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Effect of vitamin D level on quality of life in epileptic patients

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ABSTRACT

People with epilepsy suffer from poor quality of life as a result of frequent seizure cognitive dysfunction, and a high risk of psychiatric co-morbidities. Beyond the role of vitamin D in bone health, it may be implicated in the functions of other systems of the body such as cardiovascular systems, cancer, autoimmune diseases, type 2 diabetes, and depression. The present study was conducted to study the effect of vitamin D administration on the quality of life in epileptic patients treated with antiepileptic drugs carbamazepine and levetiracetam. The study was performed with the participation of 67 patients newly diagnosed with epilepsy. They were taking the enzyme-inducing agent carbamazepine, and the non-enzyme-inducing agent levetiracetam. quality of life (QOLIE-31) of all patients was calculated by using the QOLIE-31 questionnaire (version 1.0). Patients then were divided into 2 groups according to the basis of the vitamin D level of the patients into group A, 33 patients, and group B, 34 patients. Group A received vitamin D supplements based on their vitamin D levels, while group B did not. The addition of vitamin D to group A showed an increase in the % of improvement rate as compared to group B which did not receive vitamin D supplementation. This improvement includes the patient awareness about his disease and how to deal with it, how used the drug, and its side effects. This work could provide evidence for the efficacy of vitamin D supplementation to patients with epilepsy through correction of the quality of life of the patients.

1. INTRODUCTION

Epilepsy is one of the common neurological disorders, which require immediate medical attention and long-term therapy. The incidence is approximately o.3-o.5% in different world populations with a prevalence rate of five to ten per thousand people [1]. People with epilepsy suffer from poor quality of life as a result of frequent seizure cognitive dysfunction [2], and a high risk of psychiatric co-morbidities [3]. The impact of epilepsy will differ depending on an individual's age-related stage of life, i.e. childhood, adolescence, adulthood and late adulthood [4]. Epilepsy can be associated with profound physical, psychological, and social consequences [5], and its impact on a person's quality of life (QOL) can be greater than that of chronic

conditions [6]. People with epilepsy have been shown to reported a poorer QOL because they are more likely to have poor self-esteem and a high level of anxiety and depression [7]. In some patients, the social stigma and impact on QOL can pose a greater challenge than clinical severity [8]. Beyond the role of vitamin D in bone health, it may be implicated in the functions of other systems of the body such as cardiovascular health, tumor prevention immunological functioning as well as glucose metabolism [9]. It is now assumed that vitamin D status is a major factor influencing life expectancy [10]. Deficient levels of vitamin D have been associated with several brain disorders including multiple sclerosis, Alzheimer's, Parkinson disorders [11]. A neurological role of vitamin D3 is further supported by the presence of vitamin D3 specific receptors [12] and enzymes in neurons and glial cells throughout the brain, in the spinal cord, and in the peripheral nervous system [13]. Currently, a large body of evidence indicates that several AEDs lower 25(OH) D levels and are associated with adverse effects on bones and muscles [14]. Among all antiepileptic drugs, carbamazepine and phenytoin are most studied in this regard. Many studies showed that carbamazepine and phenytoin possessing a lowering effect on 25(OH) D [15]. This effect is thought to be due to the enzyme-inducing properties of those anti-epileptics. Induction of the cytochrome p450 system is known to increase the catabolism of vitamin D by up-regulating enzymes converting 25 (OH) D into inactive metabolites [16]. In one study which is carried out almost 40 years ago and was controlled by placebo [17], supplementation of vitamin D2 (4000IU/day), resulted in an overage seizure reduction of 30%. In another study done in 2011, vitamin D3 supplementation was administered in 13 therapy resistant epilepsy patients [18], a significant reduction of seizure numbers with a median of 40 % was obtained.

Found in a systemic review of 93 studies that an increase in seizure frequency, seizure severity, level of depression and anxiety, and the presence of a co-morbid condition were strongly associated with a reduced health-related quality of life [19]. And since the administration of vitamin D supplementation can reduce the frequency and severity of seizures. The present study was conducted to study the effect of vitamin D administration on the quality of life in epileptic patients treated with anti-epileptic drugs carbamazepine and levetiracetam.

2. AVAILABILITY OF DATA AND MATERIALS

This was a case-control, questionnaire-based study conducted in the department of pharmacology, college of medicine, university of Mosul. The study was performed with the participation of 67 patients newly diagnosed with epilepsy (age>18years) receiving antiepileptic drugs monotherapy. The patients were separated into 2 groups according to the vitamin D levels that were less than 20ng/m. Sample recruitment from a private neuro medicine clinic in Mosul/ Iraq.

Study approval:
The approval of the study protocol by an ethic committee has been obtained from College of Medicine - University of Mosul – Iraq (no. 234). Before starting the study, each patient was informed about the study design, purpose of the study and his approval was obtained.

Inclusion criteria:
Newly diagnosed epileptic patients having ages>18 years.

Exclusion criteria:
1- liver disease
2- renal disease
3- drug that cause induction or inhibition of liver enzymes.
4- other conditions that affects bone metabolism e.g. hyperparathyroidism, Paget disease, osteoporosis.

5- < 18 years patients.
6- Uses of drugs that affect bones.
Vitamin D and calcium were measured before and after administration of the drug. The concentration of 25(OH) vitamin D is measured by using the LIAISON analyzer (Italy). The concentration is expressed in ng/ml.

Serum calcium concentration was measured by CA flex reagent cartridge Dimension® clinical chemistry system.

QOLIE-31 questionnaire:
After 3 months of treatment, all of the patients were given the QOLIE-31 questionnaire (version 1.0), which had been validated in Arabic. Individual and self-administered, the questionnaire takes about 10 to 15 minutes to complete. In cases of handicap or minor mental retardation, the patients completed the sociodemographic questions about themselves, either alone or with the assistance of direct family, a questionnaire was conducted and returned after 6 months of treatment again. With the use of tables and mathematical procedures previously established for this questionnaire, the scores received in the questionnaire were transformed to a scale of 0 to 100 points. The sum of the scores in each area yields the global score, which indirectly indicates the patient's quality of life [20].

Patients were divided according to the basis of the vitamin D level of the patients into groups A (33 patients) and group B (34 patients) regardless of which type of drug was used. The first group(A) received vitamin D supplements in a dose of 50000 I.U weekly based on their vitamin D levels, while the second group did not, to determine the effect of vitamin D on quality of life in epilepsy patients. For the second phase, the cut-off of vitamin D levels that were less than 20ng/ml.

3. Statistical analysis
The statistical analysis was performed using SPSS version 23 software. The distribution of data was tested by Kolmogorov–Smirnov test. Continuous variables were reported as mean ± SD.

One-way analysis of variance (ANOVA) was utilized to compare Vitamin-D level among subjects in different groups.

The independent sample t-test was used to reveal significant differences in the bone parameters (vitamin-D level) between carbamazepine users and levetiracetam users.

Paired sample t test was conducted to illustrated within-group changes in patients studied from pretreatment to the end of follow up. All tests were two-sided and values of $p \leq 0.05$ were considered to be significant (Daniel & Cross, 2018; Hazra & Gogtay, 2016; Norman & Streiner, 2014)

4. Results
Table one shows comparison of the 3 groups according to age and sex, which shows no statistical differences between the 3 groups, carbamazepine, levetiracetam and control:

Table (1): Demographic differences among the studied groups prior to the treatment with carbamazepine or levetiracetam:

variable	Group A n=33	Group B n=34

Age	18-53 years	Mean=34.74 SD=9.628	18-49 Years	Mean= 33.38 SD=9.2158
sex	Male=15 41.94%	Female=18 58.06%	Male= 18 52.78%	Female=16 47.22%
Seizure type	Focal epilepsy n=31 46%		Grand mall epilepsy n=36 56%	

The epileptic patients before the addition of vit D were divided into 2 groups. Group A, consist of 33 patients having the low values of vitamin D, who take vitamin D capsule in a dose of 50000 I.U weekly for a period of 3 months. Group B consist of 34 patients having higher values of vit D serum concentration, who take no vitamin D capsules.

Table two shows the comparison between QOLIE-31 scores of group A and group B epileptic patients before administration of vit D_3. No significant difference was found between all the scores

Table (2): Comparison in QOLIE-31 scores between group A and group B epileptic patients before administration of vit D_3.

No.	QOLIE-31 scores	Before administration of vitamin D		P-value*
		Vitamin D supplement group (A) [n = 33] Mean ± SD	No vitamin D supplement group (B) [n = 34] Mean ± SD	
1	Seizure worry	50.4 ±11.7	49.6 ±11.9	0.788
2	Emotional well-Being	60.1±11.6	56.8 ±12.1	0.266
3	Energy/Fatigue	41.4 ±9.7	43.3 ±8.7	0.401
4	Cognitive	54.2 ±12.6	53.8 ±11.8	0.874
5	Medication effect	46.6 ±10.3	55.1 ±13.2	**0.005**
6	Social function	48.2 ±12.0	46.1 ±8.9	0.400
7	Overall quality of life	44.9 ±9.9	45.8 ±9.7	0.698
	Overall score	**50.5 ±8.9**	**49.9 ±7.7**	0.797

*Independent t test for two means was used

Table three shows the comparison between QOLIE-31 scores of group A and group B epileptic patients at the end of the second 3 months i.e., after administration of vit D3. A significant difference was found between all the scores:

Table (3): Comparison in QOLIE-31 scores between group A and group B epileptic patients at 6 months follow-up.

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No.	QOLIE-31 scores	At the end of 3 months of vit D administration		P-value*
		Vitamin D supplement group (n = 33) Mean ± SD	No vitamin D supplement group [n = 34] Mean ± SD	
1	Seizure worry	58.7 ±12.6	50.7 ±11.8	**0.009**
2	Emotional well-Being	63.4±11.6	58.4 ±11.6	0.083
3	Energy/Fatigue	59.8 ±10.8	43.6 ±7.7	**0.001**
4	Cognitive	61.0 ±11.6	54.2 ±12.1	**0.023**
5	Medication effect	56.3 ±11.2	57.6 ±12.5	0.646
6	Social function	68.4 ±10.4	47.2 ±8.8	**0.001**
7	Overall quality of life	58.6 ±10.5	48.3 ±9.1	**0.001**
	Overall score	**62.1 ±7.9**	**51.1 ±7.0**	**0.001**

*Independent t test for two means was used

Table four shows the changes in QOLIE-31 scores after 3 months of vitamin D administration at the end of the studied. Significant differences were found between the 2 groups:

Table (4): The changers in QOLIE-31 scores in vitamin D supplement monotherapy group (A) at the end of the study.

No.	QOLIE-31 scores	Vitamin D supplement group [n = 33]		% Improvement rate*	P-value**
		Before administration of vit D Mean ± SD	At the end of 3 months of vit D administration Mean ± SD		
1	Seizure worry	50.4 ±11.7	58.7 ±12.6	**- 16.5 %**	**0.001**
2	Emotional well-Being	60.1±11.6	63.4±11.6	**- 5.4 %**	**0.001**
3	Energy/Fatigue	41.4 ±9.7	59.8 ±10.8	**- 44.7 %**	**0.001**
4	Cognitive	54.2 ±12.6	61.0 ±11.6	**- 12.5 %**	**0.001**
5	Medication effect	46.6 ±10.3	56.3 ±11.2	**- 20.7 %**	**0.001**
6	Social function	48.2 ±12.0	68.4 ±10.4	**- 41.9 %**	**0.001**
7	Overall quality of life	44.9 ±9.9	58.6 ±10.5	**- 30.6 %**	**0.001**

Table five shows the comparison between QOLIE-31 scores at 3 months and 6 months with no vitamin D supplements at the end of the study. A low difference was found between the two groups:

Table (5): The changers in QOLIE-31 scores in group (B) with no vitamin D supplement monotherapy group at the end of the study.

No.	QOLIE-31 scores	No vitamin D supplement group B [n = 34]		% Improvement rate*	P-value**
		Before administration of vit D Mean ± SD	After administration of vit D for 3 months Mean ± SD		
1	**Seizure worry**	49.6 ±11.9	50.7 ±11.8	**- 2.1 %**	**0.022**
2	**Emotional well-Being**	56.8 ±12.1	58.4 ±11.6	**- 2.7 %**	0.150
3	**Energy/Fatigue**	43.3 ±8.7	43.6 ±7.7	**- 0.9 %**	0.624
4	**Cognitive**	53.8 ±11.8	54.2 ±12.1	**- 0.8 %**	0.679
5	**Medication effect**	55.1 ±13.2	57.6 ±12.5	**- 4.6 %**	**0.003**
6	**Social function**	46.1 ±8.9	47.2 ±8.8	**- 2.5 %**	0.341
7	**Overall quality of life**	45.8 ±9.7	48.3 ±9.1	**- 5.5 %**	**0.021**
	Overall score	**49.9 ±7.7**	**51.1 ±7.0**	**- 2.3 %**	**0.018**

* % Improvement rate = [(before – after) / Before] × 100.
**Paired T-test of two means was used.

Table six shows the differences in % improvement rate in QOLIE-31 scores between the 2 groups at the end of the study. Significant differences were found between QOLIE-31 scores:

Table (6): The differences in % improvement rate in QOLIE-31 score between the two groups at the end of the study.

No.	QOLIE-31 scores	% Improvement rate		P-value*
		Vitamin D supplement group	No vitamin D supplement group	
1	**Seizure worry**	**- 16.5 %**	**- 2.1 %**	**0.001**
2	**Emotional well-Being**	**- 5.4 %**	- 2.7 %	0.123
3	**Energy/Fatigue**	**- 44.7 %**	- 0.9 %	**0.001**
4	**Cognitive**	**- 12.5 %**	- 0.8 %	**0.001**

5	**Medication effect**	**- 20.7 %**	**- 4.6 %**	**0.001**
6	**Social function**	**- 41.9 %**	- 2.5 %	**0.001**
7	**Overall quality of life**	**- 30.6 %**	**- 5.5 %**	**0.001**
	Overall score	**- 23.1 %**	**- 2.3 %**	**0.001**

* Z-test for two proportions was applied.

5. Discussion

Epilepsy has a considerable impact on QOL with extensive and life-long consequences. Improving the QOL in a person with a seizure disorder is an essential component of the management of such patients [21]. The Quality of Life is a notion, which is known as the level of general well-being that a person extent in his physical, mental and social aspect. In epileptic patients, this is compromised because it is a chronic disease that impact the patient's daily life, both personally and socially The main factor that causes greater concern and worsens the quality of life of epileptic patients, is due to the side effects of antiepileptic drugs [22]. Epilepsy has a considerable impact on QOL with extensive and life-long consequences. Improving the QOL in a person with a seizure disorder is an essential component of the management of such patients [23]. The impact of anti-epileptic medication on vitamin D levels and bone metabolism is the most studied aspect of epilepsy and vitamin D [24]. At present, a large body of evidence indicates that several AEDs lower 25(OH) levels [14] and are associated with adverse effects on bone and muscles [25]. Among all AEDs carbamazepine and phenytoin are most studied in this regard. Many studies showed that carbamazepine and phenytoin use were associated with 25(OH)D lowering effects [26]. These results about carbamazepine is in agreement with the results of the present study which observed a low level of vitamin D when compared with those of levetiracetam [27]. A longitudinal study of levetiracetam involving 61 patients did neither show vitamin D to be decreased [28] which is in agreement with the present study. Several anti-epileptic drugs, especially those with enzyme inducer properties, decrease vitamin D level which paradoxically may predispose to more seizures. These facts together with the world-wide problem of vitamin D deficiency at the known relationship of insufficient vitamin D levels with the major disorders of civilization warrant routine screening and supplementation of vitamin D in epilepsy patients [11].

People with epilepsy suffer from poor quality of life as a result of frequent seizures, cognitive dysfunction, and a high risk of psychiatric co-morbidities [2]. The objective of epilepsy treatment concerns not only seizure control but also minimization of the effects of the disease at the side effects of anti-epileptic drugs on the daily lives of patients with epilepsy. In the present study the administration of vitamin D to epileptic patients with low vitamin D level shows an improvement of quality of life as compared to the patients who did not administer vitamin D. There is growing concerning the role of vitamin D in various medical conditions such as diabetes and oncological, cardiovascular and CNS disorders [18]. Emerging research supports the possible role of vitamin D against cancer, heart disease, fracture and falls, autoimmune disease, influenza, type 2 diabetes and depression [29]. A meta-analysis published in 2007 showed that vitamin D supplementation was associated with significantly reduced mortality [30]. Vitamin D insufficiency affects, almost 50% of the population worldwide [31]. The high prevalence of vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor total mortality in the general population [32].

6. Conclusion

This work could provide evidence for the efficacy of vitamin D supplementation to patients with epilepsy

through correction of quality of life of the patients.

7. Limitations and clinical implications

1- To corroborate the outcomes of our investigation, more prospective studies with a large number of patients are needed for longer time.
2- Divide patients based on the type of drug used to determine the effect of the drug itself on quality of life.
3- Studies may be needed to examine the benefit of vitamin D as anti-epileptic agent and its effect on treatment of epilepsy.
4- Further studies are needed to evaluate the effect of epilepsy on serum level of vitamin D.
5- For the correlation between vitamin D supplement and QOL, perform a covariate analysis to determine the effect of the confounding factors such as the choice of AED, seizure control required.

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