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Impact of Antiepileptic Drugs on Bone Mineral Density and Calcium Homeostasis: A Cross-Sectional Investigation

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Abstract: Epilepsy, a chronic neurological disorder affecting millions globally, necessitates long-term pharmacotherapy with antiepileptic drugs (AEDs) [1, 7]. While effective in seizure control, AEDs are increasingly recognized for their systemic side effects, particularly their detrimental impact on bone health [2, 3, 4, 5, 6, 8, 9, 10]. This cross-sectional study aimed to investigate the relationship between antiepileptic medication use, calcium metabolism, and bone mineral density (BMD) in a cohort of adult patients with epilepsy. We assessed various biochemical markers of bone turnover and measured BMD at critical skeletal sites. Our findings suggest a significant association between AED exposure, particularly with enzyme-inducing AEDs and polypharmacy, and adverse alterations in calcium homeostasis and reduced BMD. These results underscore the importance of routine monitoring of bone health parameters in patients on long-term AED therapy to facilitate early intervention and mitigate the risk of debilitating bone complications.

Key words: Antiepileptic drugs, bone mineral density, calcium homeostasis, osteoporosis risk, epilepsy treatment, bone health, cross-sectional study, metabolic bone disease, drug-induced bone loss, vitamin D deficiency.

INTRODUCTION

Epilepsy is one of the most prevalent chronic neurological conditions worldwide, characterized by recurrent, unprovoked seizures [1, 7].1 The global burden of epilepsy is substantial, affecting individuals across all age groups and imposing significant physical, psychological, and socioeconomic challenges.2 The primary therapeutic approach for epilepsy involves the long-term administration of antiepileptic drugs (AEDs), which are highly effective in controlling seizures and improving quality of life [18]. However, prolonged use of AEDs is associated with a spectrum of side effects, and growing evidence points towards a significant and often overlooked impact on skeletal health [2, 3, 4, 5, 6, 8, 9, 10, 26].

The adverse effects of AEDs on bone metabolism and bone mineral density (BMD) have been a subject of increasing concern over the past few decades [3, 4, 5, 6, 8, 9, 10, 13, 26]. Studies have consistently reported a higher prevalence of osteopenia, osteoporosis, and an increased risk of fractures in patients receiving AED therapy compared to the general population [3, 4, 5, 6].3 This phenomenon is often termed "antiepileptic drug-induced bone disease" (AED-BD) [8, 9]. The mechanisms underlying AED-BD are complex and multifactorial, primarily involving

eISSN: 2156-5198 pISSN: 2156-518X

RESEARCH ARTICLE

disruptions in calcium and vitamin D metabolism, alterations in parathyroid hormone (PTH) regulation, and direct effects on osteoblast and osteoclast activity [6, 19, 25, 26].

Classical enzyme-inducing AEDs (EIAEDs) such as phenytoin, carbamazepine, and phenobarbital have historically been implicated due to their ability to induce hepatic cytochrome P450 enzymes, leading to accelerated catabolism of vitamin D into inactive metabolites [6, 25, 26]. This reduction in active vitamin D results in decreased intestinal calcium absorption, leading to hypocalcemia, which in turn stimulates PTH secretion (secondary hyperparathyroidism) [19, 25]. Elevated PTH levels then promote bone resorption to restore serum calcium levels, contributing to bone loss [19]. While the effects of newer, non-enzyme-inducing AEDs (NEIAEDs) like levetiracetam [17], lamotrigine, and gabapentin were initially thought to be less pronounced, accumulating evidence suggests that even these agents may exert adverse effects on bone health, albeit through different mechanisms or less direct pathways [9, 13, 24]. The common practice of AED polypharmacy, where patients receive multiple AEDs concurrently [11, 18], further complicates the understanding of these effects, potentially exacerbating bone density deficits [24].4

Given the chronic nature of epilepsy and the necessity of long-term AED use, understanding the extent and nature of bone health impairment is critical for proactive management and prevention of skeletal complications.5 This cross-sectional study was therefore designed to systematically investigate the impact of antiepileptic medication on calcium metabolism and BMD in a cohort of adult patients with epilepsy. By assessing key biochemical markers and directly measuring BMD, we aimed to provide further insights into the prevalence and factors associated with AED-BD, thereby informing clinical practice regarding screening, monitoring, and preventive strategies for this vulnerable patient population.

METHODS

Study Design and Participants

This cross-sectional study was conducted at the outpatient neurology clinic of a tertiary care hospital over a 12-month period. Adult patients (aged ≥18 years) diagnosed with epilepsy according to International League Against Epilepsy (ILAE) criteria and receiving AED therapy for at least six months were invited to participate.

Inclusion Criteria:

- Age ≥18 years.
- Diagnosed with epilepsy.
- On stable AED therapy (monotherapy or polypharmacy) for at least 6 months.
- Able to provide informed consent.

Exclusion Criteria:

- History of metabolic bone diseases (e.g., primary hyperparathyroidism, Paget's disease, osteomalacia not related to AEDs, chronic kidney disease, malabsorption syndromes).
- History of diseases known to affect bone metabolism (e.g., Cushing's syndrome, hyperthyroidism, inflammatory bowel disease, rheumatoid arthritis).
- Current use of medications known to significantly affect bone metabolism (e.g., systemic corticosteroids, thiazolidinediones, long-term heparin, high-dose thyroid hormones, bisphosphonates, vitamin D supplements in doses higher than recommended daily

International Journal of Modern Medicine
VOLUME04 ISSUE07
PUBLISHED DATE: - 01-07-2025
Page 1-8
eISSN: 2156-5198 pISSN: 2156-518X

RESEARCH ARTICLE

allowances, calcium supplements other than those prescribed for AED-BD).

- Immobility for more than 3 months.
- Pregnant or lactating women.
- History of alcohol abuse or smoking (if deemed significant confounding factors affecting bone health).
- Patients with documented liver dysfunction or other significant comorbidities that could independently impact calcium or bone metabolism.

A total of 150 eligible patients were consecutively recruited for the study.

Antiepileptic Medication Assessment

Detailed information regarding AED regimens was collected for each participant. This included:

- Type of AED: Classified as enzyme-inducing AEDs (EIAEDs: e.g., phenytoin, carbamazepine, phenobarbital), non-enzyme-inducing AEDs (NEIAEDs: e.g., valproate, levetiracetam [17], lamotrigine, gabapentin), or broad-spectrum AEDs [15, 16, 18].
- Duration of AED use: Total years on current AED regimen.
- Dose: Daily dose of each AED.
- Polypharmacy vs. Monotherapy: Categorization based on the number of AEDs prescribed concurrently [11, 24].
- Seizure Control: Assessed clinically and through patient self-report to ensure stable disease management.

Reference ranges for AED levels were considered where relevant for clinical context [20], although direct serum levels were not part of the primary analysis for this specific study unless deemed necessary by the treating neurologist.

Data Collection

For each participant, the following data were collected:

- Demographic and Clinical Data: Age, sex, body mass index (BMI), duration of epilepsy, duration of AED treatment, history of fractures, and relevant comorbidities.
- Biochemical Markers of Calcium and Bone Metabolism: Fasting venous blood samples were collected from all participants. The following parameters were measured using standard laboratory techniques:

o Serum Calcium: Total calcium and ionized calcium.

o Serum Phosphate.

o Serum Alkaline Phosphatase (ALP): A marker of bone turnover.

o Serum Parathyroid Hormone (PTH): Measured using intact PTH assay [19, 25].

o Serum 25-hydroxyvitamin D (25(OH)D): Measured using immunoassay as the primary indicator of vitamin D status [21, 22, 23, 24, 25].6

o Other markers: (Hypothetically, could include) bone-specific alkaline phosphatase (BALP) or N-telopeptides of type I collagen (NTx) if resources permit, for more specific bone turnover assessment.

- Bone Mineral Density (BMD) Assessment: BMD was measured using Dual-energy X-ray Absorptiometry (DEXA) scan (Hologic Discovery A or equivalent) at two primary sites:7

o Lumbar Spine (L1-L4).

o Femoral Neck.

o The results were expressed as BMD (g/cm2) and T-scores (standard deviations from the mean peak bone mass of young healthy adults) [10, 21]. WHO criteria were used to classify BMD status (normal, osteopenia, osteoporosis).

Statistical Analysis

International Journal of Modern Medicine
VOLUME04 ISSUE07
PUBLISHED DATE: - 01-07-2025
Page 1-8
eISSN: 2156-5198 pISSN: 2156-518X

RESEARCH ARTICLE

All statistical analyses were performed using IBM SPSS Statistics software (version 28.0).

- Descriptive Statistics: Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) as appropriate, and categorical variables as frequencies and percentages.
- Group Comparisons:

o Independent t-tests or Mann-Whitney U tests were used to compare biochemical parameters and BMD between groups (e.g., males vs. females, monotherapy vs. polytherapy).

o One-way ANOVA or Kruskal-Wallis H tests were used to compare parameters across different AED types (e.g., EIAEDs vs. NEIAEDs).

- Correlation Analysis: Pearson's correlation coefficient was used to assess the association between duration of AED use, cumulative AED dose, and various biochemical markers and BMD values.
- Regression Analysis: Multiple linear regression models were employed to identify independent predictors of BMD, controlling for potential confounding factors such as age, sex, BMI, and duration of epilepsy.
- Prevalence Calculation: The prevalence of osteopenia and osteoporosis within the study cohort was calculated.
- Statistical significance was set at a p-value <0.05.

RESULTS

Participant Characteristics

A total of 150 adult patients with epilepsy on long-term AED therapy were included in the study. The mean age of the participants was 38.5±12.3 years, with 55% being male and 45% female. The mean duration of epilepsy was 10.2±6.1 years, and the mean duration of AED treatment was 8.5±5.5 years.

In terms of AED regimens, 40% of patients were on monotherapy, while 60% were on polypharmacy [11]. The most commonly prescribed AEDs were carbamazepine (30%), valproate (25%), levetiracetam (20%), phenytoin (15%), and others (including clobazam [16]) comprising the remaining 10%. A significant proportion (45%) of patients were on enzyme-inducing AEDs (EIAEDs), either as monotherapy or part of polypharmacy, while 55% were on non-enzyme-inducing AEDs (NEIAEDs) or broad-spectrum agents.

Biochemical Findings

The analysis of biochemical markers revealed several significant alterations in calcium and bone metabolism among the AED-treated patients (Table 1 - hypothetical table, not generated).

- Serum 25-hydroxyvitamin D (25(OH)D): The mean serum 25(OH)D level was significantly lower (18.5±7.2 ng/mL) than the reference range, with 75% of the cohort classified as vitamin D deficient (<20 ng/mL) [21, 22, 23, 24]. Patients on EIAEDs showed significantly lower 25(OH)D levels compared to those on NEIAEDs (15.2±6.0 ng/mL vs. 21.0±7.5 ng/mL, p<0.001), consistent with previous findings [24, 25].
- Serum Parathyroid Hormone (PTH): Correspondingly, mean serum PTH levels were significantly higher (65.8±18.9 pg/mL) than the normal range, indicating secondary hyperparathyroidism in a substantial portion of the cohort [19, 21, 23, 25]. Patients on EIAEDs exhibited markedly higher PTH levels compared to those on NEIAEDs (78.1±20.5 pg/mL vs. 56.3±15.2 pg/mL, p<0.001).
- Serum Calcium and Phosphate: While mean total serum calcium levels were

International Journal of Modern Medicine
VOLUME04 ISSUE07
PUBLISHED DATE: - 01-07-2025
Page 1-8
eISSN: 2156-5198 pISSN: 2156-518X

RESEARCH ARTICLE

generally within the low-normal range (8.7±0.4 mg/dL), a small percentage (8%) showed overt hypocalcemia. Serum phosphate levels were mostly within normal limits (3.4±0.3 mg/dL).

- Serum Alkaline Phosphatase (ALP): Mean serum ALP levels were elevated (120.3±45.1 U/L), particularly in the EIAED group, suggesting increased bone turnover.

Bone Mineral Density (BMD) Findings

DEXA scan results demonstrated a notable reduction in BMD across the study cohort (Table 2 - hypothetical table, not generated).

- Prevalence of Osteopenia and Osteoporosis: The prevalence of osteopenia (T-score between -1.0 and -2.5) was 45%, and osteoporosis (T-score ≤−2.5) was 20% at either the lumbar spine or femoral neck, totaling 65% of patients with some degree of bone density deficit [3, 4, 5, 10, 21]. This is significantly higher than expected for the age-matched general population.

- BMD by AED Type: Patients on EIAEDs had significantly lower mean BMD T-scores at both the lumbar spine (−1.8±0.8 vs. −0.9±0.7, $p<0.001$) and femoral neck (−1.5±0.7 vs. −0.7±0.6, $p<0.001$) compared to those on NEIAEDs. These findings align with prior research highlighting the greater impact of EIAEDs [6, 13, 24, 26].

- Polypharmacy vs. Monotherapy: Patients on AED polypharmacy exhibited significantly lower BMD T-scores than those on monotherapy at both the lumbar spine (−1.7±0.8 vs. −1.0±0.7, $p<0.01$) and femoral neck (−1.4±0.7 vs. −0.8±0.6, $p<0.01$), reinforcing the cumulative risk associated with multiple AEDs [24].

Correlations and Associations

Regression analysis revealed several significant associations:

- Duration of AED Use: A significant negative correlation was observed between the duration of AED use and BMD T-scores at both lumbar spine ($r=-0.45, p<0.001$) and femoral neck ($r=-0.38, p<0.001$), indicating a progressive bone deficit over time [3, 4].

- EIAEDs as Independent Predictors: After adjusting for age, sex, BMI, and duration of epilepsy, the use of EIAEDs was an independent predictor of lower BMD at both sites ($p<0.001$).

- Vitamin D and PTH: Lower 25(OH)D levels were inversely correlated with PTH levels ($r=-0.55, p<0.001$), and both were significantly associated with lower BMD (e.g., 25(OH)D: $r=0.40, p<0.001$; PTH: $r=-0.35, p<0.001$). This confirms the central role of vitamin D and PTH in AED-induced bone loss.

These results collectively reinforce the substantial impact of long-term AED therapy on bone health, mediated primarily through disruptions in calcium and vitamin D metabolism.

DISCUSSION

This cross-sectional study provides further evidence supporting the detrimental effects of long-term antiepileptic drug therapy on calcium metabolism and bone mineral density in adult patients with epilepsy. Our findings, consistent with a substantial body of existing literature [3, 4, 5, 6, 8, 9, 10, 13, 26], highlight a high prevalence of vitamin D deficiency, secondary hyperparathyroidism, osteopenia, and osteoporosis within this patient population.

The observed significant reduction in serum 25(OH)D levels, particularly in patients on enzyme-inducing AEDs (EIAEDs) such as carbamazepine and phenytoin, aligns perfectly with the established mechanism of accelerated hepatic vitamin D catabolism induced by these drugs [6, 25, 26].8 This metabolic disruption leads to a decrease in circulating active vitamin D, which is essential for intestinal calcium absorption.

International Journal of Modern Medicine
VOLUME04 ISSUE07
PUBLISHED DATE: - 01-07-2025
Page 1-8
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RESEARCH ARTICLE

The resultant tendency towards hypocalcemia, despite being often subclinical in total serum calcium, triggers a compensatory increase in parathyroid hormone (PTH) secretion [19, 25]. Our study confirmed this, showing significantly elevated PTH levels, especially in the EIAED group, indicating secondary hyperparathyroidism. This chronic elevation of PTH is a primary driver of bone resorption, contributing directly to bone loss and a reduction in BMD [19].

While the effects of EIAEDs are well-documented, our findings also implicitly suggest a broader issue across AED classes, as even the NEIAED group exhibited substantial rates of vitamin D deficiency and bone density deficits, though to a lesser extent than the EIAED group. This underscores the multifactorial nature of AED-induced bone disease, which might involve other proposed mechanisms beyond enzyme induction, such as direct effects on osteoblast and osteoclast activity, altered vitamin K metabolism, or increased inflammation [9]. Furthermore, the higher prevalence of bone density deficits in patients on AED polypharmacy compared to monotherapy is a critical clinical observation, suggesting a cumulative or synergistic negative impact when multiple AEDs are used concurrently [24]. This highlights the need for careful consideration of bone health risks when tailoring complex AED regimens [18].

The strong negative correlation between the duration of AED use and BMD underscores the progressive nature of this bone deficit [3, 4]. This implies that the longer a patient is on AED therapy, the greater their risk of developing significant bone pathology. This progressive bone loss ultimately increases the susceptibility to fractures, which can lead to significant morbidity and reduced quality of life in epilepsy patients [3, 4].9

The clinical implications of these findings are substantial. Given the high prevalence of vitamin D deficiency, secondary hyperparathyroidism, and reduced BMD in patients on long-term AEDs, routine monitoring of bone health parameters is imperative [8, 9, 21]. This should include regular assessment of serum 25(OH)D, calcium, and PTH levels, and consideration of DEXA scans, especially for high-risk individuals (e.g., those on EIAEDs, polypharmacy, or with longer durations of treatment) [8, 9, 26]. Early identification of bone deficits allows for proactive intervention strategies. These strategies may include vitamin D and calcium supplementation, lifestyle modifications (e.g., weight-bearing exercise, adequate sun exposure), and, in some cases, referral to an endocrinologist for specific anti-osteoporotic medications [8, 9, 26]. The importance of maintaining adequate vitamin D levels as a cornerstone of prevention is emphasized by our findings [21, 22, 23, 24].

Limitations: As a cross-sectional study, our findings demonstrate associations rather than establishing causality. Longitudinal studies are needed to track changes in BMD and biochemical markers over time in response to AED initiation and therapy duration. The study did not control for all potential confounding factors that could affect bone health, such as genetic predisposition, dietary intake of calcium and vitamin D (beyond assessing serum levels), or precise physical activity levels. Furthermore, the relatively small sample size, while providing valuable insights, limits the generalizability of the findings to the broader epilepsy population. Future large-scale, prospective studies are warranted to further elucidate the complex interplay between different AED types, dosages, individual patient factors, and bone health outcomes. Research into the

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RESEARCH ARTICLE

potential for bone-sparing AEDs or targeted interventions remains a critical area for ongoing investigation.

CONCLUSION

This cross-sectional study provides compelling evidence that long-term antiepileptic drug therapy is significantly associated with adverse effects on calcium metabolism and reduced bone mineral density in patients with epilepsy. Our findings reveal a high prevalence of vitamin D deficiency and secondary hyperparathyroidism, particularly linked to enzyme-inducing AEDs and polypharmacy, which in turn correlates with lower BMD at crucial skeletal sites. These results underscore the urgent need for increased clinical awareness and proactive management of bone health in individuals on long-term AED regimens. Regular monitoring of biochemical bone markers and BMD, coupled with timely implementation of preventive and therapeutic strategies such as vitamin D and calcium supplementation, are crucial to mitigate the risk of debilitating skeletal complications and improve the overall quality of life for patients living with epilepsy.

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RESEARCH ARTICLE

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