



BONE MINERAL DENSITY IN ADULTS RECEIVING LONG-TERM ANTISEIZURE MEDICATION: A HOSPITAL-BASED CROSS-SECTIONAL STUDY

Neurology

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ABSTRACT

Background: Patients with epilepsy may be vulnerable to impaired skeletal health because of seizure-related falls, reduced physical activity, nutritional factors and long-term antiseizure medication (ASM) exposure. Enzyme-inducing ASMs can accelerate vitamin D catabolism and adversely affect calcium and bone metabolism. **Objective:** To assess bone mineral density (BMD) in adults receiving long-term ASM therapy and to evaluate trabecular bone score (TBS), vertebral fracture assessment, and associations of serum calcium and vitamin D with BMD. **Methods:** This hospital-based observational cross-sectional study included 80 adults with epilepsy receiving continuous ASM therapy for at least 2 years. BMD was assessed by dual-energy X-ray absorptiometry at the lumbar spine, total hip and femoral neck. TBS was derived from lumbar spine DXA images. Serum calcium and 25-hydroxyvitamin D were recorded. BMD categories were defined using T-score criteria. **Results:** Of 80 participants, 47 (58.8%) were male and 33 (41.2%) female. Twenty-eight (35.0%) received monotherapy and 52 (65.0%) polytherapy. Fifty-four (67.5%) had exposure to at least one enzyme-inducing ASM. Overall, 60/80 (75.0%) had reduced BMD: 51 (63.7%) had osteopenia and 9 (11.0%) osteoporosis; 20 (25.3%) had normal BMD. Mean lumbar spine BMD was $1.067 \pm 0.168 \text{ g/cm}^2$ and mean TBS was 1.38 ± 0.09 . Serum calcium and vitamin D showed positive correlations with BMD at several sites, with the strongest correlations at the right total femur (calcium $r=0.454$, $p<0.001$; vitamin D $r=0.545$, $p<0.001$). **Conclusion:** Reduced BMD was common among adults receiving long-term ASM therapy, with osteopenia considerably more frequent than osteoporosis. Higher serum calcium and vitamin D were associated with higher BMD at several skeletal sites. These findings support attention to skeletal health in patients receiving prolonged ASM therapy.

KEYWORDS

Epilepsy; Antiseizure Medication; Bone Mineral Density; Osteopenia; Osteoporosis; Trabecular Bone Score; Vitamin D; Calcium

INTRODUCTION

Epilepsy is a common chronic neurological disorder affecting 50 million people worldwide, requiring prolonged antiseizure medication (ASM) in many patients. Long-term skeletal complications are increasingly recognized as important comorbidity because epilepsy itself may increase fall and fracture risk, while some ASMs adversely influence bone metabolism.[1][2][23]

Fracture rate in persons with epilepsy is reported to be two to six fold higher than that of general population, attributed to seizures, reduced physical activity, nutritional factors and ASM exposure. Vestergaard et al. using Danish National Hospital Register reported relative risk 1.19 for any fracture and 1.32 for hip fracture among ASM users. Physical inactivity could result from seizures and/or AEDs, and decreased BMD may result in fractures of hip, forearm and spine, but fractures at other sites may result from AED neurotoxicity, clumsiness and falling.[2][4][23]

Enzyme-inducing agents including phenytoin, carbamazepine, phenobarbital, oxcarbazepine and felbamate have been associated with alterations in vitamin D metabolism and reduced BMD. Pack et al. in outpatient population receiving enzyme-inducing antiepileptic drugs reported reduced BMD at femoral neck and lumbar spine, with duration of therapy as independent predictor. Cytochrome P450 enzyme-inducing AEDs alter vitamin D concentrations and predispose to reduced bone mass.[3][4][15][16]

The molecular link involves pregnane X receptor (PXR) activation by xenobiotics including phenobarbital, phenytoin and carbamazepine. Pascucci et al. demonstrated PXR activation promotes expression of CYP24, an enzyme involved in 24-hydroxylation of 25-hydroxyvitamin D to inactive 24,25-dihydroxyvitamin D, reducing calcium absorption and triggering secondary hyperparathyroidism and increased bone turnover. This explains increased catabolism of 25-hydroxyvitamin D to inactive metabolites, relatively hypocalcemia, increase in parathyroid hormone level and ultimately decrease in BMD.[5][14][17]

Non-enzyme inducing ASMs such as valproate, lamotrigine, topiramate (alter osteoblastic function) may also affect bone, but to a lesser extent. Verrotti et al. reviewed that valproate activates osteoclasts and impairs osteoblast function via RANKL/OPG pathway, while topiramate causes metabolic acidosis and hypercalciuria. Nissen-Meyer et al. showed levetiracetam, phenytoin and valproate affect bone turnover differently in rats. Levetiracetam has very favorable bone profile, while lacosamide and lamotrigine have preferable bone effect compared to other sodium channel blockers.[6][15][21][18]

Recent large cohort data (JAMA Neurology 2023, $n>10,000$) showed incident epilepsy was independently associated with 41% faster time to incident osteoporosis, and both enzyme-inducing and non-enzyme inducing ASMs were associated with increased risks, accounting for 9% and 23% faster times to osteoporosis respectively. This challenges belief that non-inducers are bone-neutral and supports routine osteoporosis screening in all people with epilepsy.[11][24]

BMD measured by dual-energy X-ray absorptiometry (DXA) remains principal clinical measure of bone mineral status. However BMD reflects bone quantity and does not completely capture bone microarchitecture. Trabecular bone score (TBS), derived from lumbar spine DXA images using TBS iNspire software, provides complementary information related to trabecular microarchitecture and fracture risk prediction beyond BMD. Leslie et al. in Manitoba cohort ($n=29,407$) showed TBS predicts fractures independent of BMD. Silva et al. in 2015 ISCD official positions endorsed TBS as adjunct to BMD for fracture risk assessment.[12][13]

In children, childhood being critical period for bone mass development, bone health is particularly worthy of attention. Cansu et al. found patients treated with oxcarbazepine compared with healthy controls, alkaline phosphatase and parathyroid hormone increased significantly, 25-hydroxyvitamin D levels decreased. Babayigit et al. reported children treated with oxcarbazepine had higher alkaline phosphatase and lower bone mineral density. Patients receiving polytherapy may have higher risk of fracture than single therapy.

Intractable epilepsy and ketogenic diet correlated with worsening of bone health in children.[9][19][20][8][10]

Gender differences also exist. Sheth et al. reported gender differences in bone mineral density in epilepsy, with females more vulnerable. Coppola et al. showed reduced BMD in children, adolescents and young adults with epilepsy. Farhat et al. studied ambulatory patients and found effect of antiepileptic drugs on bone density.[8][9][22]

Despite recognition, there are no formal practice guidelines for monitoring, prevention and management of bone disease in persons receiving chronic ASMs. Judicious choice and use of AED, preferring non-enzyme inducing AEDs, adequate vitamin D supplementation, identifying patients at risk for fractures using direct measures of bone health like bone densitometry (dual-energy X-ray absorptiometry) and/or indirectly via various biochemical markers of bone turnover are few ways of alleviating magnitude of problem. Lee et al. recommended vitamin D 1000-2000 IU/day and calcium 1000-1200 mg/day.[16][25][17]

The present study evaluated BMD in adults receiving long-term ASM therapy in a tertiary care hospital in South India, and additionally assessed TBS and biochemical correlates, with particular emphasis on serum calcium and vitamin D, to inform proactive skeletal health surveillance.[7][22]

Materials and Methods

Study design and setting

This was a hospital-based observational cross-sectional study conducted in the Department of Neurology, JSS Medical College and Hospital, Mysuru.

Participants

Adults aged ≥ 18 years with epilepsy according to International League Against Epilepsy criteria, receiving one or more ASMs continuously for at least 2 years, and providing written informed consent were eligible.

Exclusion criteria included chronic kidney disease, chronic liver disease, primary hyperparathyroidism, thyroid disorders affecting bone metabolism, malignancy with skeletal involvement, pregnancy or lactation, prolonged corticosteroid use, anti-osteoporotic therapy, known metabolic bone disease and non-epilepsy-related immobility.

Assessment

Demographic and clinical variables included age, sex, height, weight, BMI, duration of epilepsy, duration and dose of ASM therapy, monotherapy/polytherapy status and relevant comorbidities. Serum calcium and 25-hydroxyvitamin D were recorded.

BMD was measured by DXA at L1–L4 lumbar spine, total hip and femoral neck and expressed as g/cm² with T-scores and Z-scores. For classification, normal BMD was defined as T-score ≥ -1.0 , osteopenia as T-score between -1.0 and -2.5 , and osteoporosis as T-score ≤ -2.5 . TBS was derived from lumbar spine DXA using TBS iNsight software. The study protocol also included vertebral fracture assessment and whole-body body-composition assessment.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics. Correlations between biochemical variables and BMD were assessed using correlation coefficients with corresponding p values. A p value < 0.05 was considered statistically significant.

RESULTS

Participant characteristics and ASM exposure

A total of 80 patients were included. Forty-seven (58.8%) were male and 33 (41.2%) were female. Twenty-eight patients (35.0%) received monotherapy and 52 (65.0%) polytherapy. Fifty-four (67.5%) had exposure to at least one enzyme-inducing ASM and 26 (32.5%) had no documented exposure to an enzyme-inducing ASM.

Phenytoin was used by 37 patients (46.2%), carbamazepine by 20 (25.0%) and phenobarbital/phenobarbitone by 23 (28.7%). Because several participants received polytherapy, medication categories were not mutually exclusive. The longest mean duration of exposure was reported for clonazepam (8.62 years), followed by phenytoin (6.23 years) and sodium valproate (6.12 years).

Table 1: Participant characteristics (n=80)

Characteristic	n (%)
Male	47 (58.8%)
Female	33 (41.2%)
Monotherapy	28 (35.0%)
Polytherapy	52 (65.0%)
Enzyme inducing ASM Yes	54 (67.5%) [3,4]
Enzyme inducing ASM No	26 (32.5%)
Phenytoin	37 (46.2%)
Carbamazepine	20 (25.0%)
Phenobarbital	23 (28.7%)

Using the lowest available T-score among femoral neck, total femur and lumbar spine, 20 participants (25.3%) had normal BMD, 51 (63.7%) had osteopenia and 9 (11.0%) had osteoporosis. Thus, 60/80 (75.0%) had reduced BMD.

Table 2: BMD Categories

Category	T Score	n (%)
Normal	≥ -1.0	20 (25.3%)
Osteopenia	-1.0 to -2.5	51 (63.7%)
Osteoporosis	≤ -2.5	9 (11.0%)
Total	Osteopenia and Osteoporosis	60 (75.0%) [1,2]

Mean left and right femoral neck BMD values were 0.910 ± 0.175 and 0.915 ± 0.161 g/cm², respectively. Mean left and right total femur BMD values were both 0.947 g/cm² (SD 0.160 and 0.171 , respectively). Mean lumbar spine L1–L4 BMD was 1.067 ± 0.168 g/cm².

TBS and biochemical measures

Mean TBS was 1.38 ± 0.09 among 78 participants with available TBS data. Mean serum calcium was 8.65 ± 1.31 mg/dL and mean vitamin D was 23.15 ± 7.29 ng/mL.

Correlation of calcium and vitamin D with BMD

Serum calcium correlated positively with lumbar spine BMD ($r=0.470$, $p<0.001$), left total femur BMD ($r=0.279$, $p=0.013$), right total femur BMD ($r=0.454$, $p<0.001$), and right femoral neck BMD ($r=0.257$, $p=0.022$). The association with left femoral neck BMD was not statistically significant ($r=0.211$, $p=0.060$).

Vitamin D correlated positively with lumbar spine BMD ($r=0.479$, $p<0.001$), left total femur BMD ($r=0.312$, $p=0.005$), right total femur BMD ($r=0.545$, $p<0.001$), and right femoral neck BMD ($r=0.253$, $p=0.024$). The association with left femoral neck BMD was not statistically significant ($r=0.169$, $p=0.134$).

DISCUSSION

This study demonstrates a high burden of reduced BMD among adults receiving long-term ASM therapy. Three-quarters of the study population had low BMD, predominantly osteopenia. The finding is consistent with the established concern that chronic ASM exposure may adversely affect skeletal health[3,4]

The high proportion of participants exposed to enzyme-inducing ASMs is clinically relevant. Phenytoin, carbamazepine and phenobarbital have historically been associated with altered vitamin D metabolism and reduced BMD. Pack et al. reported reduced BMD in patients receiving enzyme-inducing ASMs, while experimental and clinical data have also supported direct effects of phenytoin and carbamazepine on bone cells[3,5,8]

The observed biochemical associations further support the relationship between mineral metabolism and skeletal status. Calcium and vitamin D were positively correlated with BMD at several measured sites, with the strongest association for vitamin D and right total femur BMD. These findings are biologically plausible because vitamin D contributes to calcium homeostasis and skeletal mineralization. However, the cross-sectional design precludes establishing causality.

The mean TBS was 1.38 ± 0.09 . TBS provides information

complementary to BMD and can reflect aspects of trabecular microarchitecture that are not captured by areal BMD alone.

The results should be interpreted in the context of the study design. There was no control group, and several ASM groups were small. Medication categories overlapped because of polytherapy; therefore, the observed proportions for individual drugs should not be interpreted as causal drug-specific effects. Prospective studies with larger samples, appropriate comparator groups and adjustment for age, sex, BMI, menopause, duration and type of ASM, physical activity and nutritional factors would better clarify independent predictors of skeletal deterioration.

CONCLUSION

Reduced BMD was common in this hospital-based cohort of adults receiving long-term ASM therapy, with osteopenia substantially more frequent than osteoporosis. Most participants were exposed to at least one enzyme-inducing ASM. Serum calcium and vitamin D were positively associated with BMD at multiple skeletal sites. TBS provides an additional dimension of skeletal assessment beyond BMD. These findings support proactive assessment of skeletal health and attention to modifiable bone-health factors in patients requiring prolonged ASM therapy.

Limitations

The study has several limitations. First, its cross-sectional design limits the ability to establish temporal or causal relationships between ASM exposure and skeletal abnormalities. Second, there was no healthy control group, and therefore the prevalence of reduced BMD in the study population cannot be directly compared with an age- and sex-matched general population.

Third, a substantial proportion of participants were receiving polytherapy, making it difficult to isolate the skeletal effects of individual medications. The individual drug subgroups were also small, particularly for newer ASMs, limiting meaningful statistical comparison between drugs.

Fourth, although serum calcium and vitamin D were assessed, other important biochemical markers such as parathyroid hormone, phosphate and bone turnover markers were not included in the reported analysis.

Despite these limitations, the study provides clinically relevant descriptive data regarding the burden of reduced BMD among adults receiving long-term ASM therapy and demonstrates the complementary value of biochemical and DXA-derived skeletal parameters.

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