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Prevalence and Risk Factors for Vitamin D Insufficiency among Adults with Epilepsy at University Hospital in Jeddah, Saudi Arabia: A Cross Sectional Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Vitamin D is essential for bone physical condition, and vitamin D insufficiency may add to further autoimmune diseases, infections or even cancer. Enzyme-inducing antiepileptic drugs have been predominantly linked with osteoporosis hazard proved their impacts on vitamin D. The study aim was to determine the prevalence of vitamin D insufficiency and deficiency and the covariates associated with it among the adult epileptic patients attending King Fahd neurology outpatient clinics.
Subjects and Methods: 297 adult epilepsy patients joined this cross-sectional study at King Fahd Hospital in 2017. Vitamin D level was considered as deficiency (<10ng/ml), insufficiency (<30ng/ml), or normal (≥30ng/ml). Antiepileptic drugs were sorted out according to their enzyme inducing criteria.

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Results: 87.88% adult epileptic patients were between 18 – 50 years of age, more than half were females, married, and with higher degree of education, less than half received monthly income of less than 5,000 SR, nearly two third were either smokers or ex-smokers. Multiple linear regression model for predictors of vitamin D insufficiency and deficiency declared that; enzyme induced antiepileptic drugs, polytherapy, and smoking were significantly correlated with vitamin deficiency and insufficiency ($p < 0.05$).
Conclusion: Vitamin D insufficiency and deficiency is widespread among adult epileptic patients. Screening of vitamin D level should be taken into consideration as part of the regular follow up of epileptic patients.

Keywords: Vitamins D insufficiency; vitamins d insufficiency; epilepsy.

1. INTRODUCTION

Vitamin D is not considered a real vitamin it is a pro-hormone [1]. Sunlight is considered the chief supply of vitamin D. 7-dehydrocholesterol is transformed into vitamin D3 using ultraviolet rays. Liver metabolized vitamin D3 into 25-hydroxyvitamin D, and after that kidney makes its action and metabolized it into the active metabolite 1α,25-hydroxyvitamin D, that tasks through a receptor, paced in various special body tissues [2].

Vitamin D has multiple physiological functions as a result of the prevalent circulation of its receptor [3] Its deficiency causes osteoporosis and osteopenia, also it ends up with circumstances such as diabetes, autoimmune rheumatoid arthritis, neurodegenerative conditions, epilepsy, vascular disorders and depression, diabetes [4].

Enzyme inducing antiepileptic drugs (EIAEDs), have been connected with risk of decreased bone mineral mass and enhanced fracture [5]. Among epileptic children, researchers found decreased vitamin D level from four to 75%, though vitamin supplement was linked with improved bone biomarkers [6].

However, Vitamin D level among adult epileptic patients is not as much obvious. It was difficult for the studies to prove the link between vitamin D deficiency and EIAEDs compared to non-EIAEDs, [7] and a current systematic review set up inadequate proof to conclude if AEDs modify serum 25-hydroxyvitamin D intensity. Vitamin D insufficiency among adult epileptic patients and its association to explicit AEDs stay tentative [8].

Surprisingly, around 10% of population worldwide who survive usual natural life could anticipate one epileptic seizure [9]. Developing countries seem to have most of these cases [10-13]. In Saudi Arabia, epilepsy and its unclear determinants is considered of public health concern.

Due to the prevalent major effects, it is of greatest significance not only to powerfully recognize vitamin D insufficiency among epileptic patients but also to screen and supplement them appropriately when they arrive at outpatient clinic. Consequently, this brief exploring research provides prevalence determination of low vitamin D, and possible vitamin D predictors among adult epileptic patients at King Fahd Hospital.

2. MATERIALS AND METHODS

2.1 Study Nature

An observational cross-sectional study was conducted between 1st February 2017 to 8th November 2017. Piloting was applied and continued for fourteen days.

2.1.1 Primary outcome

Prevalence of low vitamin D level: Insufficiency for “vitamin D levels < 30ng/ml” and Deficiency for “vitamin D level < 10 ng/ml” [14,15].

2.1.2 Exposure

The associated risk factors with the presence of low vitamin D level among adult epileptics.

2.2 Research Location

The current research was carried out at an university hospital, in the neuropsychiatry outpatient clinics.

2.3 Participants

All Arabic speaking adult patients (18+ years old), and following up at neuropsychiatry outpatient clinics at an university hospital, treated

with AED since at least six months and uncontrolled seizure status. Patients who are severely ill, intellectually disabled, with kidney, liver, endocrine impairment, thyroid dysfunction, metabolic bone disorder and on bone metabolism modifying drugs.

2.4 Sample Size

A mean of 32.88 vitamin D level in adult epileptic patients, which was derived from a research carried out in India by Jaydip et al. [16]. Using version 13 Stata, "one sample assessment of mean" with assumption of hypothesized mean 32.88±10, postulated mean 30.84, two tailed test, 95% Confidence Interval, 90% power; the minimum required sample was calculated as 253; and raised 20% to reach 304 to consider any non-response.

2.5 Study Instrument

A structured interview based questionnaire was used as an instrument. The questionnaire includes the following; first page note clarifying the objective and significance of the research, all contact details of the researcher, and written informed consent. All the patients were guaranteed about privacy of the data, and highlighted regarding their rights to withdraw from the study without touching the excellence of the applied services. The study tool was divided into three parts. *The first part,* included patients` demographic characteristics, *the second part*, contained questions about clinical characteristics of adult epileptic patients and *the third section,* assessed through Biochemical markers.

2.6 Sampling Technique

Three hundred and four adult patients with epilepsy were requested at clinics to join in the research through convenient sampling technique; two hundred and ninety seven accepted and completed the interview, with response rate of 97.7%. A convenient sample was the selected technique to collect data.

2.7 Statistical Analysis Phase

Data was analyzed through version 13 Stata (Stata Corp, College Station, Texas USA). Fortunately there was missing data this was because the investigator conducted the interview himself and filled in the laboratory findings from the records. Association between the dependent variable vitamin D Insufficiency and deficiency and other explanatory covariates were tested through chi square and Fisher`s Exact tests. Multivariate linear and logistic regression models were constructed (independent variables with p value 0.1 were added, while covariates with p value more than 0.101 were not included in the model). Significant level at *alpha level* of less than or equal 0.05, two-sided and 95% confidence interval.

3. RESULTS

Table 1 showed that nearly two third of adult epileptic patients experienced deficient vitamin D level.

Table 1. Vitamin D Level among adult epileptic patients attending King Fahd neuropsychiatry clinic (Deficiency < 10ng/ml). Jeddah, Saudi Arabia, 2017

Vitamin D Level	N	%
Normal	20	6.73
Insufficiency	77	25.93
Deficiency	200	67.34
Total	297	100.00

Table 2 demonstrates the relation between different socio-demographic characteristics and vitamin D insufficiency and deficiency. Females (53.79%) had a significant elevated occurrence of vitamin D insufficiency contrasted to males (46.21%). Furthermore, those who were not married significantly less likely experienced vitamin D insufficiency (84.48%) in contrast to ever married patients ($p < 0.01$). Regarding smoking, being smokers or ex-smokers the adult epileptic patients more likely significantly experienced vitamin D insufficiency compared to non-smokers.

Stratification of low vitamin D level according to BMI are figured out in Table 3. Overweight and obese adult epileptic patients were significantly more likely to experience vitamin D insufficiency compared to their counterparts.

Relating low vitamin D level by medication characteristics among adult epileptic patients is demonstrated in (Table 4). All enzyme inducer adult epileptic patients users and those on poly-therapy treatment regimen significantly experienced vitamin D insufficiency ($p<0.001$).

Table 2. Distribution of vitamin D insufficiency and deficiency related to Socio-demographic covariates of adult epileptic patients at King Fahd neurology clinic "vitamin D level<30ng/ml". Jeddah, Saudi Arabia, 2017

Variables	Normal		Vit D Ins. & Def.		χ^2	p
	N	%	N	%		
Age						
18-30 years	8	6.25	120	93.75	3.44	0.18
31-50 years	7	5.26	126	94.74		
55+ years	5	13.89	31	86.11		
Sex						
Male	4	3.03	128	96.97	*	0.03
Female	16	9.70	149	90.30		
Marital Status						
Not Married	19	15.57	103	84.43	*	<0.001
Married	1	0.57	174	99.43		
Education						
Illiterate	1	2.04	48	97.96	*	0.26
Less than Secondary	6	11.32	47	88.68		
High school	9	7.83	106	92.17		
University or higher	4	5.00	76	95.00		
Monthly Income						
< 5000 SR	10	7.19	129	92.81	*	0.45
5000-1000 SR	8	8.33	88	91.67		
>1000 SR	2	3.23	60	96.77		
Nationality						
Saudi	1	5.26	18	94.74		
Non-Saudi	19	6.83	259	93.17	*	0.62
Occupation						
Not-Working	5	4.24	113	95.76	1.94	0.16
Working	15	8.38	164	91.62		
Smoking						
Non-Smokers	18	17.14	87	82.86	*	<0.001
Ex-Smokers	1	0.86	115	99.14		
Smokers	1	1.32	75	98.68		

**Fisher`s Exact Test*

Table 3. Association between Vitamin D Insufficiency and Deficiency according to body mass index in adult epileptic patients attending King Fahd neurology clinic. Jeddah, Saudi Arabia, 2017

Variables	Normal		Vit D Ins & Def		χ^2	p-value
	N	%	N	%		
BMI						
Normal Weight	20	33.33	40	66.67	*	<0.001
Overweight	0	0.00	78	100.00		
Obese	0	0.00	159	100.00		

Multiple linear regression models of predictors of low vitamin D level are figured out in Table 5. Antiepileptic drug category, poly-therapy treatment regimen, and smoking status were significantly correlated with vitamin D level. Controlling for poly-therapy and smoking status; mean vitamin D level among patients using enzyme inducer was 6.89 units lower than patients using non-enzyme inducer AEDs.

Table 6 reported high frequency of deficient vitamin D among patients using enzyme inducer AEDs independent of AEDs regimen, smoking

status, and marital status. Adult epileptic patients used to enzyme inducer AEDs are 16.59 times more liable to experience vitamin D deficiency compared to patients on non-enzyme inducer AEDs. Participants who were adherent to poly-therapy treatment regimen are 18.32 times significantly further liable to have vitamin D deficiency than mono-therapy individuals, controlling for all variables in the regression model. Smokers and Ex-smokers adult epileptic patients are 5.41 & 4.48 times more experienced vitamin D deficiency in contrast to non-smokers, controlling for the other variables in the model. Married adult epileptic patients are 9.72 highly liable to experience vitamin D deficiency compared to not married patients after adjusting for AEDs category, regimen and smoking.

4. DISCUSSION

The main result in the current research showed that vitamin D insufficiency is frequent among adult epileptic patients. Vitamin D insufficiency prevalence varied according to AEDs classes. Even though we set up that low vitamin D level is significantly frequent among patients on enzyme inducers, it is frequent among non enzyme drug user patients as well. Married, smoker, male epileptic patients had significantly lower vitamin D level, this is similar to what were reported in other study [14].

Table 4. Distribution of vitamin D level according to medication characteristics among adult epileptic patients attending King Fahd neurology outpatient clinic. Jeddah, Saudi Arabia, 2017

Variables	Normal		Vit D Ins & Def		χ^2	p
	N	%	N	%		
AEDs category						
Non Enzyme Inducer	20	19.42	83	80.58	*	<0.001
Enzyme Inducer	0	0.00	194	100.00		
AEDs regimen						
Mono-therapy	20	22.47	69	77.53	*	<0.001
Poly-therapy	0	0.00	208	100.00		

**Fisher`s Exact Test*

Table 5. Multivariate Linear Regression Model of possible predictors of Vitamin D Insufficiency and deficiency in adult epileptic patients attending King Fahd neurology clinic (N=297). Jeddah, Saudi Arabia, 2017

Variables	B*	CI	P	B**	CI	P
AEDs Category (Ref: Non-Enzyme Inducer)						
Enzyme Inducer	-15.48	-16.94 - - 14.02	<0.001	-6.89	-9.42 - -4.37	<0.001
AEDs Regimen (Ref: Mono-therapy)						
Poly-therapy	-15.63	-17.20 - -14.05	<0.001	-7.07	-9.36 - -4.79	<0.001
Smoking Status (Ref: Non-Smokers)						
Smokers	-14.25	-16.06 - - 12.44	<0.001	-4.56	-6.73 - - 2.39	<0.001
Ex-Smokers	-13.52	-15.55 - -11.49	<0.001	-3.61	-5.90 - -1.31	0.002

B: Unadjusted Beta Coefficient, B**: Adjusted Beta Coefficient*

Table 6. Multivariate Logistic Regression Model of Vitamin D Deficiency predictors in adult epileptic patients attending King Fahd neuropsychiatry clinic (N=297). Jeddah, Saudi Arabia, 2017

Variables	OR*	CI	P	OR**	CI	P
AEDs Category (Ref: Non-Enzyme Inducer)						
Enzyme Inducer	13.60	4.56 – 20.76	<0.001	16.59	4.59 – 20.95	<0.001
AEDs Regimen (Ref: Mon-therapy)						
Poly-therapy	12.66	7.02 – 19.14	<0.001	18.32	4.61 – 20.79	<0.001
Smoking Status (Ref: Non-Smokers)						
Smokers	5.80	2.38 – 9.34	<0.001	5.41	0.77 – 8.76	0.09
Ex-Smokers	4.95	2.78 – 10.97	<0.001	4.48	1.10 – 10.15	0.04
Marital Status (Ref: Not-married)						
Married	6.75	2.65 – 10.03	<0.001	9.72	2.40 – 15.45	0.001

"OR: Unadjusted Odds Ratio - OR**: Adjusted Odds Ratio"*

Focusing on the connection between lower vitamin D level and class of antiepileptic drugs, it was found that enzyme inducing antiepileptics are linked to vitamin D deficiency, an irresistible proof to hold up this statement. While there is limited number of studies about this fact, patients getting anti-epileptics might have affected bone density for certain rationales. It was anticipated that anti-epileptic drugs dropped efficient vitamin D metabolism throughout improvement of liver enzymes. This might be also attributed to direct effect of antiepileptics on calcium metabolism [15].

67.34% of patients in the current study have vitamin D deficiency and which is higher than USA epileptic patients [4]. This difference is present could be attributed to the fact the our population is from the KSA with religious costume and many indoor activities which interfere with exposure to sun directly, while the USA epileptic patients also incorporated patients from northern regions with poor vitamin D levels. Moreover, the variation could not be accredited to obesity as the level of obesity in the current study (53.54%) is alike the USA patients (50%) [17].

We noted that, 25-hydroxyvitamin D insufficiency was significantly reported among adult epileptics (93.27%), which is a constant finding noted by similar studies [18-20]. Twenty five percent of adults with epilepsy had insufficiency of vitamin D [19]. Serum vitamin D insufficiency was 75% of patients with epilepsy [21].

Vitamin D deficiency among epileptic was prevailing among patients, so this necessities the significance of monitoring and optimum management among those patients. We did not thoroughly explore all diseases that raise the jeopardy of vitamin D insufficiency. The present research declared that vitamin D insufficiency was greater within EIAEDs (100%) compared to Non-EIAEDs (80%). This is inline with what was reported by Pack et al [22] Moreover, a double blinded randomized trial has confirmed that 4,000 IU/day vitamin D improves bone compactness [23].

Subsequently, “The Endocrine Society’s Guidelines” advocate screening of vitamin D level among patients might exposed to vitamin D deficiency, which incorporates epileptics using enzyme inducing antieplepics [3].

Ahead of bone density, numerous researches have recommended that vitamin D deficiency may make a payment negatively to rheumatoid arthritis, depression and vascular complications [1-4]. Additional, surveys propose that vitamin D deficiency may deteriorate convulsions [24]. Further research is required to prove these findings.

Unfortunately, besides Endocrine Society’s recommendation there were not any formal strategy for screening of vitamin D level and bone integrity among epileptics on enzyme inducing drugs [25]. While further study is considered necessary to investigate vitamin D and calcium levels, we believe that vitamin D have to compulsory for all epileptic patients on EIAEDs.

The present study recognized that lower mean calcium and phosphate levels were insignificantly associated with vitamin D insufficiency among adult epileptic patients compared to normal patients ($P>0.05$), our observation was accounted by other studies which have found no significant association of calcium levels with epilepsy [26-28].

The mechanism underlying low levels of calcium in epileptics may be multi-factorial. Antiepileptic drugs are connected to alterations in bone metabolism and phosphate concentration and thus a change in calcium homeostasis in the body [18]. Thus, the main pathogenetic mechanism seems to be based on reduced active value of vitamin D, possibly caused by initiation of hepatic enzymes by AEDs, leading to its conversion to inactive ingredients in the microsomes of the liver. Hypocalcemia can be due to decreased absorption from the gut secondary to the state of hypovitaminosis D [29].

There has been a lot of debate on whether the enzyme enhancing criteria of AEDs are to blame. Initial studies reported an association of reduced bone compactness with mainly EIAEDs [5,30]. However, recent studies have found no difference between EIAEDs and Non-EIAEDs in their action on 25-hydroxyvitamin D status [31].

In this study, the most commonly used antiepileptic drug was enzyme inducer EIAEDs in 65.32% of patients. Our study established that vitamin D insufficiency and deficiency were significantly linked with EIAEDs (100% & 97.42% respectively) usage; similar studies have advocated our findings [32-34]. While, Misra et al. found 21.7% of epileptic patients on EIAEDs to have vitamin D deficiency [32]. However, a

50% elevated incidence of vitamin deficiency also noticed in EIAEDs users [35].

Verrotti et al. established an independent relationship between AEDs usage and vitamin D deficiency [36] However, some studies did not declare a significant relation [37].

Additionally, it appears that patients using poly-therapy with antiepileptics are further prone to low vitamin D level. The present study revealed that, almost all adult epileptic patients on poly-therapy regimen experienced either vitamin D insufficiency or deficiency.

Long term usage of AEDs was radically correlated with 25-hydroxyvitamin D deficiency [38-41]. Various studies reported that epileptics with deficiency of vitamin D had drastically longer duration of treatment than to those with normal vitamin D. In addition to, studies have found deficiency of vitamin D significantly related to long term usage of AEDs >10 years [42-43] This is contradicting to the current study.

However, in agreement with our findings, some studies have found no correlation between 25-hydroxyvitamin D deficiency and duration of treatment with AEDs [44-45].

There is no clear information on the exact duration of AEDs which leads to low vitamin D level. Farhat et al, noted that exposure to AEDs for more than six month leads to vitamin D deficiency in 35%.[44] In our study 94.25% & 75.61% of cohort of epileptics who exposed to AEDs for more than 10 years insignificantly experienced low vitamin D.

This emphasizes the consequence of AEDs on bone integrity and it is consistent with current worldwide literature [45]. Till now, there are no established strategy for avoiding and managing vitamin D deficiency among epileptic patients. Some authors suggest that doses of approximately monthly 50,000 IU vitamin D were necessary for patients with epilepsy [41]. Others have recommended a supplementation dose of 400-4000 IU/day of vitamin D for treating these changes. For prophylaxis, two studies have recommended 600- 2000IU/ day of vitamin D for all epileptics as soon as they are started on AEDs [46-47].

Unfortunately, prophylactic calcium or vitamin D supplementation is prescribed by nearly third of neurologists and just tenth of paediatric neurologists and, along with AEDs in epileptic patients [48].

By building multiple linear regression model of covariates of vitamin D insufficiency, this current research demonstrated that antiepileptic drug category, poly-therapy treatment regimen, and smoking status were significant predictors associated with vitamin D level.

5. CONCLUSION

The outcomes of the current research propose that certain avoidable behaviors as smoking, poly-therapy and drug category “Non-enzyme inducers” are aspects more commonly connected to vitamin D. As vitamin D insufficiency was more common among smokers, ex-smokers, married epileptic patients who were on enzyme inducing poly-therapy drug AEDs regimen.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

DATA AVAILABILITY

The data used to support the findings have not been made available due to restrictions from the participant consent.

CONSENT AND ETHICAL APPROVAL

After getting the acceptance from “King Abdul-Aziz University: Institutional Review Board”, the principal investigator took the official agreement from “King Fahd Hospital Ethical Committee”. Patients also were given their written informed consent. Privacy and Confidentiality were guaranteed throughout the duration of the survey. Patients were being knowledgeable about their voluntary participation and right to withdraw from the study at any time without influencing the receiving cervices.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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