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SHORT COMMUNICATION

Vitamin D in epilepsy: vitamin D levels in epilepsy patients, patients on antiepileptic drug polytherapy and drug-resistant epilepsy sufferers

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The objective of this study was to assess vitamin D levels in epileptic patients and to compare its serum levels in patients on antiepileptic monotherapy and polytherapy. We analyzed the serum 25-hydroxy (25-OH) vitamin D levels in 98 consecutive subjects (43 epileptic patients and 55 non-epileptics). Factors influencing its serum levels such as degree of sun exposure, physical activity and dietary intake were taken into consideration. Overall, 41% had deficient, 49% had insufficient and 9% had sufficient levels of serum vitamin D. Elderly individuals (>60 years) and people employed in offices and schools had lower blood vitamin D levels. Across both the sexes, epileptic patients and non-epileptics, epileptic patients on monotherapy and polytherapy and patients with drug-responsive and -resistant seizures, there were no significant differences in serum 25-OH vitamin D levels. Our study shows that people with epilepsy suffer with vitamin D deficiency along with their normal peers.

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INTRODUCTION

Vitamin D deficiency is common in patients with epilepsy.[1] Drugs used for epilepsy themselves diminish the serum vitamin D levels.[2] Patients with epilepsy might suffer with more severe vitamin D deficiency if they are on polytherapy with antiepileptic drugs (AEDs) and if their condition is drug resistant. Each AED has its own action on vitamin D metabolism, the combined action of which might affect serum 25-hydroxy (25-OH) vitamin D levels. This may especially be more in drug-resistant patients who on the average are exposed to more number of AEDs in high doses. To test the hypothesis, we analyzed 25-OH vitamin D levels in epileptic patients, patients on polytherapy and patients with drug-resistant epilepsy.

MATERIALS AND METHODS

A total of 98 consecutive epileptic patients (43) and their non-epileptic (55) relatives attending the Epilepsy OPD in Government General Hospital, Guntur, Andhra Pradesh, India, were analyzed by clinical and demographic data, orally administered sun exposure, physical activity, dietary vitamin D questionnaires and serum levels of 25-OH vitamin D. Fitzpatrick skin color testing and SEM-Q scale[3] were used to measure sun exposure. The score was expressed multiplied by a factor of 100. The population belonged to the city of Guntur, Andhra Pradesh, located at 16.20 °N 80.27 °E. Data were collected in the month of July 2013 with a mean temperature of 32.6 ± 5°C and 10 h of cloud-less sunlight. The average daily solar horizontal radiation was 4.17 kWh/m^2 per day.

Physical activity questionnaire was used to assess the number of hours of active labor per week, considering extra effort for exercise and physical sport.

Weekly dietary intake was calculated by an oral questionnaire measuring the intake of vitamin D-rich food such as egg yolk and fish.

Five microliters of blood was collected and analyzed on Siemens ADVIA Centaur (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA), and standardized against isotope dilution-liquid chromatography-tandem mass spectrometry, as per Vitamin D Standardization Program using fully automated chemiluminiscent immuno assay.

Vitamin D deficiency[4] was defined as a serum level of 25-OH vitamin D below 20 ng/ml (50 nmol/l) and vitamin D insufficiency as between 21 and 29 ng/ml (52.5–72.5 nmol/l). Patients with levels above 29 ng/ml were termed sufficient.

This study was approved by the Institutional Ethical Committee of Guntur Medical College, Guntur with written informed consent from all participants.

Statistics

Sample size was calculated to compare the mean 25-OH vitamin D levels in epileptics vs controls, with 95% power and 99% confidence interval. Student's *t*-test (two-sample assuming unequal variances) was used to compare means and Mann–Whitney *U*-test for medians between epilepsy patients and control subjects. Mann–Whitney *U*-test was used for testing the significance of difference between mean serum 25-OH vitamin D levels in epileptic patients and non-epileptics and also between patients on monotherapy and those on polytherapy using Microsoft Excel 2007. All tests of significance were two-sided.

RESULTS

With a mean serum 25-OH vitamin D of 22.4 ± 0.63 ng/ml, 41% of the people sampled were deficient, 49% insufficient and 9%

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sufficient with vitamin D. People (Supplementary Appendix Figure 1) >60 years of age had low (mean = 18 ± 0.21 ng/ml) average serum blood vitamin D levels. Both men (mean = 22.3 ± 0.41 ng/ml) and women (mean = 22.5 ± 0.35 ng/ml) had equally insufficient levels of vitamin D.

Students had lower levels of vitamin D (mean = 17.2 ± 0.55 ng/ml) in spite of extra exercise in addition to their daily activities (Supplementary Appendix Table 2). Vitamin D-rich food such as fish and egg seems to be less palatable to women and extremes of age groups (Supplementary Appendix Table 1).

There were no statistically significant differences between the serum 25-OH vitamin D levels of epileptic and non-epileptic persons (Table 1). Both groups fall short of the recommended daily allowance of 200 IU of vitamin D. The mean duration of antiepileptic treatment was 6 ± 1.1 years. Epileptic patients on polytherapy for a mean duration of 5.8 ± 1.4 years and those on monotherapy with phenytoin for a mean duration of 3.7 ± 1.7 years, with carbamazepine for a mean duration of 1.6 ± 0.3 years, had similar blood levels of vitamin D (Supplementary Appendix Figure 2). Patients with drug-resistant epilepsy also had equivalent serum 25-OH vitamin D values with those of drug-responsive patients (Table 2).

DISCUSSION

In concordance with Indian studies,[5,6] our findings suggest that vitamin D-deficient diet is an important cause for vitamin D deficiency in spite of being a sunshine-rich country. Working under the sun, men are typically clad in dhoti, which covers the lower body from the waist down up to the knees, and women are similarly clad with additional clothing covering the upper torso also (our study has been performed in July, with April to June being the hottest months in the district). Although this may account for the similar average levels in blood, the low set values remain unexplained. Diet-based theories proposed in various studies include inadequate intake[5] and high dietary phytates[7] inhibiting good absorption.

Foods rich in vitamin D-like cod liver oil and egg yolk are sparingly consumed in most strata in the country.[8] Many Indian studies support the need for vitamin D supplementation for optimal health in various cohorts.[9,10] Strategies to fortify milk,[11] laddoo[12] and tablet[13] form of vitamin D supplementation have reported improved bone mineral densities and growth patterns in children.

Elderly people tend to have lesser appetites, lesser capacity of gut absorption and generally enjoy the shade. Relative immobility of this cohort tends to increase bone turnover and decrease production of parathyroid hormone.[14] These may explain their lower blood vitamin D levels.

Schools, colleges and offices lock up people away from sunshine during most of the daylight hours. Rapid urbanization leading to low sun exposure in the populace with sedentary jobs compounds the already deficient vitamin D status. In our study, people in sedentary sun-protected occupations (17 ± 1.5) had much lower 25-OH vitamin D levels compared with the sun-exposed counterparts (31.5 ± 2.1). Attempts to calculate the optimum sun exposure for adequate vitamin D synthesis in India are confounded by its varied landscape, sunlight duration, skin color and cultural practices. Not only do these factors affect the sun exposure of the particular cohort but they completely vary the dietary patterns and physical activities, which also contribute to vitamin D synthesis. In our particular study, people with sufficient vitamin D (>29 ng/ml) had a mean sun exposure time of 4.2 ± 1.0 h per day.

Osteomalacia during usage of AEDs such as carbamazepine and more so with phenytoin therapy[15] may be caused by enzyme induction in the liver, leading to increased breakdown of vitamin D to inactive products.[16] These drugs also stimulate parathyroid hormone production and thereby depress the levels of vitamin D in the blood.[17] Prolonged duration of treatment seems to cause more reductions in vitamin D levels.[18] However, the dose of AED has not been found to correlate with serum 25-OH vitamin D levels.[19] In spite of studies with conflicting data,[20,21] these are some of the factors that can explain the vitamin D deficiency in epilepsy patients.

In various studies,[22,23] polytherapy with AEDs has been shown to decrease serum vitamin D levels. However, other studies[24] show higher serum 25-OH vitamin D levels in polytherapy users. This may be because of the complex interaction of different AEDs on vitamin D metabolism.

Our study does not show any significant difference in the serum 25-OH vitamin D levels of epilepsy patients (on any type of AED therapy) from the general population. We also did not find any

Table 1. Characteristics of epilepsy patients and controls

Characteristic	*Epilepsy patients* (n = *43*)	*Controls* (n = *55*)	P-*value*
Mean age (s.e.m.)	26 (1.7)	39 (1.9)	
Women	17	32	
Mean sun exposure units (s.e.m.)	53.2 (3.6)	50 (4.3)	0.78
Mean dietary Vit D (IU) intake per week (s.e.m.)	411 (89.7)	323 (48)	0.05
Mean 25-OH Vit D (ng/ml) (s.e.m.)	23.5 (0.6)	21.6 (0.4)	0.21
Deficient (< 20 ng/ml)	15	23	0.05
Insufficient (20–29 ng/ml)	25	33	0.43
Sufficient (>29 ng/ml)	7	3	0.33

Abbreviations: OH, hydroxy; Vit, vitamin.

Table 2. Characteristics of the epilepsy patients

	Monotherapy (n = *16*)	*Polytherapy* (n = *21*)	P-*value*
Mean serum 25-OH Vit D	24.6 ± 0.4	21.2 ± 1.2	0.3
	Drug responsive (n = *29*)	*Drug resistant* (n = *5*)	P-*value*
Mean serum 25-OH Vit D	22.2 ± 1.9	23.1 ± 1.1	0.4

Abbreviations: OH, hydroxy; Vit, vitamin.

statistically significant difference in vitamin D levels between polytherapy and monotherapy with AEDs.

In concordance with recent studies,[22,19] drug-resistant seizure patients in our study were not different from their responsive peers with respect to serum 25-OH vitamin D levels. Taken together, the data suggest that the levels of vitamin D in epilepsy patients are a complex product of mechanisms still unclear to present studies. However, theoretically our results may be supported if serum vitamin D level lowering effect of AEDs may only be seen at a minimum threshold value of vitamin D. This hypothesis needs to be tested.

People in developing countries, including epilepsy patients, suffer from deficiency of vitamin D in spite of substantial sun exposure, thereby stressing the inadequacy of dietary intake. Elderly age group and people in desk-bound jobs are at risk for profound vitamin D deficiency. As more and more people spend less time in active physical work, a trend that is on the rise in our country, there will be an alarming increase in the degree of vitamin D deficiency.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on European Journal of Clinical Nutrition website (http://www.nature.com/ejcn)