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Comparison of indices of bone health among Indian adults with drug-resistant versus well-controlled epilepsy: A cross-sectional analytical pilot study

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ABSTRACT

Objectives: An association of antiseizure drugs and the frequency of seizures with abnormalities in bone metabolism resulting in low bone mineral density (BMD) and fractures have been hypothesised. The objective of the study was to compare the indices of bone health between people with drug-resistant and well-controlled epilepsy.

Materials and Methods: Forty people each were recruited into two groups for the cross-sectional study. Adults with well-controlled epilepsy formed Group I, whereas adults with refractory epilepsy were included in Group II. Gender- and age-matched people of 18–40 years who had been on antiseizure medications for more than 5 years were included. Smokers, known hypertensive and diabetic patients, people with alcohol use disorder, people with infections or head injuries and lactating women were excluded. Biochemical parameters, fasting glucose, 25OH Vitamin D, C-telopeptide of type 1 collagen, procollagen type 1 N-terminal propeptide, malondialdehyde, total antioxidant status, Ca, P and alkaline phosphatase were estimated. A Hologic dual-energy X-ray absorptiometry scan estimated the total hip, neck of femur and L1 to L4 lumbar spine BMD with trabecular bone scores.

Results: The bone health biochemical indices and BMD, as well as the proportion of people with low bone mass and degraded bone at the lumbar spine, were not different between the two groups of people with epilepsy.

Conclusion: Bone health appears to be unaffected and was comparable in both well-controlled and drug-resistant people with epilepsy.

Keywords: Bone mineral density, Bone turnover markers, Drug-resistant epilepsy, Vitamin D, Well-controlled epilepsy

INTRODUCTION

Epilepsy is one of the most disturbing lifelong neurologic disorders.[1] Among one-third of persons with epilepsy (PWE), seizures are not fully controlled. The probability of success with another drug is unlikely after the failure of two suitably selected antiseizure medications (ASMs).[2] As per the definition of an ad-hoc Task Force of the international league against epilepsy, drug resistance is 'failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom'. It is assumed as a working hypothesis that is testable and needs to be modified over time.[3] The well-controlled PWE are those who have been seizure-free for the past year after receiving a current ASM monotherapy regimen and or have been seizure-free for the past 2 or more years after receiving two or more ASM regimens.[4] An association of antiseizure drugs and the frequency of seizures with abnormalities in bone metabolism, low BMD and fractures have been observed. Therefore, the deterioration of bone health in epilepsy can be due to both seizure activity and antiepileptic drugs. Oxidative stress and inflammation are expected to be more in drug-resistant epilepsy, which can affect their bone health more than in people with well-controlled epilepsy. Other than the oxidative stress index (OSI), no other information is available in the literature that compares indices of bone health between the epilepsy groups. The present study hypothesised that people with drug-resistant epilepsy have higher derangements of bone health in comparison to people with well-controlled epilepsy and are at increased risk for the development of bone fractures. The results from the study may help neurologists to introduce necessary measures in their treatment protocols which may address the health of bone among PWE. The present study aimed to compare the serum levels of procollagen type 1 N-terminal propeptide (P1NP), 25 OH Vitamin D, C-telopeptide of type 1 collagen (CTX), Ca, P, alkaline phosphatase and OSI as well as BMD between adults with drug-resistant and well-controlled epilepsy.

MATERIALS AND METHODS

Inclusion criteria

We consecutively recruited PWE of both genders with 18–40 years of age on ASM for more than 5 years from the epilepsy clinic of a tertiary care hospital. We divided them into two age- and gender-matched groups.

Study groups

Group I: The PWE with well-controlled epilepsy, consisting of those who had been seizure-free for the past year after receiving a current ASM monotherapy regimen or those who had been seizure-free for the last 2 or more years after receiving two or more ASM regimens.[4] Group II: The PWE with drug-resistant epilepsy, consisting of those in whom there was a failure in achieving sustained seizure freedom during the past year despite undertaking adequate trials of two appropriately chosen and tolerated antiepileptic drug schedules either as monotherapies or polypharmacy.[3]

The people with epilepsy were recruited from the same population with a comparable socio-economic background, matching the factors which may affect Vitamin D metabolism and thereby bone health. The samples were collected from the participants by the consecutive sampling method.

Exclusion criteria

Persons who were already diagnosed to have hypertension and diabetes, people with infections or head injuries, alcohol use disorder, pregnant and lactating women as well as women who were planning to become pregnant, were excluded from both groups. People with a family history of endocrinal disorders that could affect bone health and bone diseases and on treatment with drugs that could affect bone metabolism (e.g., those on supplementation with Vitamin D and Ca) were also excluded from this study.

Ethical clearance

The study commenced after obtaining clearance from the Human Ethics Committee for observational studies of the institute (JIP/IEC-OS/2023/47 dated 17 April 23). Informed consent was taken from the participants. The study was conducted in the departments of biochemistry, neurology and endocrinology.

Blood sample collection

After an overnight fasting of 12 h, 5 mL of blood samples were collected from the people only when they were free from seizures for at least 1 week to estimate biochemical parameters.

Anthropometric parameters

Age, height, weight, body mass index, waist circumference and blood pressure were documented at the time of recruitment.

Preliminary data

Information on the duration of ASM, seizure frequency in people with refractory epilepsy and period of seizure freedom in well-controlled epilepsy were collected.

Biochemical indices of bone health

Commercial ELISA kits were used for the estimation of 25OH Vitamin D (Calbiotech, VD315B), procollagen type 1 N-terminal propeptide (PINP) (Elabscience, E-EL-H0185) and CTX (Elabscience, E-EL-H0835). The method of Yagi K was adopted for malondialdehyde (MDA) estimation.[5] Benzie and strain method was used to estimate the total antioxidant status (TAS).[6] The ratio of MDA/TAS was expressed as the OSI. We also estimated the Ca, P and alkaline phosphatase values.

Clinical indices of bone health

We assessed the BMD by a dual-energy X-ray absorptiometry (DXA) scan in the department of endocrinology. We measured the bone mineral density (BMD) of the total hip, neck of femur and lumbar spine (L1 to L4) with trabecular bone scores (TBS) by Hologic DXA. An experienced technician performed the BMD measurement in all PWE.

Sample size calculation

Since this was a pilot study, the approximate sample size was calculated based on the available information on TAS.[4] Assuming the reported mean difference in TAS of 0.2 units between the two groups, the sample size was 40, with a confidence interval of 95% and a power of 80%.

Statistical analysis

Normally distributed variables are represented as the mean with standard deviation. Median with interquartile range is used for parameters with a non-normal distribution. Mann–Whitney U-test or independent *t*-test was employed to compare the continuous data between the groups based on the normality of distribution. We used the Chi-square test/Fisher's exact test for comparing the proportions of unpaired data.

Theory/calculation

Bone health among people with drug-resistant epilepsy is inferior to people with well-controlled epilepsy on account of polytherapy as well as higher levels of oxidative stress and inflammation. This could be revealed by comparing the biochemical and clinical indices of bone health.

RESULTS

Among 40 PWE with well-controlled seizures, 32 were on monotherapy of sodium valproate or phenytoin (DPH). The remaining 8 PWE were on a combination of sodium valproate and carbamazepine (CBZ). PWE with drug-resistant seizures were on polytherapy with lacosamide, clonazepam, CBZ, levetiracetam, sodium valproate, idebenone, DPH sodium and clobazam in varying combination.

Comparison of general characteristics among the study groups

The general characteristics of the study groups are presented in Table 1.

Table 1: Comparison of general characteristics between people with well-controlled and drug-resistant epilepsy.

Parameters	Normal range	Well-controlled epilepsy (*n*=40)	Drug-resistant epilepsy (*n*=40)	*P*-value
Age (years)		29.0±7	30.0±6	0.458
Male/female (%)		22/18 (55/45)	22/18 (55/45)	
BMI (kg/m^2)	18.5–24.9	25.2±4.2	24.3±5.1	0.383
Fasting serum glucose (mg/dL)	70–100	100±11	100±11	0.933
Waist circumference (cm)	≤90 for males and≤80 for females	89±14	86±19	0.419
History of fractures		Nil	Nil	
Use of medications affecting bone density		Nil	Nil	
Nutrient intake:		Mixed diet	Mixed diet	
Socio-economic level		Middle/lower	Middle/lower	
Consumption of calcium and Vitamin D in the diet		Sufficient	Sufficient	
Level of physical activity		Moderate	Moderate	
Level of sun exposure		Moderate	Moderate	
Incidence of osteoporosis or fractures in family members		Nil	Nil	
Age at seizure onset (years)		17.5±6.5	17.0±7.5	
Seizure types		FIAS, BTCS, GTCS, TCS	FIAS, BTCS, GTCS and TCS	
Exposition to ASM		PHT, VPA, CBZ	PHT, VPA, CBZ, LCM, CZP, LEV, IDB and CLB	

A *P*-value less than 0.05 was considered statistically significant. BMI: Body mass index, FIAS: Focal impaired awareness seizure, GTCS: Generalised tonic clonic seizures, BTCS: Bilateral tonic clonic seizures, TCS: Tonic clonic seizures, PHT: Phenytoin, CBZ: Carbamazepine, VPA: Valproic acid, LCM: Lacosamide, CZP: Clonazepam, LEV: Levetiracetam, IDB: Idebenone, CLB: Clobazam, ASM: Antiseizure medications

Comparison of biochemical markers of bone health between people with well-controlled and drug-resistant epilepsy

The biochemical markers of bone health are compared between the groups in Table 2.[7]

Comparison of markers of bone density between people with well-controlled and drug-resistant epilepsy

The markers of bone density are compared between the groups in Table 3.

Comparison of the proportion of people with low bone mass and degraded bone between well-controlled and drug-resistant epilepsy

Comparison of the proportion of people with low bone mass and degraded bone at lumbar spine between well-controlled and drug-resistant epilepsy is presented in Table 4.

Comparison of markers of oxidative stress between people with well-controlled and drug-resistant epilepsy

The comparison of oxidative stress between the two groups of the study is presented in Table 5.

Well-controlled epilepsy group – Seizure freedom

The well-controlled epilepsy group was free from seizures on average for 1 year and 6 months.

Drug-resistant epilepsy group – Frequency of seizures

The person with drug-resistant epilepsy had seizures on an average of three to four episodes per month.

Duration of ASM

The average duration of ASM in well-controlled epilepsy and drug-resistant epilepsy groups was 6 years and 7.5 years, respectively ($P < 0.01$).

DISCUSSION

Fifty million people are affected by epilepsy globally, and among them, 30–40% are resistant to drugs.[9] The hypothesis of our study was that the bone health in people with drug-resistant epilepsy would be inferior to that of people whose epilepsy is well controlled. However, our study did not find differences in any of the parameters related to bone health between the two groups. The biochemical indices

Table 2: Comparison of biochemical markers of bone health between people with well-controlled and drug-resistant epilepsy.

Parameters	Normal range	Well-controlled epilepsy (*n*=40)	Drug-resistant epilepsy (*n*=40)	*P*-value
Calcium (mg/dL)	8.8–10.6	9.5±0.4	9.5±0.5	0.358
Phosphorus (mg/dL)	2.5–5	3.5 (3.3, 3.9)	3.6 (3.1, 4.0)	0.992
Vitamin D (ng/mL)	30–100	53.6±22.4	63.6±22.8	0.051
P1NP (ng/mL)	15–80[7]	2.3±0.9	2.3±0.9	0.965
CTX (ng/mL)	0.1–0.7[7]	0.1 (0.03,0.27)	0.1 (0.03, 0.33)	0.641
ALP (IU/L)	30–120	79.00 (65, 92)	82.00 (65, 104)	0.547

A *P*-value less than 0.05 was considered statistically significant. P1NP: Procollagen type 1 N-terminal propeptide, CTX: C-telopeptide of type 1 collagen, ALP: Alkaline phosphatase. Values are mean±standard deviation or median (interquartile range)

Table 3: Comparison of markers of bone density between people with well-controlled and drug-resistant epilepsy.

Parameters	Normal range	Well-controlled epilepsy (*n*=40)	Drug-resistant epilepsy (*n*=40)	*P*-value
DXA lumbar spine				
BMD (g/cm³)		1.01 (0.92, 1.06)	0.96 (0.91, 1.08)	0.470
Z-score	>−2	−0.35 (−1.30, 0.20)	−0.80 (−1.50, 0.275)	0.348
DXA neck of femur				
BMD (g/cm³)		0.83±0.10	0.81±0.14	0.463
Z-score	>−2	−0.38±0.79	−0.61±1.00	0.258
DXA hip-total				
BMD (g/cm³)		0.95 (0.89, 1.02)	0.92 (0.78, 0.99)	0.220
Z-score	>−2	−0.15±0.71	−0.47±0.93	0.084
TBS	≥1.310	1.398±0.061	1.398±0.068	0.955

A *P*-value less than 0.05 was considered statistically significant. TBS: Trabecular bone score, DXA: Dual-energy X-ray absorptiometry, BMD: Bone mineral density

Table 4: Comparison of the proportion of people with low bone mass and degraded bone between well-controlled and drug-resistant epilepsy.

Parameter	Well-controlled epilepsy (*n*=40)	Drug-resistant epilepsy (*n*=40)	*P*-value
Lumbar spine			
(Z-score) Normal bone mass: Low bone mass	34:6	35:5	0.75
Neck of femur			
(Z-score) Normal bone mass: Low bone mass	40:0	38:2	
Hip-total			
(Z-score) Normal bone mass: Low bone mass	40:0	40:0	
TBS			
Normal: Degraded	38:2	38:2	1

A *P*-value less than 0.05 was considered statistically significant. TBS: Trabecular bone score

Table 5: Comparison of markers of oxidative stress between people with well-controlled and drug-resistant epilepsy.

Parameters	Normal range	Well-controlled epilepsy (*n*=40)	Drug-resistant epilepsy (*n*=40)	*P*-value
MDA (μmol/L)	2.02–4.65[8]	6.91±1.56	6.86±2.37	0.904
TAS		1145±445	1258±378	0.224
OSI ($*10^{-3}$)		8.52 (6.51, 11.44)	8.69 (4.70,14.59)	0.908

MDA: Malondialdehyde, TAS: Total antioxidant status, OSI: Oxidative stress index. Values are mean±S.D or median (interquartile range)

of bone health, serum Ca, alkaline phosphatase, P and Vitamin D levels were comparable between the groups and the general population.

The BTMs (bone turnover markers), CTX and P1NP were comparable between the two groups. Preferential use of two BTMs, CTX and PINP have been recommended by International Osteoporosis Foundation and International Foundation for Clinical Chemistry.[10] The CTX is resorption-specific BTM, while PINP is a bone formation-specific marker. Among the two markers, the resorption specific CTX was not much different among the epilepsy people from the levels reported in the general population. The normal reference range for BTM is not well established, especially in the population of southern India. Furthermore, age- and gender-related variations have been reported in different populations. As per some of the reported reference ranges in other populations, the bone formation-specific P1NP among epilepsy people was lesser than the general population.[7,11] It may be concluded that bone formation is more affected than its resorption in epilepsy. For research purposes, BTMs have been used in the past to investigate the pathology of diseases and the effectiveness of medications. However, the utility of BTM in clinical practice is inferior and is not recommended for want of evidence in predicting bone loss and fracture risk.[12]

The BMD of the lumbar spine and femur, evaluated by DXA scan as Z-score, was also comparable between both groups. The Z-scores of both well-controlled and drug-resistant PWE were within the reported normal range of the general population. Based on the Z-scores of lumbar spine, neck of femur and hip-total, it was found that the proportion of people with low bone mass was comparable between drug-resistant versus well-controlled epilepsy groups. The proportion of people with degraded bone at lumbar spine were also comparable between two groups based on the TBS. Among the people with epilepsy, 12% were having low bone mass in the lumbar spine; 3% in neck of femur and none in hip-total. Further, 5% of the people were having degraded bone at lumbar spine. The BMD, evaluated by DXA scan as TBS, was comparable between the two groups and with the general population.

The indices of oxidative stress, MDA, TAS and OSI were also comparable between the two groups in the study. However, the levels of MDA were higher among both the groups in comparison to the general population, indicating higher oxidative stress among the people with epilepsy.[8]

The rate of fracture among people with epilepsy, when compared to the general population, is reported to be 2 to 6 times.[13] Oxidative stress and inflammation are reported to be higher in people with drug-resistant epilepsy,[4] which can affect their bone health more than in well-controlled people. The fracture risk was reported to be higher for phenobarbital, CBZ and DPH, which are hepatic enzyme-inducing ASMs (EI-ASMs) when compared to the non-inducing ASMs.[14] With the newly introduced ASMs and ethosuximide, no significant effect on bone has been reported.[14] Since people with drug-resistant epilepsy receive more vigorous polytherapy for the control of their seizures, it is expected that they are more vulnerable to bone fractures. Polytherapy and the increased frequency of seizures among people who are drug-resistant may lead to oxidative stress. This can increase the abnormalities of bone metabolism among them. Epilepsy per se and ASMs can influence free radical formation, leading to oxidative stress.[15,16] The continuous neuronal excitation related to seizure causes increased reactive oxygen species (ROS) production and can affect bone health. The ROS in bone micro-environment plays a role in osteoblast and osteoclast apoptosis.[17,18]

Among PWE treated with ASMs, several biochemical abnormalities that affect bone metabolism have been reported.[19,20] Increased parathormone (PTH) levels, low Vitamin D levels, hypocalcemia and hypophosphatemia have been reported among people with epilepsy.[21] The biochemical abnormalities are more common among people treated with ASMs, which induce the hepatic enzymes. They increase the turnover of Vitamin D, which leads to secondary hyperparathyroidism. Despite abundant sunlight, up to 70–90% of Indians have Vitamin D deficiency due to indoor lifestyle and clothing practices (reduced sun exposure), darker skin (reduces Vitamin D synthesis) and vegetarian diet (low in Vitamin D sources). Thus, epilepsy patients in India start at a disadvantage that their Vitamin D baseline is already low. The cellular response to PTH is also inhibited by ASMs, which results in increased bone remodelling.[22] The predicted bone loss in epilepsy is associated with several factors: Gender difference, polypharmacy and the duration of ASM treatment.[23] It has been reported that high-dose Vitamin D therapy in ambulatory adults on antiepileptic drugs significantly increased BMD.[24] Our study, which compared bone health of adults with well-controlled and drug-resistant epilepsy, did not find any differences between the two groups.

Multifactorial pathophysiological mechanisms are involved in bone alterations induced by ASMs.[25] These include age, types of ASMs, dose of ASM, duration of ASM therapy, female gender and sun exposure.

Although some clinical studies have shown that CYP450 EI-ASMs have a more significant impact on plasma Vitamin D levels and BMD with respect to non-EI-ASMs, there are no conclusive data.[25] Further, there are only few recommendations for administering prophylactic doses of Vitamin D and calcium in people treated with EI-ASMs and valproate.[26,27]

Limitations

The smaller sample size might have been a source of potential bias and imprecision. However, the chosen inclusion and exclusion criteria would have minimised the magnitude of the bias. Despite our efforts in matching the duration of treatment with ASM, the duration in the drug-resistant group was higher than in the well-controlled group. In general, the drug-resistant group had a higher duration of treatment in comparison to the well-controlled group. It is interesting to note that, despite the higher duration of treatment with ASM in the drug-resistant group, the indices of bone health were comparable with that of the well-controlled group. Several factors would have influenced the availability of Vitamin D in the two groups. However, since the blood levels of Vitamin D and Ca were comparable between the two groups, it is expected that the other factors mentioned will be also similar between the two groups.

CONCLUSION

In our study conducted in a cohort of PWE from southern India, bone health in the well-controlled and drug-resistant groups was comparable. The biochemical indices of bone health were not different from those of the general reference population except the BTM for bone formation. The BMD was not different from the general population. Ethnicity and age of people could be factors that may explain the observed bone health protection.

CLINICAL RELEVANCE AND FUTURE DIRECTIONS

The results of this study need not be generalised with other populations with epilepsy due to variability in the factors, including genetic factors, which might influence Vitamin D metabolism and bone health.

DATA STATEMENT

We, hereby, state the availability of data of the manuscript.

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Ethics approval: The study commenced after obtaining clearance from the Human Ethics Committee for observational studies of the institute (JIP/IEC-OS/2023/47 dated 17th April 2025). The study was conducted in the departments of biochemistry, neurology and endocrinology. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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