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Effect of Long-term Carbamazepine Therapy on Bone Health

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ABSTRACT

Introduction: Recent research reported that prolonged use of AET is associated with changes in bone metabolism, with consequent reduction in bone mineral density (BMD) and increased risk of fractures. **Objectives:** Therefore, the aim of our study was to investigate the effects of carbamazepine on serum levels of 25 -hydroxyvitamin D and on biomarker of bone formation and resorption (serum levels of osteocalcin). **Material and methods**: We measured serum levels of 25-OHD and osteocalcin (OCLN) in normal controls (n=30) and in epilepsy patients taking carbamazepine (CBZ) (n=50) in monotherapy for a period of at least twelve months. For each participant, mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry method. **Results:** The average value of vitamin D in serum was significantly lower in CBZ group than in control group (Vit D 17.03±12.86 vs. 32.03±6.99, p=0.0001). The average value of osteocalcin in serum was significantly higher in CBZ group than in control group (26.06±10.78 vs. 19.64±6, 54, p=0.004).BMD value in CBZ group was significantly lower than in control group (T. score CBZ: 0.08±1.38 vs. T. score control: 0.73± 1.13, p=0.031; Z score CBZ:-0.05±1.17 vs. Z. score control: 0.55±0.79, p=0.015). **Conclusion**: AEDs are associated with bone disease, as evidenced by biochemical abnormalities and decreased BMD. Patients on long-term antiepileptic therapy, especially with enzyme-inducing agents, could benefit of routine measurement of biochemical markers of bone turnover, and BMD measurement as part of osteoporosis investigation.

Keywords: antiepileptics, carbamazepine, osteoporosis.

1. INTRODUCTION

In the past years, minor attention was paid to metabolic changes associated with long-term use of antiepileptic therapy (AET). Recent studies reported that prolonged use of AET is associated with changes in bone metabolism, with consequent reduction in bone mineral density (BMD) and increased risk of fractures. This is a particularly unfavorable circumstance because epilepsy itself increases bone loss and the risk of fractures by a variety of mechanisms such as reduction of physical activity imposed by seizures, coexisting neurological deficits, and seizure-related falls (1).

People with epilepsy have a 2-6 times higher risk of fracture than the general population, and especially the increased incidence of spinal cord fractures and neck of the thorax (2). The risk of fracture depends not only on bone mass, but also on risk factors that increase the risk of fracture regardless of bone density. The seizure type may also influence the fracture propensity. Fractures have been more reported in patients experiencing generalized tonic clonic attacks than in other patients groups (3).

In recent years, there is more and more evidence suggesting that epilepsy and its treatment may have negative effects on bone mineralization and calcium metabolism. While long term use of glucocorticoids, aromatase inhibitors and anti-androgens are often associated with osteoporosis, the influence of antiepileptic use is less well known.

It has been suggested that CYP450 inducing antiepileptic drugs alter the activity of the enzymes responsible for vitamin D metabolism, resulting in a lower level of 1.25 (OH) 2 vitamin D leading to reduced calcium absorption, with consequent secondary hyperparathyroidism, increased bone resorption and accelerated bone mass loss (4-6).

Other mechanisms rather than modification of vitamin D metabolism also have been suggested, and there is a still ongoing debate whether the osteopoenic effect of CYP450 inducing antiepileptic drugs may be a result of something else rather than decrease in 25-OHD.

2. OBJECTIVES

Therefore, the aim of our study was to investigate the effects of carbamazepine (CBZ) on serum levels of 25 -hydroxyvitamin D and on biomarker of bone formation and resorption (serum levels of osteocalcin).

Material and Methods

A cross-sectional study in patients under treatment with CBZ monotherapy was carried out between the years 2016 to 2017, in Epilepsy Center at Neurology Clinic in Sarajevo. Only patients with CBZ monotherapy for a period of at least twelve months were entered in this study (n=50). Patients who had any condition known to affect bone metabolism (e.g., renal disease, recent fracture, hyperparathyroidism, Paget disease, osteoporosis) or taking any drug known to cause or treat osteoporosis, were excluded. The results were compared with age-matched healthy controls, with no evidence of metabolic bone disease (n=30).

The study was conducted according to the standards of the Declaration of Helsinki (1975, revised 2000), and the protocol was approved by the local Bioethical Committee (decision reference numbers 0207-28784).

All participants were asked to complete a questionnaire including medical history, fractures, falls and injuries, and vitamin D or calcium supplements. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry method called DXA technology. DXA was performed using a Hologic QDR-4000A densitometer (Hologic, Bedford, MA, U.S.A.). DXA measured bone mineral content (BMC in grams) and bone area (BA, in square centimeters), then calculated "area" BMD in g/cm2 by divided BMC by BA. T-score, the value used for diagnosis osteoporosis, is the mean BMD of a young-adult reference population from the patients' BMD divide by the standard deviation (SD) of young-adult population. Z-score, used to compare the patients' BMD to a population of peers, calculates by subtracting the mean BMD of an age, ethnicity and sex-matched reference population from the patients' BMD and divide by the SD of the reference population.

For each subject the level of vitamin D and osteocalcin in serum was determined in laboratory findings. Serum 1, 25-dihydroxyvitamin D (3) (normal range, 20–74 pg/ml) was measured by radioimmunoassay. Serum osteocalcin level was determined by Elisa. Because of laboratory errors, not every test was obtained for every patient. The precisen for each test in each patient group is noted in tables.

Statistical analysis

Statistical analyses were done using the SPSS for windows, version 16 (SPSS Inc., Chicago, IL). Continuous data were presented as mean ± standard deviation (SD). Student's t-test or the Mann–Whitney U-test was used for continuous variables at baseline comparisons between the cases and controls. All continuous variables of interest (e.g., bone mineral parameters) were tested for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests prior to data analysis. A p value of ≤0.05 was considered as significant.

3. RESULTS

The study involved 50 subjects, 20 males and 30 females with mean age 36.74±10.25 years. Average duration of epilepsy was 11.32±6.86 years. Average duration of carbamazepine therapy was 6.16±3.33 years. The average value of vitamin D in serum was significantly lower in CBZ group than in control group (Vit D 17.03±12.86 vs. 32.03 ±6.99, p=0. 0001) (Table 1).

Vitamin D (ng/ml)						
	N	$\bar{x}$	SD	SEM	Minimum	Maximum
Control	30	32.03	6.99	1.28	21.30	50.30
Carbamazepine	49	17.03	12.86	1.84	3.00	72.90
Total	79	22.73	13.17	1.48	3.00	72.90

Table 1. The average value of 25-hydroxyvitamin vitamin D in serum in patients and control group. F=14.440; p=0.0001

The average value of osteocalcin in serum was significantly higher in CBZ group than in control group (26.06±10.78vs. 19.64±6.54, p=0.004) (Table 2).

Osteocalcin (ng/ml)						
	N	$\bar{x}$	SD	SEM	Minimum	Maximum
Control	30	19.64	6.54	1.19	11.10	36.40
Carbamazepine	50	26.06	10.78	1.52	11.90	77.10
Total	80	23.65	9.88	1.10	11.10	77.10

Table 2. The average value of osteocalcin in patients and control group. F=8.671; p=0.004

Reduced bone density was observed among 44.8% of patients compared to 16.6% subjects in our control group. BMD value in CBZ group was significantly lower than in control group (T. score CBZ: 0.08± 1.38 vs. T. score control: 0.73± 1.13, p= 0.031; Z score CBZ: -0.05±1.17 vs. Z. score control: 0.55 ±0.79, p = 0.015) (Table 3 and 4).

T. scores						
	N	$\bar{x}$	SD	SEM	Minimum	Maximum
Control	30	0.73	1.13	0.21	-2.70	2.10
Carbamazepine	49	0.08	1.38	0.20	-3.40	3.90
Total	79	0.33	1.32	0.15	-3.40	3.90

Table 3. T. scores in patients and control group. F=4.853; p=0.031

Z. scores						
	N	$\bar{x}$	SD	SEM	Minimum	Maximum
Control	30	0.55	0.79	0.14	-1.00	1.80
Carbamazepine	49	-0.05	1.17	0.17	-3.10	1.50
Total	79	0.18	1.08	0.12	-3.10	1.80

Table 4. Z. scores in patients and control group. F=6.750; p=0.015

4. DISCUSSION

Although second and third generation AEDs are increasingly being used to treat seizures, carbamazepine as first generation drug has been still widely prescribed to the patients with epilepsy (7). The special effects of AEDs on bone metabolism and the endocrine system are

not completely recognized (8-11). Most of the patients with epilepsy require a long-term therapy and, therefore, they are exposed to the potential negative metabolic side effects of medical treatment (12).

CYP450 inducing antiepileptic drugs cause rapid bone metabolism, indicating an increased concentration of biochemical markers of bone resorption and degradation in both serum and urine. These molecular indicators of bone metabolism demonstrate the dynamics of metabolic imbalance caused by antiepileptics, ultimately leading to an accelerated loss of bone mass.

Several theories have been suggested about the mechanism of antiepileptic drugs for inducing bone diseases but none of the suggested theories alone can explain all findings. In general, it is believed that antiepileptic drugs, such as carbamazepine, that induce P450 cytochrome hepatic enzyme, increase conversion of vitamin D to inactive metabolites and subsequent increase in parathyroid hormone (PTH), ultimately leading to increased bone turnover (13-16). However, this mechanism has not been considered in studies that have shown accelerated bone turnover or bone loss irrespective of vitamin D deficiency (17-19). Direct effects of the drugs on bone cells, intestinal calcium transport and resistance to parathyroid hormone has been proposed as alternative-mechanism rather than single decreased serum 25-OH vitamin D (20, 21).

The present study investigated the effects of carbamazepine on bone metabolism at two levels of lumbar and femoral BMD (bone mineral density) as well as bone biochemical markers among epileptic patients.

The results of this study indicate that patients taking CBZ in monotherapy have significant reductions in 25-OHD levels and significant increases in the bone-formation marker OCLN.

Our results are consistent with the results of several studies (22-30), but not with others (31, 32). In contrast, a marked increase in bone turnover markers has been documented in children and adolescents after initiation of carbamazepine therapy for epilepsy (33, 34). High serum levels of osteocalcin with AED treatment have been described (12, 13, 31). Two studies found significant increases in bone turnover after CBZ treatment regardless to any change in 25-OHD levels (13, 17).

In some novel studies, genetic variations were associated with reduction of bone mineral density and active vitamin D metabolism in patients receiving antiepileptic drugs (35, 36). The average value of vitamin D in our control group was 32.03 ±6.99 which may implicate the problem of generally lower level of vitamin D in our population, and may be the subject for further research. Nevertheless, further studies are warranted with larger samples from each group to validate our findings.

The relationship between the type of antiepileptic drug (AEL) and the risk of fractures remains unclear. Many studies recommend that patients with epilepsy under treatment with AEDs have an increased risk of fracture, low BMD, and variations in bone metabolism (26, 27, 37, 38). Fracture risks in patients with CBZ have been reported by many authors as 1.88% (95% CI; 1.33–2.65), 1.31% (95%CI; 1.14–1.51) (22).

In this study, density of patients' bones was assessed dual-energy X-ray absorptiometry method called DXA technology. Bone mineral density (BMD) is a differentiation that could be made between osteopenia versus osteoporosis (T score; –1 to –2.5 vs.< –2.5 SD) respectively. Reduced bone density was observed among 44.8% of patients compared to 16.6% subjects in our control group, respectively.

A number of studies in adult patients have reported a significant decrease in the BMD at the ribs and spine,(39) neck of femur, and hip (18, 40) using DXA. Similar results have been reported in children and adolescents on AED treatment as compared with the control subjects (41). A very high prevalence (80%) of low BMD was found in a recent study carried out in a group of in patients with chronic epilepsy (42).

Lado et al. measured the BMD of 130 sequential patients who had received AEDs for more than 3 years. They reported a higher than expected prevalence of clinically significant low BMD; 39% of patients had osteopenia and 16% had osteoporosis. These results are consistent with findings of this study (43).

On the other hand, Pack et al. examined changes in bone density over a 1-year period in young women on AED immunotherapy. According to their results, only phenytoin was associated with significant femoral neck bone loss over 1 year, but the study included only small numbers of patients in each treatment group (44).

El Hajj Fuelihan (45) showed that hip and lumbar bone mineral density (T score) was significantly lower in the patients treated with carbamazepine compared to the group treated with the non-inducing cytochrome P450 enzyme agents.

Literature search exposes that the data on bone-specific effects of newer AEDs are limited with conflicting results.

5. CONCLUSION

AEDs are associated with bone disease, as evidenced by biochemical abnormalities and decreased BMD. Patients on long-term antiepileptic therapy, especially with enzyme-inducing agents, could benefit of routine measurement of biochemical markers of bone turnover, and BMD measurement as part of osteoporosis investigation.

- **Author's contribution** All authors were included in all steps of preparation this article. Enra Mehmedika Suljic contributed to the interpretation of the results, supervised the project and gave a final approval. All authors provided critical feedback and helped shape the manuscript.
- **Conflict of interest:** There is no conflict of interest of any of listed authors.

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