

# The Effect of Some Anti-Epileptic Drugs on Bone Health among Epileptics in Mosul Iraq

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## ABSTRACT

To this day, there is increasing evidence that epilepsy and its medications can have harmful effects on bone mineralization. The purpose of the current study is to evaluate whether carbamazepine and levetiracetam as monotherapy are associated with vitamin D deficiency and calcium deficiency among epilepsy patients. A case series study with serum calcium and vitamin D tests was conducted on 97 participants, 67 of them were patients with epilepsy, while 30 were control groups. Epilepsy patients had been receiving antiepileptic drugs (AEDs) for at least six months, and they were separated into 2 groups CAR group, patients receiving carbamazepine (31), and LEV group patients receiving levetiracetam (36). Calcium and vitamin D concentrations in serum were measured and compared in both groups at the start of taking epilepsy medication and after 3 months of it. The results showed a significant deficiency of calcium and vitamin D in epilepsy patients who were treated with CAR for more than 3 months when compared with the start of taking it. Therefore, the vitamin D and calcium status of patients taking CAR should be monitored regularly, and vitamin D and calcium supplementation should be considered on an individual basis.

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## 1. INTRODUCTION

Epilepsy can be defined as a chronic neurological illness described by repeated seizures associated with abnormal neurological activities in the brain. About fifty million people worldwide have epilepsy, 85% of whom live in developing countries [1], [2]. It is usually managed with standard antiepileptic (AEDs) or anticonvulsant medications which often provide seizure symptom relief without complete cure, so their long-term use causes various health problems for patients with epilepsy. Carbamazepine (CAR) and levetiracetam (LEV), both of which belong to the more common traditional antiepileptic drugs [3], [4]. Carbamazepine is a first generation antiepileptic drug. It is aptly treated with partial and generalized tonic-clonic attacks, in addition to its effectiveness in the management of neuropathic pain and bipolar disorder [5], [6]. Levetiracetam is a safe and effective second-generation antiepileptic drug, most commonly used in the treatment of focal and generalized epilepsy [7]. It has proven its worth in managing epilepsy in pediatric

and adult patients, preventing seizures from post-traumatic brain injuries, as well as neuropathic pain [8]. Long-term treatment with antiepileptic drugs is the fate of the majority of people with epilepsy in order to control seizures and reduce side effects [9], [10]. The incidence of bone deformities and disorders such as osteoporosis, chronic pain, falls and fractures in patients with epilepsy is at least 50%, which requires much attention to be paid to the relationship between bone safety and epilepsy drugs [11- 13]. The biochemical and radiological evaluation of the side effects of the metabolism of vit. D and calcium (Ca) that are detrimental to bone health, through several previous studies [14- 16]. It is precious evaluating their effects on vit. D and Ca to try to reduce and prevent these effects. To achieve this, the current study attempted to measure those parameters among epilepsy patients in the city of Mosul, northern Iraq, who take antiepileptic drugs.

## 2. Methods

A case series study was conducted on adult patients with newly diagnosed epilepsy who had been receiving an antiepileptic drug (carbamazepine or levetiracetam) for 6 months. It was performed between October 2020 and August 2021 in a private neurology clinic and Al Salam Teaching Hospital (Mosul city, Iraq). The study was approved by the Ethics Committee, College of Medicine/ University of Mosul. 76 participants with epilepsy were enrolled in this study and divided into two groups as follows: CAR group, which included 31 patients who received carbamazepine at a dose of 7-15 mg /kg /day in two divided doses for the extended-release preparation or 2-4 divided doses for the regular preparation, for a period 6 months. LEV group, which included 36 patients who received levetiracetam at a dose of 500-750 mg twice daily as a maintenance dose, for 6 months. While 30 participants were non-epileptic as the control group (CON). Data were obtained directly from patients and the control group by interviewing the researcher with them, using a specially prepared formula. Epilepsy patients who had any condition affecting bone metabolism such as kidney disease, recent fractures, hyperthyroidism, Paget's disease, osteoporosis, or taking any medication that causes or treats osteoporosis were excluded. The concentrations of vitamin D and calcium in the blood serum were measured before taking the drug and 3 months after that. Biochemical analyzes were performed in a private laboratory. Standard kits were used to measure biochemical parameters in this study and were interpreted following the outline of the instructions in each one. Descriptive and analytical statistics were performed using the statistical software Minitab version 18. Descriptive statistics included mean  $\pm$  standard deviation (SD) for personal and biochemical quantitative variables. Two independent t-test methods (unpaired) were used to compare each of the two biochemical parameters (two groups). A two-way (t-test) was used for comparison. P values  $\leq$  0.05 were considered statistically significant during data analysis.

## 3. Results

A total of 97 individuals participated in the current study, including 67 cases and 30 controls. Table (1) shows the basic demographics of the studied groups before treatment, noting the ages and the percentages of males and females in the three groups: CAR, LEV and CON.

**Table 1:** Proportion of all participants in the study by age and gender.

Basic Demographic		Epileptic Patients(N=67)		CON (N=30)
		CAR (N=31)	LEV (N=36)	
Age	<b>Years old</b>	19-53	18-49	18-51
	<b>Mean<math>\pm</math> SD</b>	34.74 $\pm$ 9.628	33.38 $\pm$ 9.2158	33.6 $\pm$ 9.4817

Gender	<b>Male</b>	13 (41.94%)	19 (52.78%)	17 (56.6%)
	<b>Female</b>	18(58.06%)	17 (47.22%)	13 (43.3%)

Table 2 demonstrates the serum levels of vitamin D and calcium in CAR, LEV and CON groups. There was no significant difference at  $P < 0.05$  between the three participating groups at the start of the study.

**Table 2:** Serum levels of vit. D and Ca for groups at the start of the study.

Parameters	At starting of the study			P-value*
	<b>CAR</b>	<b>LEV</b>	<b>CON</b>	
Vitamin D (ng/ml)	23.47±3.95	24.03 ±6.72	23.90±5.44	0.891
Calcium (mg/dl)	9.54±0.54	9.62±0.58	9.31±0.61	0.080

\* One-way ANOVA was applied with Turkey's pairwise comparisons. No significant difference was observed.

On the other hand, table 3 illustrates the comparison of serum vitamin D and calcium concentrations between baseline and after 3 months of carbamazepine treatment. Statistically significant differences were found between them.

**Table 3:** Serum levels of vit. D and Ca in the carbamazepine group.

Parameters	CAR		P-value*
	<b>Baseline</b>	<b>Three months later</b>	
Vitamin D (ng/ml)	23.47 ±3.95	21.56±5.62	0.004
S. Calcium (mg/dl)	9.54±0.54	9.14±0.44	0.002

\* Dependent t-test was used for two means.

While, table 4 explains the comparison of vitamin D and serum calcium concentration between baseline and after 3 months of treatment with levetiracetam. Non-significant differences were found between them.

**Table 4:** Serum vit. D and Ca levels in the levetiracetam group.

Parameters	LEV		P-value*
	<b>Baseline</b>	<b>Three months later</b>	
Vitamin D (ng/ml)	24.03 ±6.72 <sup>B</sup>	24.33 ±5.02 <sup>B</sup>	0.58
S. Calcium (mg/dl)	9.62±0.58 <sup>A</sup>	9.46 ±0.44 <sup>AB</sup>	0.12

\* Dependent t-test was used for two means.

Finally, table 5 represents the comparison of the concentrations of vitamin D and serum calcium between

the two groups of carbamazepine and levetiracetam. After 3 months of treatment. Where a significant statistical difference was found between the two groups.

**Table 5:** Serum levels of vitamin D and calcium in carbamazepine and levetiracetam groups.

Parameters	Three months later		P-value*
	CAR	LEV	
Vitamin D (ng/ml)	21.56±5.62	24.33 ±5.03	0.037
S. Calcium (mg/dl)	9.14±0.44	9.46 ±0.44	0.004

\* Independent t-test was used for two means.

#### 4. Discussion

In this study, we demonstrated evidence that epilepsy patients experienced significant changes in bone metabolism after 3 months of taking carbamazepine compared to when they first started taking it. Conversely, we did not observe that levetiracetam monotherapy significantly reduced vitamin D and calcium levels three months after taking LEV compared to when they started taking the drug. Previous studies support what we have mentioned, they have shown that a significant decrease in bone mineral density and an increased risk of bone fracture occurred in epileptics treated with enzyme-inducing antiepileptics such as carbamazepine [17]. Our findings provide identification at a glance the important association between carbamazepine and bone metabolic disturbances in patients with epilepsy. There are many previous studies that explored the effect of anti-epileptic drugs on minerals in the body and concluded that the most common effects of these drugs were on calcium and vitamin D [18- 20]. In 2005, compared 119 patients treated with antiepileptic drugs with 119 controls to prove the effect of these drugs on bone minerals, especially parathormone [21]. It is worth noting that vitamin D is essential for calcium absorption and helps lateness further bone loss [22]. The hepatic cytochrome P450 enzyme, which is directed mainly by carbamazepine, increases serum levels of inactive forms of vitamin D. Moreover, carbamazepine accelerates bone metabolic activity [23]. Confirmed that the riskiness of bone fracture associated with the use of AEDs is well established [24]. As for levetiracetam in this regard, there are limited studies that revealed no unhealthy effects [25]. This is consistent with the findings of this study.

#### 5. Conclusions

According to our findings, in epileptics who are being treated with carbamazepine on a long-term basis, periodic checks of Vit. D and Ca levels can be carried out, in order to avoid their deficiency in the body and prevent the following consequences.

Conflict of interest

None.

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