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Original Research Article

The Analysis of Association between Anticonvulsantsand Bone Mineral Density

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Abstract

Introduction: Anti-convulsant drugs are being used increasingly for various conditions including migraine, bipolar disorder, peripheral neuropathy, etc. Along with Conventional anti-convulsants, the newer anti-convulsants are also in use extensively. It is said that the tolerability of newer anticonvulsants is more, but there is rising concern with bone density with the use of anti-convulsants. Many studies have shown that the conventional ones are causing decreased bone mass density leading to fractures.

Aims and Objectives: To evaluate the significant effect on bone mass density due to usage of different anti-convulsants.

Materials and Methods: This restrospective study assessed the patients for Bone Mineral Density, who were on anti-convulsants for various conditions. According to the patients' exposure to anticonvulsants, they were classified into five groups. Among them, one of the groups (group 5) was not exposed to anti-convulsant and were considered as the reference group for comparing T-scores with the other groups.

Results: It has been observed that T-score is lower with conventional anticonvulsants while newer anticonvulsants (both group 1 and group 2) caused significant ($P < 0.01$) T-score compared to the unexposed or reference group, when femoral neck is considered. In all the anatomical sites including femoral neck, lumbar spine and hip, T-score in group 2 came to be significantly higher ($P<0.05$).

Conclusion: The study has concluded that newer anti-convulsants does not cause decrease of bone mass density and therefore, there is no risk of causing fractures with the usage of newer anti-convulsants.

Keywords: Anticonvulsants, Bone Mineral Density, Migraine, Gabapentine

Introduction

It has been long known that drugs used in treatment of epilepsy have been long associated with bone disease [1]. Studies that were initially done in thid field exhibitedflorid bone [2] disease which was confirmed after pathological biopsies [3]. But the limiting factor here was that these were performed on mainly on institutionalized patients that had many otherwise common factors like improper diet, restricted outdoor activity in sunlight, no/ limited exercise that would have likely influenced the results thus obtained [4]. Since then, many advances have occurred and relevations from studies done on ambulatory people state that they suffer

from radiographic [5,6] and biochemical abnormalities [7,8,9] along with reduced bone mineral density (BMD) [10, 11]. Much frequent bone mineral metabolism anomalies have also been reported from them [12,13]. The most common occurring feature of experiencing frequent fractures [14, 15] is a vital characteristic found in epileptic patients on AEDs [16, 17]. A latest and very sensitive DXA technique is now operating that can detect 5% (and even lesser)bone mass decrement [18]. Children suffering from this disease exhibit diminished whole-body bone mass (19) along with other specific losses like axial &, appendicularbone loss. The most frequent types of anomalies that characterize this particular situation are "hypocalcemia, hypophosphatemia, reduced serum levels of biologically active vitamin D metabolites, and hyperparathyroidism". Amount of bone turnover markers found, related of bone formation and bone resorption also can be detected beyond acceptable norms. Calcium is an important element related to bones whose homeostasis gets hampered AEDs [20]. The chances where hypocalcemia can deteriorate bone health vary from 3% - 30% [21,22, 23]. In these kinds of patients serum phosphate also declines [24, 25]. The important vitamin for bone health the vitamin D [26] which is expressed in terms of serum 25(OH)D concentration [27] thatexpresses the vitamin D status [28,29] of any being, is found to be reduced in adult patients as well on AEDs drugs [30, 31]. The parathyroid gland present in human bodyis secretes that holds high importance in calcium level monitoringa hormone that (PTH)is secreted by the parathyroid gland and is directly involved in calcium regulation; as serum calcium gets diminished secretion of parathyroid hormone gets triggered leading to bone breakdown/resorption & AED therapy is known to enhance the release of this hormone in the body [32]. There are certain kind of markers that indicate formation of bone in the body like osteocalcin; one among them is Alkaline phosphatase whose secretion is enhanced in patients of all ages [24,25], this substance despite of being a vital component lacks sensitivity and specificity (as it has many sources of origin). Osteocalcin, an indicator of declining bone health is known to elevate in patients on AED therapy [33]. There are certain medicines generally used in epilepsy that are also known for their impairment of bone metabolism and are also responsible for wearing bone density; they include phenytoin, Phenobarbital, carbamazepine etc. [34]. Earlier almost no deleterious effects of valproate (VPA) on bones [29] were recognized. But now a study on 40 patients [10] under long-term valproate reported enhanced bone resorption and formation markers and serum calcium and reduced serum 1,25[OH]2D concentration. DXA results from the same study [10] reported about 14% BMD reduction in group consuming VPA monotherapy (adult patients) when seen parallel to group comprising healthy controls. Experimental works on children with epilepsy exhibit that those on VPA therapy had lesser BMD [35,36]. A study on kids about impact of VPA (alone) or on combo of lamotrigine and VPA concluded on the patients suffering from low bone mass, and reduced bone formation & short stature were commonly caused [19]. Bones were at higher risk in cases of Polytherapy [37].

Materials and Methods

Study Design

This cohort study is of retrospective design which derived its data from ABC Hospital. The patients were assessed for Bone Mineral Density by employing Dual Energy X-Ray (DXA) between December, 2021 and May, 2022. It is a standard clinical practice that patients who are on anticonvulsants should be screened with DXA. The patients are grouped according to their exposure to number and types of groups

anticonvulsants. T-scores of BMD were assessed for determining the outcome of the BMD status of the patient. Applying inclusion and exclusion criteria, the study considered 125 patients in total.

According to the patients' exposure to anticonvulsants, they were classified into five groups. Group 1 patients are those who were on newer enzyme-inducing anticonvulsants (like topiramate), group 2 patients are those who took newer nonenzyme-inducing anticonvulsants like levetiracetam or gabapentin, group 3 patients are those who took conventional enzyme-inducing anticonvulsants like phenytoin, group 4 patients are those who were on conventional nonenzyme-inducing anticonvulsants like valproic acid and group 5 patients who did not take any anticonvulsants. Group 5 patients were considered as the reference group with whom, T - score of all other groups were compared.

Inclusion and Exclusion criteria

The patients who were included in this study are those who received treatment from our hospital, tested for BMD assessment and cooperated with our hospital protocol. The patients who were excluded from the study are those who did not complete the whole study protocol and patients with other chronic conditions.

Data Assessment and Management

The data regarding Bone Mineral Density reports were considered from the patients' records and T-scores of BMD were determined and recorded for femoral neck, total hip, lumbar spine, osteopenia or osteoporosis. The measurement of BMD was done by densitometer. DXA was performed by experienced radiologist. If the radiologist has taken more than one result of DXA, then, the most recent one was considered.

The study also considered determination of Body Mass Index (BMI) from patient's height and weight, history of drugs, its dosage and duration of the drug treatment. Thebaseline characteristics of the patients considered for this study were recorded including their prescribed anticonvulsant class. The patients were grouped according to their exposure to anticonvulsants. Even they were classified according to the number of classes of anticonvulsants prescribed. The outcome on the study populationwas determined by T-score.

Statistical Analysis

The study used SPSS 25 and excel software for statistical analysis and other analyses. The descriptive data are expressed as mean ± standard deviation. The study has employed χ^2 test for analyzing categorical variables while student *t*-test has been used for continuous variable. The level of significance was considered to be $\alpha = 0.05$.

Results

The study has recorded baseline characteristics of the whole study population. The study has classified them in each group and equal number of patients have been assigned to each group. The

Table 1: Basic characteristics of the study population in each group

Characteristic	Group 1	Group 2	Group 3	Group 4	Group 5
Number of patients (N)	25	25	25	25	25
Age[a]	55.25 ± 12.22	54.15 ± 11.89	51.25 ± 11.56	53.25 ± 11.52	54.12 ± 10.36
Male	15	16	18	13	15
Female	10	09	07	12	10
Body Mass	25.6 ±3.2	24.9 ± 3.8	26.1 ±2.9	26.5 ± 2.8	25.2 ± 3.3

Index (BMI)[a]					
Alcohol users[b]	15, 60%	16, 64%	13, 52%	14, 56%	15, 60%
Previous history of fracture[b]	3, 12%	2, 8%	2, 8%	3, 12%	2, 8%
Corticosteroidusers[b]	4, 16%	3, 12%	1, 4%	3, 12%	2, 8%
Vitamin D users[b]	3, 12%	2, 8%	2, 8%	1, 4%	2, 8%

[a]Expressed as mean value ± standard deviation

[b]Expressed as number of patients followed by the percentage of patients in that group

The study has found that the use or exposure to anticonvulsant agents to the patients, does not necessarily lower Bone Mass Density. It has been observed that T-score is lower with conventional anticonvulsants while newer anticonvulsants (both group 1 and group 2) caused significant ($P < 0.01$) T-score compared to the unexposed or reference group, when femoral neck is considered. Therefore, the bone density increased with newer anticonvulsant as compared to the conventioanl ones. But in case of lumbar spine or total hip bone, there is hardly any significant changes in T-scores with respect to the reference group. Again, group 2 patients who were given newer non-enzyme anticonvulsant agents showed significantly higher T-score with respect to the patients of reference group. In all the anatomical sites including femoral neck, lumbar spine and hip, T-score in group 2 came to be significantly higher ($P<0.05$).

Table 2: The mean difference in T - scores between each group and group 5 (reference group)

		Femoral Neck	Lumbar spine	Total Hip
Group 1	Mean T-score	0.13	0.11	0.07
	P-value[a]	< 0.01	0.08	0.06
Group 2	Mean T-score	0.07	0.09	0.05
	P-value[a]	< 0.01	<0.01	0.04
Group 3	Mean T-score	- 0.03	0.05	- 0.03
	P-value[a]	0.48	0.268	0.025
Group 4	Mean T-score	0.06	-0.06	0.02
	P-value[a]	0.059	0.395	0.041

[a]P-value is computed between respective group with that of group 5 (reference group)

Discussion

There exist many possible theories that establish a relation between AEDs and bone disease. We shall be discussing over here a few of the possible ones of them. There is hepatic induction of the cytochrome P450 enzyme system that aggravates catabolism of vitamin D which is one of the dominant reasons reported [38]. But it was a contradiction to other similar studies that were based those medicines (viz. VPA) that hamper functioning of cytochrome P450 enzyme system. All studies are not unanimous on the concept of insufficiency of vitamin D also as there are studies that exhibit bone turnover which is not dependent on vit. D [32,34]. Few more to list possibilities comprise of- improper parathyroidism functioning, decreased concentration of calcitonin [38] etc. Those drugs that cause secretion of hepatic cytochrome P450 enzymes might unnecessarily change useable form of vit. D to inactive metabolites (liver microsomes are

responsible for this action); this process is known to limit availability of vitamin D [39]. This triggers the instestional mucosa to reduce calcium absorption that results into hypocalcemia which stimulates the parathyroid to release more parathyroid hormone, which in turn aggravates bone turnover by mobilizing bonecalcium stores [40, 41].

Bone loss management in women- Women of elderly age group not on ant-epileptic drugs (but irregular calcium intake) can improve bone health by increasing calcium uptake (supplements, sunlight and otherwise) [42]. In post-menopausal women hormone replacement is capable of reducing bone loss [42]. But its side effects are much more damaging and include mainly –malignancy of breast region, cardiac ailments etc. [43]. Also, in epileptic females this therapy accelerates seizure activity [44].

Hip joint and epilepsy drugs- When two different groups of patients receiving EIAED & non-EIAED were compared no significant findings were obtained in values of bone mineral density in 'the Ward triangle, trochanter, or total hip'. It was thus concluded that one ROI might report bone resorption and other might exhibit normal bone mineraldensity. It was also suggested that accumulation and discussion of vast data available 'on the femoral neck, greater trochanter, and Ward triangle into total-hip BMD' could result into misinterpretation of results concerning changes in BMD in these regions. An agreement on this was gained out of study by Selby *et al.* who declared there might be errors while resolving information derived from the hip subregions (59%) while deciding bone mineral density hence it cannot be implied to extract any clinically meaningful outcome [45]. Also, as various type of scanners are utilized in hip subregion significant difference might happen while working on total-hip calibration formulas; hence application of subregion calibration formulas is suggested only while calibratingabsolute changes [46].

Although well accepted and established that treating the disease with more than one type of drug enhances chances of fracture in post-reproductive females [51] but study by [49] fount contradicting results and did not notice any such finding in their study. The probable reason might be either the type of population chosen for the study, or the choice of drugs taken into consideration. Moving forwand with gender specific studies we wish to state here the study by

Andress *et al*., who reported age and duration of treatment as critical risk factors for low BMD in men receiving AEDs [47], but this was refuted by the study by [49] which concluded that both these factors are not responsible for laying any influence on bone health of males. This discrepancy could be because the study [49] comprised of patients of both genders and most of them were on combination therapy. A study comprised on usage of latest drugs like gabapentin, lamotrigine, and topiramate reported that in patients receiving these drugs incidences of osteoporosis are much lesser 'at the lumbar spine, femoral neck, and total hip' [48]. It has been observed that patients receiving carbamazepine monotherapy (33 patients) suffered bone loss at lumbar and femoral neck, on the contrary another group that was provided with valproate (22 patients) or some kind of polytherapy exhibited bone mineral density that matched very near to that of the control group [49].

Chou *et al*. in their pediariatic study revealed that those children that were getting carbamazepine monotherapy reported lesser bone density, than those on having valproate monotherapy [50]. Smoking might be or might not be relatable with bone loss [52].

Conclusion

The study has concluded that the usage of newer anticonvulsant agents for longer

time is associated with lower BMD. The study has inferred that the T-score of newer nonenzyme - inducing anticonvulsants like levetiracetam or gabapentin, are significantly higher than individuals who have no exposure to anticonvulsants. Thus, newer nonenzyme - inducing anticonvulsants should be prescribed for shorter duration for avoiding increase of T-score. The author also suggests conducting more studies evaluating relationship between anti-convulsants and T-score, on larger and more varied population. However, this current study has efficiently brought forward the significant relationship between anti-convulsant exposure and BMD, which can further add to the clinical guidance regarding the treatment involving anti-convulsants to the individuals with abnormalities in bone mass density. However, the study has concluded that newer anti-convulsants does not cause decrease of bone mass density.

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