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Evaluation of Osteoporosis among Epileptic Patients on Monotherapy

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Abstract

Epilepsy is a chronic neurological disorder that affects nearly 50 million people worldwide. Most patients require long-term treatment with antiseizure medications (ASMs). Our case control study aimed to evaluate the long-term effects of carbamazepine (CBZ) and valproate (VPA) on bone mineral density and bone health biochemical markers among 50 patients with newly diagnosed epilepsy who had no prior history of ASMs intake. The patients were divided into two groups: the first group received CBZ monotherapy, while the second group received VPA monotherapy. Another 25 healthy individuals were included as a control group.

Our primary outcome was to evaluate the percentage of osteoporosis compared to the duration of ASM therapy measured by the T score at two different sites in the body at baseline, after 3 and 6 months of therapy. The measurements of bone biomarker variables were considered secondary outcomes.

The study found that both CBZ and VPA significantly decreased the level of vitamin D3, calcium (Ca), phosphorus (P), the 3rd – 5th lumbar spine (L3-L5) and right femoral neck T score with prolonged treatment duration, while the level of ALP increased with increasing duration of treatment in patients treated with CBZ but not in the VPA group. CBZ significantly decreased bone health biomarkers and T score earlier than VPA and the control group, with no significant differences between the two sexes who received CBZ or VPA therapy on bone biomarkers.

In conclusion, the findings suggest that valproate may not affect bone biomarkers earlier, but with a longer duration of therapy, it may have the same effect as carbamazepine. Therefore, it is recommended to prescribe supportive vitamin D and Ca along with ASMs to prevent the development of osteoporosis in patients with epilepsy.

Keywords: Epilepsy, Valproate, Carbamazepine, T- Score, Osteoporosis.

تقييم هشاشة العظام لدى مرضى الصرع مع الادوية الأحادية المضادة للصرع

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الخلاصة:

الصرع هو اضطراب عصبي مزمن شائع يصيب ما يقرب من ٥٠ مليون شخص في جميع أنحاء العالم. يحتاج معظم المرضى إلى علاج طويل الأمد، وأحيانا مدى الحياة بالأدوية المضادة للصرع. أن مرضى الصرع لديهم مضاعفات الكسور وتنخر العظام يتراوح من ضعفين إلى ستة أضعاف مقارنة بالأشخاص العاديين. الغرض من هذه الدراسة هو تقييم النسبة المئوية لهشاشة العظام مع الاستخدام المطول للأدوية المضادة للصرع حيث سجلت الدراسة ذات شواهد حالة ٥٠ مريضا يعانون من الصرع الذي تم تشخيصه حديثا والذين لم يكن لديهم تاريخ من تناول الأدوية المضادة للصرع من قبل وتم تقسيمهم إلى مجموعتين. في المجموعة الأولى البالغ عددهم ٢٥ مريضا تم اعطاؤهم دواء الكاربامزبين، بينما تضمنت المجموعة الثانية ٢٥ مريضا تم اعطاؤهم علاج فالبروايت. بينما تم اعتبار ٢٥ فردا آخر من الأصحاء كمجموعة ضابطة. تتمثل النتيجة الأولية لدراستنا في تقييم النسبة المئوية لهشاشة العظام مقارنة بمدة العلاج المقاسة بمقياس T لتقييم هشاشة العظام في موقعين مختلفين من الجسم قبل وبعد ٣ و ٦ أشهر من العلاج. اظهرت نتائج الدراسة ان علاج الكارباماز بين والفالبروايت خفضتا بشكل ملحوظ مستوى فيتامين D٣ و Ca و P ودرجة مقياس T للفقرات القطنية الثالثة والخامسة و عنق الفخذ الأيمن مع اطالة مدة العلاج، بينما زادت مستوى ALP في المرضى الذين عولجوا بالكارباماز بين بخلاف مجموعة الفالبروايت. علاوة على ذلك، خفضت الكارباماز بين بشكل كبير المؤشرات الحيوية لصحة العظام ومقياس T في وقت أبكر من الكارباماز بين مقارنة بالمجموعة الخاضعة للرقابة، وكذلك لم تكن هناك فروق ذات دلالة إحصائية بين الذكور والإناث الذين تلقوا العلاجين المذكورين على المؤشرات الحيوية للعظام حيث تم الاستنتاج ان علاج فالبروات لم تؤثر على المؤشرات الحيوية للعظام في وقت مبكر، ولكن مع اطالة مدة العلاج ، قد يكون لها نفس تأثير الكارباماز يبين الذي يتطلب دعم المرضى بتناول فيتامين دي والكالسيوم جنبا إلى جنب مع الادوية المضادة للصرع.

الكلمات المفتاحية: الصرع، فالبروايت، كارباماز يبين، مقياس تي، هشاشة العظام.

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Introduction

Epilepsy is a common chronic neurological disorder that affects almost 50 million people worldwide. Most patients require long-term, and sometimes lifelong therapy with antiseizure medications [(1)]. It is reported that epileptic patients have a two to six fold increased risk of skeletal fractures compared to normal subjects [(2)]. It's well known that antiseizure medications may had adverse effects on normal growth of children [(3)].

There are several reasons for the increase in the risk of fractures in epileptic patients, including the risk of a seizure-related fracture and fall, as well as an imbalance between bone formation and bone resorption as a side effect of ASM. Different studies report that the enzyme inducer, the non-enzyme inducer and enzyme inhibitor ASM were associated with an increase in the fracture rate in epileptic patients [(4-7)]. These ASM cause abnormalities in calcium metabolism, including hypocalcemia, hypophosphatemia, elevated serum alkaline phosphatase, serum parathyroid hormone, and low vitamin D, which in turn affects bone metabolism [(8)]. However, the mechanism of this side effect is not yet clear. Some authors argued that enzyme-inducer antiseizure medications (EIASM) increase vitamin D metabolism, causing secondary hypocalcemia and hyperparathyroidism [(9, 10)], and recent research has shown that non-enzyme-inducer antiseizure medications (NEIASM) can also lead to bone mineral deficiency [(11)]. These recent results suggest that other factors, other than enzyme induction, play a role in the development of this side effect, raising the question of whether ASMs have a direct impact on bone turnover.

Mechanisms of the effect of ASM on bone suggest that P450 cytochrome enzyme is most induced by ASMs lead to negative impacts on bone. It is assumed that CYP450 induced by ASMs (e.g., phenytoin, phenobarbital, oxcarbazepine, carbamazepine) increases enzymes involved in vitamin D metabolism, resulting in the conversion of 25 (OH) vitamin D into inactive metabolites. As a result, the absorption rate of 1,25(OH)2 D from the intestine was reduced and subsequent secondary hyperparathyroidism, hypocalcemia, bone resorption increased, and bone loss accelerated [(12)].

This study was designed to evaluate the percentage of T score and laboratory bone health markers in epileptic patients before, after 3 and 6 months of therapy with EIASM and NEIASM, in addition to identifying the effect of the gender risk factor on bone mineral density in these patients to facilitate the physician in choosing the appropriate anti-osteoporosis drugs for their patients.

Materials and Methods

This case-control study was carried out in the outpatient clinic of Azadi Teaching Hospital in Kirkuk City / Iraq, after receiving informed consent from 1 June 2020 to 1 June 2022.

Seventy five subjects whose age ranged between (15 to 45) years were enrolled in this study. Fifty patients with newly diagnosed epilepsy who had no history of ASM intake before began receiving ASM monotherapy and were divided into 2 groups. The first group included 25 patients 12(16%) males and (17%)13 Females started to receive CBZ monotherapy with a dose ranging (400 – 800mg/day), and the second group included 25 patients 13(17%) males and 12(16%) Females started to receive VPA monotherapy with a dose ranging (400 – 1000mg/day), while other 25 healthy individuals 13(17%) males and 12(16%) Females matched for age and sex with the patients were considered a controlled group. The exclusion criteria were age more than 50 years old, history of any chronic diseases or drug use, history of chronic renal or liver disease, endocrinal disorders like (thyroid, parathyroid, and adrenal disorders) and postmenopausal females. All cases and the controlled group were instructed not to use supportive vitamin D3 or calcium treatment during this study. Blood samples were taken for Vitamin D3, Calcium (Ca), Phosphorus (P) and alkaline phosphatase (ALP) between 9-10 am after an overnight fasting from all cases and controlled groups before receiving any treatment and then at 3 and 6 months after receiving ASM treatment.

Serum Ca = 8.4-11.6 mg / dl 'Kit Ref. no. 43991/24S", Phosphorus=2.5-5mg/dl" kit Ref. no. 41391/24S", ALP= (Male 40-129U/L, Female 35-104U/L)" Kit Ref.no.40201/24S assessed by Biolis 24 Japan 2014", Vitamin D3 (<20ng/ml deficiency, 20-29ng/ml insufficiency, 30-100ng/ml sufficient, >100ng/ml toxicity)" Kit Ref.no.30463 measured by Vidas France 2010".

According to the World Health Organization, the bone mineral density results were expressed in the form of a T score that usually shows how much bone density is higher or lower than the bone density of a healthy 30-year-old adult. T score − 1 or above is considered normal bone density, a score between − 1 and − 2.5 is classified as osteopenia, and a score below − 2.5 is classified as osteoporosis [(13, 14)]. For the lumbar spine (LS), the patient lies supine on the imaging table and the legs are raised by support for the lower legs. For femur scans, the femur must be rotated and held in position with a positioning device. There are also dual hip scanning protocols that position both hips simultaneously. However, the positioning device may need to be adjusted between scans to scan both hips with correct abduction [(15)].

The primary outcome of our study is to assess the percentage of osteoporosis compared to the duration of ASM therapy measured by the T score at two different sites: the lumbar spine (L3-L5) and the proximal hip (right femoral neck) using the Dexa

scan (dual-energy X-ray absorptiometry) before starting treatment and repeating again after 3 and 6 months, while measurements of bone biomarker variables are considered secondary outcomes. Statistical analysis was done using IBM SPSS Statistics 24. The continuous data is presented as a mean value (standard error mean (SEM), and the category variables are summarized as numbers (n) and percentages (%). The Kolmogorov-Smirnov test is used to evaluate the normal distribution. Comparisons between groups were made using Chi-square tests for categorical variables, independent sample t tests for normally distributed continuous variables, and Mann-Whitney U tests when distributions are skewed. Quantity analysis was tested using an ANOVA test to compare the three groups studied and determine the degree of significance between them. A p. value <0.05 is considered statistically significant.

Results

Fifty newly diagnosed epileptic patients (mean age 31.26 years, range 15 - 45), of whom 25 were male and 25 were female, were treated with ASM monotherapy and divided into three groups: CBZ, VPA, and controlled. There were no statistically significant differences in age among the three groups. Additionally, 25 healthy controls (13 male and 12 female) participated in this study. Of the 50 patients, 25 (50%) received CBZ and 25 (50%) received VPA treatment. There were no statistically significant differences in sex among the three groups **(Table 1)**.

Table 1. Descriptive statics of the age and sex of the studied groups

Variables	CBZ	VPA	Control	P-value
Sex no. (%)				
Males	12 (16%)	13 (17%)	13 (17%)	0.106 [a]
Females	13 (17%)	12 (16%)	12 (16%)	
Age (year)				
Mean	31.76	30.76	31.32	0.90 [b]
SEM	1.50	1.52	1.60	
Range	16-45	16-43	16-45	
[a] Chi square t test, [b] One way ANOVA				

The percentage of osteoporosis of T scores in the L3-L5 spine and the right femoral neck was significantly reduced in the CBZ but not in the VPA and the control group after 3 months of treatment, while both treated groups significantly reduced their percentage of T score after 6 months of ASM starting compared to the control group **(Table 2)**.

Table 2. The frequency distribution of osteoporosis according to T scores in the L3-L5 spine and right femoral neck among the studied groups

		CBZ		VPA		Control		P-value
		No.	%	No.	%	No.	%	
T score in the L3-L5 spine								
Baseline before treatment	OP	0	0.0	0	0.0	0	0.0	NA
	No OP	25	100.0	25	100.0	25	100.0	
3 months after treatment	OP	12	48.0	2	8.0	0	0.0	0.001 ** [a]
	No OP	13	52.0	23	92.0	25	100.0	
6 months after treatment	OP	25	100.0	20	80.0	0	0.0	0.025 * [b]
	No OP	0	0.0	5	20.0	25	100.0	
T score in the right femoral neck								
Baseline before treatment	OP	0	0.0	0	0.0	0	0.0	NA
	No OP	25	100.0	25	100.0	25	100.0	
3 months after treatment	OP	13	52.0	2	8.0	0	0.0	<0.001 ** [c]
	No OP	12	48.0	23	92.0	25	100.0	
6 months after treatment	OP	24	96.0	18	72.0	0	0.0	<0.001 ** [d]
	No OP	1	4.0	7	28.0	25	100.0	

One way ANOVA**, *** Significant (p<0.05), **** Highly significant (p≤0.001) OP: osteoporosis, NA: not applicable. [a] Control vs CBZ; CBZ vs VPA.
[b] Control vs VPA; Control vs CBZ. [c] Control vs CBZ; CBZ vs VPA
[d] Control vs VPA; Control vs CBZ

Furthermore, there were no statistical changes in the biochemical parameters Vitamin D, Ca, P, and ALP between the three groups (CBZ, VPA, and control) before receiving any treatment, except for the measurement of phosphorus, which is significantly higher but still in the normal range in the controlled group (P= 0.046). When comparing the level of biochemical parameters between the studied groups after 3 months of treatment, we observed that the level of Vitamin D3, Ca and P was significantly lower in the CBZ treated group than in the VPA and controlled groups, while the level of ALP was higher in the CBZ treated group compared to the VPA and controlled groups.

After 6 months of therapy, both treated groups (CBZ and VPA) compared to the controlled group had a significantly low level of Vitamin D3, Ca, and P, while the ALP level was higher in the group treated with CBZ than in the other 2 groups **(Table 3).**

Table 3. Blood levels of vitamin D3, Ca, P, ALP according to study groups before, after 3 and 6 months of treatment.

	Carbamazepine group(n=25)		Valproate group(n=25)		Control group(n=25)		P Value
	Mean	SE	Mean	SE	Mean	SE	
Before treatment							
Vitamin D3 (ng/ml)	36.04	1.73	33.76	2.23	33.36	2.22	0.675
Ca (mg/dl)	9.46	0.22	9.79	0.25	9.42	0.25	0.496
P (mg/dl)	3.33	0.16	3.24	0.14	3.78	0.16	0.046 *
ALP (U/L)	84.96	2.95	82.56	3.04	80.40	3.29	0.751
3 months after treatment							
Vitamin D3 (ng/ml)	21.68	1.18	31.04	1.73	34.16	2.17	<0.001 **
Ca (mg/dl)	8.11	0.21	9.25	0.18	9.85	0.25	<0.001 **
P (mg/dl)	2.63	0.11	3.16	0.14	3.25	0.14	<0.001 **
ALP (U/L)	216.80	11.65	81.68	3.32	83.60	2.73	<0.001 **
6 months after treatment							
Vitamin D3 (ng/ml)	20.88	1.15	20.76	1.20	36.12	1.93	<0.001 **
Ca (mg/dl)	7.98	0.17	7.83	0.10	9.36	0.25	<0.001 **
P (mg/dl)	2.22	0.07	2.44	0.11	3.47	0.15	<0.001 **
ALP (U/L)	283.68	16.59	85.40 †	2.81	82.08	3.79	<0.001 **

One way ANOVA, * Significant ($p<0.05$), ** Highly significant ($p\leq0.001$), † ALP in the VPA group before vs after 3 and 6 months of treatment, was not significant ($p = 0.624$).

There were no statistically significant changes in the level of biochemical parameters and the T score on the L3-L4 spine and the right femoral neck between males and females before receiving CBZ and VPA treatment, except that the ALP level was significantly higher in females than in males before VPA treatment, and there were no statistically significant changes in the level of laboratory bone health markers and the T score between both sexes after 6 months of treatment with CBZ and VPA (**Table 4).**

Table 1. Blood levels of vitamin D3, Ca, P, ALP and T scores according to sex in both treated groups before and after 6 months of therapy

Variables			Vitamin D3 (ng/ml)	Ca (mg/dl)	P (mg/dl)	ALP (U/L)	L3-L5 T score	T- score on right femoral neck
CBZ group (n=25)	Before treatment	Male	44.00 ± 0.72	8.98 ± 239	3.10 ± 0.112	88.60 ±2.84	1.44 ±0.116	0.368± 0.227
		Female	34.050 ± 1.686	9.585 ± 220	3.385± 0.169	84.05± 3.024	0.585 ±0.223	0.753± 0.210
	After 6 months of treatment	Male	21.60 ± 0.996	7.560 ± 0.081	2.180± 0.046	261.800± 19.68	-4.766± 0.212	-5.170 ± 0.188
		Female	20.700 ± 1.204	8.090 ± 0.185	2.225± 0.388	289.150± 16.123	-4.663± 0.173	-4.472 ± 0.245
VPA group (n=25	Before treatment	Male	40.000± 0.485	9.771 ± 0.049	3.129± 0.023	70.429± 0.659	0.476± 0.047	0.433± 0.047
		Female	31.333± 2.0113	9.794 ± 0.253	3.283± 0.155	87.278± 2.415 *†	0.897± 0.217	0.897± 0.217
	After 6 months of treatment	Male	23.286± 0.877	7.857 ±0.0662	2.343± 0.079	86.286± 2.870	-4.216 ±0.271	-3.953± 0.354
		Female	19.778± 1.272	7.817± 0.114	2.478± 0.119	85.056± 2.87	-3.102± 0.277	-3.165± 0.42

T-test, *****Significant, † ALP before treatment female vs male p=0.01, All other comparisons between mean level of biomarkers and the T score in both treated groups before and after 6 months of therapy were not significant. All values are presented as mean ± Standard Error of Mean

Discussion

Long-term anticonvulsant therapy is known to have a vast impact on calcium metabolism and bone mineral thickness. The disorders that may arise due to the use of these drugs are defined as osteopenia/osteoporosis, osteomalacia and bone fractures; meanwhile, the frequency of osteomalacia in patients receiving long-term anticonvulsant drugs has been reported as 10-30% [16-19]. Examination of biochemical parameters demonstrating changes in bone metabolism will aid in clarifying the anticonvulsant drug components of activity in bone and calcium metabolism [20].

Despite numerous hypotheses that have been proposed to explain the cause of bone diseases due to the use of anticonvulsant drugs, the precise mechanism is not known [17], the current study shows the effects of long term anticonvulsant therapy with different mechanism of action "hepatic enzyme inducer like carbamazepine and inhibitor like Valproate" on bone metabolism and increase the risk of fractures.

As there were no statistically significant changes in age, sex, bone biomarkers, and density before starting therapy between treated groups and the control, Apart from the statistically significant difference in the level of phosphorus between the controlled group and the other two groups of epileptic patients before receiving ASM, as this can be explained by several studies reported that phosphate is depleted in those who had a seizure, and some hypothesize that it is a nonspecific marker of seizures [21]. It is well known that low levels of phosphorus can also affect the energy demand needed by the brain, causing various neurological symptoms, such as numbness, weakness, seizures, and coma, in patients with low levels of phosphorus (1.0 mg/dL or less) [22], and this was also supported by the study done by (Barras et al., 2019) [23] that found most of their convulsion patients had hypophosphatemia.

The current study shows that the level of Vitamin D3, Ca and P after 3 months of treatment was significantly lower in the CBZ treated group than in the VPA and control groups, while the ALP level was higher in the CBZ treated group compared to the VPA and control groups. Furthermore, patients with CBZ therapy show a statistically low level of percentage of L3, L5 and right femoral neck T score compared to the other groups. Meanwhile, there was no statistical significance in the parameters studied between VPA and the controlled groups as shown, and these results were comparable to the study of (Zhang et al., 2020) [24] that studied the effect of CBZ on bone biomarkers, and this supports the fact that active vitamin D, also known as 1,25-dihydroxy vitamin D, improves calcium absorption in the intestine [25], the catabolism of active vitamin D to inactive vitamin D metabolites resulting from the induction of cytochrome p450 by the enzyme inducer ASM, in turn, will decrease calcium absorption, causes hypocalcemia, and increases the

level of parathyroid hormone (PTH). In response to lower serum calcium levels, PTH increases renal calcium reabsorption, stimulates 1-hydroxylase in the kidneys, and mobilizes skeletal calcium [26]. In addition, persistently high levels of PTH increase bone turnover, promoting bone resorption over bone production [27].

On the other hand, VPA is a liver enzyme inhibitor that is the most widely used ASM, but its impact on bone metabolism remains controversial. It is believed to stimulate osteoclast activity and cause an imbalance between bone formation and resorption leading to bone loss [28].

However, our study found that there was a statistically significant decrease in bone biomarkers (vitamin D3, Ca, and P) after 6 months of therapy for both treated groups, while the level of ALP was significantly high in the CBZ but not the VPA treated group, also both treated groups show a statistically significant low percentage of L3, L5 and right femoral neck T score than the controlled group, but these changes are more significant with the CBZ group compared to the VPA group, this finding is inconsistent with the study of (Triantafyllou et al., 2010) [29] that proposed prolonged VPA therapy for 10 years would not have any significant effect on bone health. Meanwhile, it is comparable to the study that done by (Ecevit et al., 2004) [17] that proved valproate monotherapy significantly reduces serum calcium level and femoral neck area bone mineral density in children which is also similar to study of (Guo et al., 2020) [30] that done in adult patients. This inconsistency between studies can probably be explained by the study of (Griepp et al., 2021) [31] which proposes that serum markers of bone turnover are not clinically reliable for assessing changes in bone mineral density in patients taking ASM.

Regarding gender, our research clarifies that there were no statistically significant changes in the level of biochemical parameters and the T score between male and female before receiving CBZ and VPA treatment, as well as after 6 months of therapy as compared to controlled groups, which agrees with the result of the study that done by (Pack et al., 2003) [32], except that the level of ALP was significantly higher in female than male before VPA treatment, and this may be due to variations in total serum alkaline phosphatase activity with age and sex, as mentioned in the study of (Broecker-Preuss et al., 2023) [33].

Limitations of study

The limitation in the current study is that the numbers of our patients were not enough high due to COVID pandemics and quarantine, many of our registered patients were drawn and excluded because they had taken vitamin D supplements out of their doctor's prescription and were thinking that it would increase their immune defense mechanism against infection, so we were unable to enroll more cases and compare patients who used other types of ASM as an example for enzyme inducer and non-inducers. In future studies, we can identify more underlying causes of bone health problems in epileptic patients by increasing the number of patients, using more ASMs with different mechanisms of action, and selecting more specific markers of bone turnover.

Conclusion

Valproate "hepatic enzyme inhibitor ASM" will not affect bone biomarkers earlier, but later with a longer duration of therapy, they may have the same effect as carbamazepine "hepatic enzyme inducer ASM" on bone health that requires the prescription of supportive vitamin D and Ca along with ASMs.

List of abbreviations

ASM = Antiseizure medication
VPA = Valproate
CBZ = Carbamazepine
Ca = Calcium
P = Phosphorus
ALP = Alkaline phosphatase
L3 – L4 = third lumbar spine - fourth lumbar spine
T score = The T score compares the bone density of patients with the average bone density of healthy young adults of the same patients' sex and is expressed in standard deviations above and below the average.
BMD = Bone Mineral Density
ANOVA = Analysis of variance
EIASM= Enzyme inducer antiseizure medication
NEIASM= Non Enzyme inducer antiseizure medication

Conflict of interest

There is no conflict of interest.

Ethical clearance

The study was approved by the College of Medicine/University of Kirkuk's research ethics committee (document no. 19, date:15/11/2022).

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Study Contribution

Mufeed Akram Taha, the neurologist was responsible for the selection, examination, treatment, and follow-up of the patients. Neven Nihal Hana Istifo, the pharmacist was responsible in follow up the patient's compliance on treatment, collecting of cases, data analysis and writing draft.

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