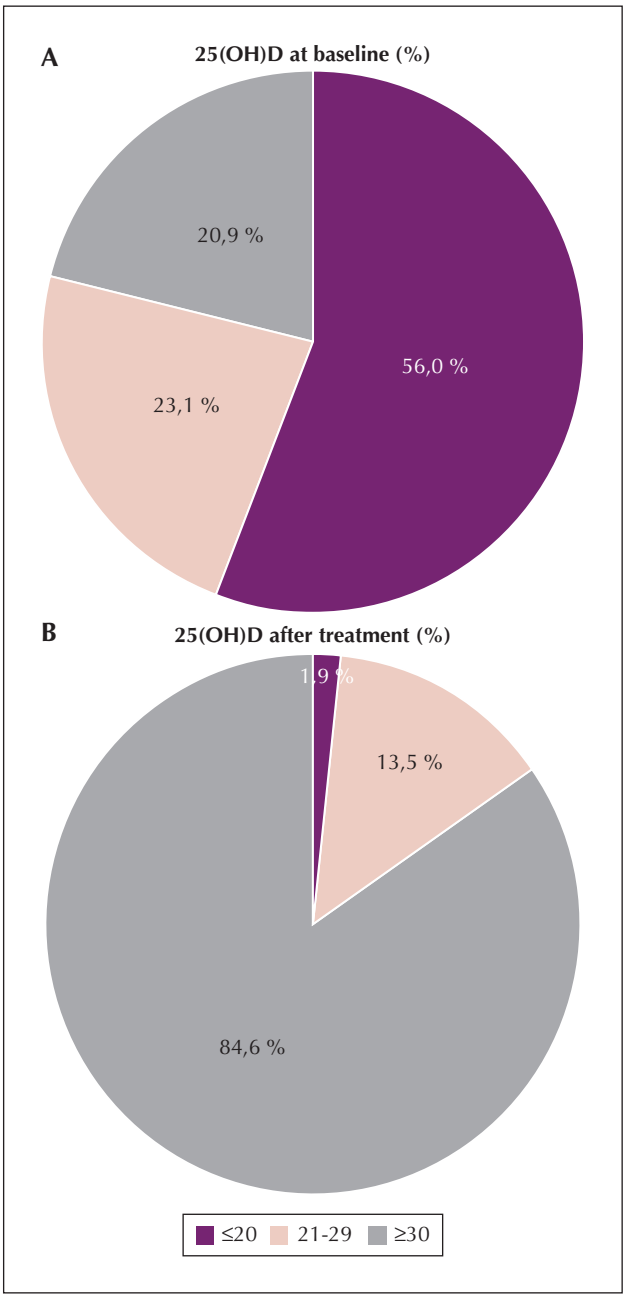
## Results

Among the 92 Caucasian patients included in this study, 44.6% were male and the mean age was 41.0 ± 14.8 years (range: 18-73). Details of all their demographic and clinical features are shown in *table 1*. Sixty-two patients had other comorbidities and 55 patients were also on medication other than AEDs. Other comorbidities and lifestyle habits of the total patients are presented in *table 2*.
The mean serum 25(OH)D level at baseline was 19.5 ± 9.4 ng/mL; 56.0% of the patients were 25(OH)D deficient, 23.1% 25(OH)D insufficient and 20.9% registered a vitamin D level within the normal range (*figure 1A*).
To evaluate the risk factors with impact on 25(OH)D serum level, five independent variables were found to be statistically significant: number of AEDs ($p$=0.001), type of AEDs ($p$=0.01), sun exposure ($p$=0.03), BMI ($p$=0.02) and seizure frequency in the previous three months ($p$=0.02). Treatment with three or more AEDs

▼ **Table 1.** Clinical and demographic profile of the patients.

| Variable | n= 92(%) |
|---|---|
| **Age** (yr) | 41.0±14.8 |
| **Male** | 41(44.6) |
| **Caucasian** | 92(100.0) |
| **Weight (kg)** | 73.3±17.9 |
| **Height (m)** | 1.7±0.09 |
| **BMI** (kg/m$^2$) | 26.4±5.6 |
| Preobesity (%) – BMI 25.0-29.9 | 35(38.1) |
| Obesity – BMI ≥30.0 | 20(21.7) |
| **Epilepsy features** | |
| Age of onset (yr) | 16.8±14.5 |
| Duration of epilepsy (yr) | 24.0±14.8 |
| **Epilepsy Type (%)** | |
| Focal | 71(77.2) |
| Generalized | 18(19.6) |
| Combined Focal and generalized | 0(0.0) |
| Unkonwn | 3(3.2) |
| **Epilepsy side (n=80)** | |
| Right | 25(31.3) |
| Left | 33(41.3) |
| Both | 22(27.4) |
| **Etiology (%)** | |
| Structural | 53(57.6) |
| Mesial Sclerosis | 31(58.3) |
| Cortical Dysplasia | 20(37.5) |
| Other | 2(4.2) |
| Genetic | 14(15.2) |
| Infeccious | 2(2.2) |
| Unkown | 21(22.8) |
| Structural and other | 2(2.2) |
| **Number of seizures in the previous 3 months** | |
| 0 | 50(54.3) |
| 1-45 | 42(45.7) |
| **Refractory Epilepsy** | 55(59.8) |
| **Number of AEDs** | |
| 1 | 30(32.6) |
| 2 | 26(28.3) |
| ≥ 3 | 36(39.1) |
| **AEDs type (%)** | |
| NEIAEDs | 44(47.8) |
| EIAEDs | 9(9.8) |
| Both | 39(42.4) |

Age, weight, height, BMI and age of onset and duration of epilepsy are expressed as mean and standard deviation (SD). BMI, body mass index; AEDs, antiepileptic drugs; EIAEDs, enzyme inducing AEDs; NEIAEDs, non-enzyme inducing AEDs.



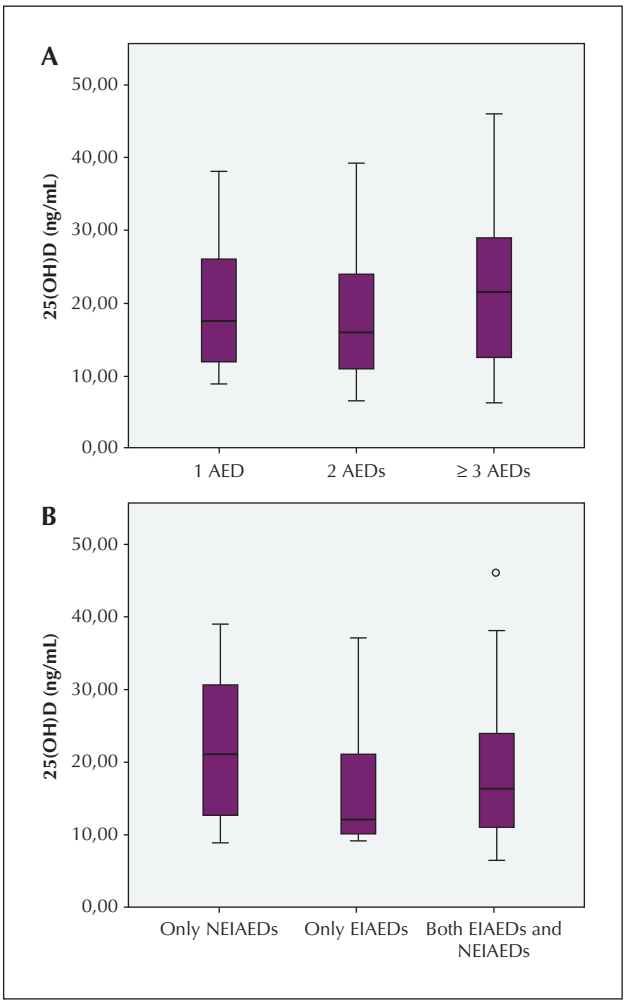

■ **Figure 1.** Percentages (%) of epileptic patients with: vitamin D deficiency (25(OH)D ≤20 ng/mL), vitamin D insufficiency (25(OH)D: 21–29 ng/mL) and normal values (25(OH)D ≥30 ng/mL). 25(OH)D before (n=92) (A) and after (n=52) (B) vitamin D supplementation.

▼ **Table 2.** Comorbidities and lifestyle habits.

| Variable | n= 92(%) |
|---|---|
| **Comorbidities** | 62(67.4) |
| Systemic | 40(43.4) |
| Neurological | 21(22.8) |
| Psychiatric | 16(17.4) |
| Osteopenia/osteoporosis | 6(6.6) |
| **Allergies** | 17(18.5) |
| **Other medication** | 55(59.8) |
| **Diet** | |
| Normal | 92(100) |
| Vegetarian | 0(0.0) |
| Vegan | 0(0.0) |
| **Toxic habits** | |
| None | 77(83.7) |
| Tobacco | 6(6.5) |
| Alcohol | 3(3.3) |
| Substance abuse | 0(0.0) |
| Tobacco + Alcohol | 6(6.5) |
| **Physical activity** | |
| < 1h/week | 62(67.4) |
| ≥ 1h/week | 30(32.6) |
| **Sun exposure** | |
| < 1h/week | 35(38.0) |
| ≥ 1h/week | 57(62.0) |
| **Season of Vitamin D measurement** | |
| Spring | 7(7.6) |
| Summer | 8(8.7) |
| Autumn | 48(52.2) |
| Winter | 29(31.5) |

Sun exposure was evaluated from 10 a.m. to 3 p.m.; autumn: 21st September to 20th December, winter: 21st December to 20th March, spring: 21st March to 20th June, summer: 21st June to 20th September.

was associated with higher 25(OH) serum levels when compared to patients with two or one AEDs (as shown in *figure 2A*). A more detailed analysis of the 36 patients that were on three or more AEDs revealed that 28 (77.8%) of them were on both EIAEDs and NEIAEDs. For all of these 28 patients there was a predominance in the number of NEIAEDs over the number of EIAEDs (26 patients used only one EAIAED and two to four NEIAEDs; two patients used two EIAEDs and three NEIAEDs). The remaining eight (22.2%) patients who were on three or more AEDs only used NEIAED type and no patient used only EIAEDs. Considering the type of AEDs, taking EIAEDs was associated with lower 25(OH)D serum levels when compared to taking NEIAEDs (*figure 2B*). Sun exposure inferior to one hour per week was associated with lower 25(OH)D serum levels ($p$=0.03). BMI and seizure frequency also had a statistically significant impact on 25(OH)D serum levels ($p$=0.02 and $p$=0.03, respectively). Higher BMI




■ **Figure 2.** Serum levels of 25(OH)D in patients according to the number of AEDs (A) and type of AED (B). AEDs: antiepileptic drugs; NEIAEDs: non-enzyme inducing antiepileptic drugs; EIAEDs: enzyme-inducing epileptic drugs.

values and higher seizure frequency were also associated with lower 25(OH)D serum levels. Among patients with seizures in the previous three months, 22 (52.4%) patients used both EIAEDs and NEIAEDs and 16 (38.1%) used only NEIAEDs. Among seizure-free patients in the previous three months, 17 (34.0%) used both EIAEDs and NEIAEDs and 28 (56.0%) were only on NEIAEDs. Considering that NEIAEDs were associated with higher levels of 25(OH)D, the type of AED may potentially affect the levels of vitamin D in patients with seizures when compared to seizure-free patients. Using the statistically significant independent variables, the corresponding parameter estimates were computed using a generalized linear model, leading to the results presented in *table 3*. These values,

▼ **Table 3.** Model parameter estimates.

| Variable | Estimate |
|---|---|
| Number of AEDs | 7.3943 |
| AED type | 5.9247 |
| Sun exposure | 3.4389 |
| BMI | -0.4438 |
| Seizure frequency | -0.3285 |

AEDs: antiepileptic drugs; BMI: body mass index (kg/m$^2$).

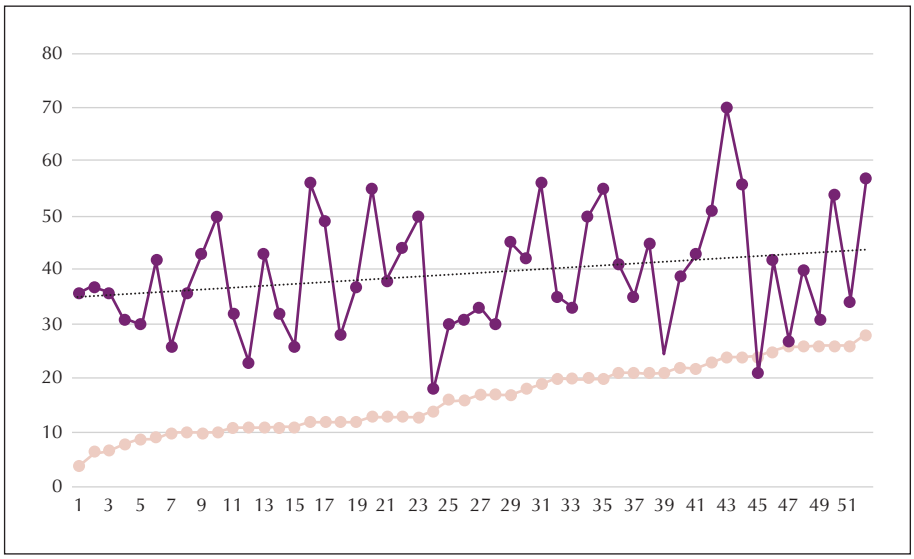
computed from a statistical multivariate perspective, reflected the main effects of the independent variables over the 25(OH)D serum levels: being on three or more AEDs led to an increase in 7.4 ng/mL of 25(OH)D when compared to patients with two or one AEDs; using EIAEDs led to a decrease in 5.9 ng/mL of 25(OH)D compared to using NEIAEDs; sun exposure inferior to one hour per week led to a decrease in 3.4 ng/mL of 25(OH)D; BMI led to a decrease in 0.4 ng/mL of 25(OH)D per kg/m$^2$ gained; and each epileptic seizure was associated with a decrease in 0.3 ng/mL of 25(OH)D. Furthermore, the mean absolute error of the generalized linear model, when used to compare predicted versus observed values was 6.5 ng/mL, thus also confirming the statistical validity of this model.

## Follow-up

After the treatment period with cholecalciferol, 25(OH)D serum levels were remeasured and the mean value was shown to increase by 22.10 ng/mL (mean±SD= 39±11.0 ng/mL). A pairwise statistical comparison of means demonstrated that the differences between 25(OH)D serum levels before and after this supplementation were statistically significant ($p$<0.001).
A daily oral dose of 6,670 IU of vitamin D3 resulted in correction of vitamin D levels, leading to values that were higher or equal to 30 ng/mL for 44 out of 52 (84.6%) of the patients (*figure 1*). From the 52 considered patients, a deficient level was maintained in only one patient (with an increase from 14 ng/mL to 18 ng/mL) and was corrected to an insufficient level in seven (13.5%). For one patient, a slight decrease in 25(OH)D serum level was observed, from 24 ng/mL to 21 ng/mL (*figure 3*).

## Discussion

Our study tried to shed light on the importance of vitamin D deficiency in patients with epilepsy on AEDs,




■ **Figure 3.** Serum levels of 25(OH)D before (pink line) and after (purple line) oral vitamin D treatment. The dotted black line corresponds to linear regression for serum levels after treatment.

other relevant risk factors, and how to treat vitamin D deficiency in this population. This study revealed a high rate of vitamin D deficiency and insufficiency (79.1%) among epileptic patients on AEDs, corroborating previous reports [4].

Considering the risk factors with an impact on low vitamin D levels, the type of AED was found to influence vitamin D levels – EIAEDs were associated with lower 25(OH)D levels, confirming previous knowledge [13,18,19]. In a clear disagreement with previous studies [20], a higher number of AEDs was associated with higher levels of 25(OH)D. This result, however, may be explained by the fact that our patients on multiple AEDs were taking more NEIAEDs than EIAEDs and consequently were less likely to be affected by vitamin D deficiency linked to EIAEDs. Patients with less than one hour per week of sun exposure had lower vitamin D levels, illustrating the well-known role of UV radiation on vitamin D synthesis. Higher BMI was associated with lower 25(OH)D serum levels – the sequestration of the fat-soluble vitamin D in adipose tissue has been previously reported[8]. Concerning seizure frequency, patients who had epileptic seizures within the three months before the study had lower vitamin D levels. This could be explained by the type of AEDs used by these patients. In fact, the majority of patients with seizures used both NEIAEDs and EIAEDs and, consequently, the EIAEDs could be the potential cause for the lower levels of 25(OH)D. On the other hand, the majority of seizure-free patients used only NEIAEDs – which could account for the higher levels of 25(OH)D observed in these patients. Previous published data also suggested an anticonvulsant role of vitamin D [21,22].

Although we were expecting the season in which the measurements were performed to have an impact on vitamin D levels, no association was found. However, this could be due to the fact that only 15 (16.3%) patients were evaluated during spring and summer, thus a larger sample of patients would probably be necessary to determine significant statistical differences. This result also suggests that even during spring and summer, patients have insufficient solar exposure (either regarding exposure time, sunscreen use or clothing) to maintain normal vitamin D levels.

Another important result was the lack of association between vitamin D serum levels and any of the epilepsy features. The role of vitamin D in neuroprotection, brain development and immunomodulation has been documented in many studies [19]. The majority of genetic epilepsies involve ion channels, such as vitamin D receptors, which can affect normal neuronal function, and multiple inflammatory mediators including vitamin D can play multifaceted roles in different types of epilepsy, affecting network excitability. As the modes of action are complex and intricate, further research on the underlying mechanisms is needed to provide valuable insight into the pathophysiology of epilepsy.

Data from the follow-up showed that the 25(OH)D mean level increased by 98.99% and only one patient had a slight decrease in 25(OH)D serum level. Therefore, this seems to indicate that the two to three-fold

higher dose supplementation recommended for patients on AEDs by the Endocrine Society Guidelines may not be needed, at least for the majority of the patients. The duration of treatment as well as the maintenance therapy require further investigation.

Our study has some limitations that should be taken into consideration. The study was a single-centre study, designed as a longitudinal observational investigation to include a select cohort of patients with epilepsy, and therefore, not necessarily representative of the general epilepsy population. Very few patients were on monotherapy with EIAEDs, and all EIAEDs were analysed as a single group due to the limited sample size. Besides, we did not take into account AED changes beyond three months before the study or the duration of treatment in patients with EIAEDs, factors that can also influence vitamin D deficiency. Evidence-based guidelines regarding vitamin D assessment and monitoring, as well as appropriate treatment of vitamin D deficiency in epileptic patients on AED therapy, are needed.

This study reinforces the high percentage of vitamin D deficiency among epileptic patients. The identified risk factors for vitamin D deficiency were: the number of AEDs, treatment with EIAEDs, low sun exposure, high BMI and a high frequency of epileptic seizures. The results obtained highlight the importance of promoting a healthy lifestyle, including appropriate sunlight exposure and a balanced diet with physical exercise, in order to maintain an adequate BMI, as well as monitoring vitamin D levels as part of the routine management of epileptic patients. Moreover, the correction of vitamin D deficiency or insufficiency in epileptic patients is possible by taking 6,670 IU/day of oral vitamin D3, even in obese patients or patients treated with EIAEDs. ■

**Supplementary data.**
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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## TEST YOURSELF

**(1) Is vitamin D deficiency common in epileptic patients?**

**(2) Which of the following are risk factors for vitamin D deficiency:**

A. Treatment with enzyme-inducing AEDs
B. High sun exposure
C. Low body mass index (BMI)
D. High frequency of epileptic seizures

**(3) Which of the following statements is true regarding cholecalciferol?**

A. A standard dose successfully leads to correction of vitamin D deficiency
B. A higher dose in obese patients or in patients taking EIAEDs is always warranted

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".*