



Bone health in epilepsy



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ABSTRACT

Epilepsy is one of the most common neurological disorder usually requiring life long treatment. Long term treatment with antiepileptic drugs (AED's) is associated with chronic side effects which includes effect on bone health

There is a growing volume of literature suggesting that chronic use of AED in patients with epilepsy significantly reduces bone mineral density (BMD) with an increased fracture risk. The causes of these associations are likely to be multifactorial. Unlike other chronic side effects, symptoms of bone loss are insidious and asymptomatic; hence they are usually not recognized, and thus untreated. Hence one needs to determine the presence of osteoporosis before the overt signs are evident to reduce fracture risk. Evaluation of bone health is mandatory for a comprehensive treatment and to provide calcium and 25-OH vitamin-D 3 supplementation if needed. The goals of epilepsy treatment are to achieve seizure freedom while minimizing adverse effects of treatment. Management goal should include a comprehensive care of the patient and this includes much more than controlling seizures.

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1. Introduction

There have been reports of AED induced osteomalacic biochemical abnormalities dating back to early 70's.¹ Long term AED use in patients with epilepsy have been known to induce

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hypocalcemia, hypophosphatemia, increased levels of serum alkaline phosphatase, hyperparathyroidism, hypovitaminosis D, radiographic changes of rickets,

Chronic AED therapy in patients with epilepsy causes abnormalities in calcium metabolism, including hypocalcemia, hypophosphatemia, elevated levels of serum alkaline phosphatase and serum parathyroid hormone, reduced serum levels of biologically active vitamin D metabolites, radiologic evidence of rickets, and histologic evidence of osteomalacia.^{2–5} Earlier studies have shown that 20 to 65% of patients on AED predominantly institutionalized progressed to show evidence of rickets or osteomalacia.^{3,5–7} This results in fracture and reports of increased incidence of fracture are seen in patients receiving AED. There is growing evidence of literature, which shows AED induced side effects on bone health, which includes the newer AED's too.

2. Bone health

Bone is a dynamic active tissue, which is under constant reconstruction all through life. Bone cells include osteoblasts which builds bone, osteocytes maintains strength, and osteoclasts, which resorb bone. The balance between the types of cells determines the bone density. Osteoblasts deposit an organic matrix, which is followed by mineralization by calcium and phosphorus. This mineral phase of bone is called hydroxyapatite. The formation of hydroxyapatite is determined by the concentration of calcium and phosphorus in plasma and extracellular fluid. There is a critical limit for the concentrations of calcium and phosphorus ions below, which the mineralization of organic matrix does not occur.⁸ Vitamin D and calcium play an important role in disorders of bone metabolism and their deficiency leads to skeletal abnormalities, ranging from varying from osteopenia to osteomalacia. Hypovitaminosis D has been implicated as a major cause for bone loss in patients with epilepsy. Bone loss is dependent on various factors like increasing age, physical inactivity, comedication acting on the bone metabolism, hormonal changes in women and various genetic factors.

Nutrition plays a key role in the maintenance of bone health. Needless to say, the nutrient store in early childhood and adolescent determines the bone status in old age.⁹ A diet low in calcium leads to hypocalcemia, which triggers secondary hyperparathyroidism leading to osteoclast activity and calcium release from bone

Aging changes the calcium metabolism leading to reduced intestinal calcium absorption and formation but with increased bone resorption. The demand of calcium increases in women of childbearing age group, postmenopausal women and old age.

Keeping in mind the role of nutrition, proper counseling about dietary calcium needs to be emphasized in women in preconception period, during pregnancy and during lactation as this affects the health and nutrition of the offspring.

3. Indices of bone and mineral

AED affects calcium and phosphate concentration in the body affecting the bone metabolism. Reports of AED induced hypocalcemia have ranged between 3% and 30%.^{1,2,10–12} Hypophosphatemia has also been reported with AED's.^{13,14} Maintenance of bone health requires vitamin D. Vitamin D level is the most common index of Vitamin D status and hypovitaminosis D have been reported in both adults and children taking AEDs.^{1,12–18} 1,25[OH]₂D, the most active metabolite of vitamin D has been found to be low in adults taking AEDs.¹⁹ Parathyroid gland secretes parathyroid hormone (PTH) and is directly involved in the regulation of calcium. With hypocalcemia, PTH levels increase, which in turn increases bone breakdown or resorption. AED therapy has been

reported to cause hyperparathyroidism.^{10,20} Markers of bone formation have been assessed in patients receiving AEDs, which include alkaline phosphatase, osteocalcin, and the C-terminal extension peptide of type I procollagen. The most commonly used marker for bone formation was usually alkaline phosphatase and increased levels have been noted in both children and adults on AEDs.^{12,14,21,22} However as serum total alkaline phosphatase is also derived from other sources like bone and liver, it loses its sensitivity and specificity as a marker for bone disease. Hence studies addressing levels of serum total alkaline phosphatase measured the isoenzymes of bone fraction.^{16,23} High levels of osteocalcin, or bone-gla protein, synthesized predominantly by osteoblasts is a small noncollagenous protein that is specific for bone tissue have been reported in patients on AED treatment.^{21,24,25} Elevated levels of Procollagen type I molecules secreted by osteoblastic cells have been seen in patients taking AEDs.^{21,25} Markers of bone resorption in patients on AED such as cross-linked carboxy-terminal telopeptide of human type I and hydroxyproline in the urine are elevated.^{21,25} The markers have been found to be elevated even with normal vitamin D and PTH levels.²⁶

4. Diet and bone health

Calcium and vitamin D form the framework of the bone and skeletal system. Body produces Vitamin D, a fat-soluble vitamin after exposure to ultraviolet (UV-B) rays from the sun. Sunlight is the predominant source of vitamin D. The food sources of Vitamin D are salmon, mackerel, tuna fish, sardines, liver, beef, swiss cheese, fortified milk and cereals. Indian diet lacks these food supplements. Moreover the food is not fortified with vitamin D in India. The calcium requirement changes with different stages of bone growth i.e. during growth spurt, pregnancy and lactation, elderly. The dietary sources of calcium in the diet are milk and other dairy products, such as hard cheese, cottage cheese, yogurt, as well as green vegetables, like spinach. Hence calcium can be obtained through diet, vitamin D source remains sunlight exposure and fortified food. Fortification of milk is followed in most countries, however not followed in India. Recommended Dietary Allowances (RDA) of calcium of 600 mg in adult men, women and 1000 mg pregnant and lactating women as per the Indian Council of Medical Research (ICMR) guidelines.²⁷ This is in contrast to 800 to 1000 mg/day for adult men and women and 1200 to 1300 mg/day for pregnant and lactating mothers by United States.²⁸ (Table 1). A study evaluating the dietary pattern in people with epilepsy (PWE) on AED with regard to calcium and related minerals concluded that the dietary consumption of calcium of all the patients was far below the recommended daily dietary allowance (RDA).²⁹ Bone is a dynamic active tissue, which is under constant reconstruction all through life. Low calcium in diet causes hypocalcemia, which in turn triggers secondary

Table 1
Recommended Dietary Allowances of calcium in India and USA.

Category	India (27)	India (27)
Units	mg/day	mg/day
<i>Infants</i>		
Infants 0–6 months.	500	500
Infants 6–12 months.	500	750
<i>Children Boys & Girls</i>		
1–9 years.	400	800
10–15 years.	500	1200–1300
16–18 years.	500	1200–1300
<i>Men</i>	400	800–1000
<i>Women</i>	400	800–1000P
<i>Pregnant & Lactating Mothers</i>	1000	1200–1300

hyperparathyroidism, which causes increased osteoclast activity, and finally calcium releases from bone making bone weak.

5. Epilepsy, bone health and fracture

The association of epilepsy and increased risk of fractures have been noted. Factors related to this increased fracture risk include falls during a seizure or drowsiness and incoordination due to AED effect or part of symptomatic epilepsy.^{30,31} Low BMD associated with epilepsy and AED may also play a contributory role.^{31,32} Antiepileptic drug (AED) treatment has adverse effects on bone and mineral metabolism increasing the fracture risk.³³ Patients with epilepsy have two to six times more frequency of fractures than general population.^{33–35} Patients older than 40 years, taking enzyme inducing AED's for 2 years have significantly lower BMD at strategic areas of fracture risk sites.³⁶ Moreover, unexpected pathological fractures occurring during normal activity are also increased.³¹ Pathologic and traumatic fractures may be due to the underlying AED induced osteopenia or osteoporosis.³⁷ Long term AED treatment with enzyme-inducing drugs (EIAED) induces vitamin D metabolism reducing BMD, however, non enzyme inducing AED (NEIAED), valproate (VPA), has also been reported to reduce bone density.¹⁹ Pathologic fractures occur in 20 to 40% of patients on AED who are generally in low risk group for developing fractures.³¹ AED use increases the risk of fracture by 2- to 4-fold at clavicle spine or ankles with 69% of the reported fractures being not related to seizures.³⁸ High risk factors are chronic AED use and elderly women with increased rates of bone loss at the calcaneus and hip. The risk of hip fracture increases by 29% over 5 years among women age 65 years and older.³⁹ A cohort study evaluating the risk of fracture in patients with active epilepsy from 1993 to 2008 concluded that EIAED might increase the risk of fracture in patients with epilepsy. The result showed that for every 10,000 women treated with NEIAEDs for one year; there could be 48 additional fractures, including 10 additional hip fractures. For every 10,000 men treated with EIAEDs for one year, there could be 4 additional hip fractures.⁴⁰

A meta-analysis of twenty-two studies to evaluating the link between use of AEDs and fracture risk, both though both EIAED's and NEIAEDs were associated with increased fracture risk, it was more for enzyme-inducing AED's (RR = 1.18; 95% CI 1.11–1.25). Considering individual AED's phenobarbiturate (PB), topiramate (TPM) and phenytoin (PHT) suggested an increase in fracture risk of 78%, 39% and 70%, respectively.⁴¹

6. Mechanism of bone loss with AED (Table 2)

There are several mechanisms for the AED drug induced reduction in bone density.⁴² (42) AEDs such as carbamazepine (CBZ), phenobarbital, and phenytoin accelerate hepatic microsomal metabolism of vitamin D to polar metabolites other than (25-OH) vitamin D (25-OHD) and increase the metabolism of 25-OHD into biologically inactive products.⁴³ AEDs such as phenytoin (PHT), carbamazepine (CBZ), primidone (PRM), and phenobarbital (PB) are inducers of the cytochrome P450 enzyme system and are most commonly associated with altered bone metabolism and decreased bone density.^{21,44,45}

AEDs may interfere with intestinal absorption of calcium causing hypocalcemia, which leads to hyperparathyroidism due to negative feedback. Experimental studies in rats showed markedly decreased calcium absorption with PHT but not with PB.⁴⁶ Animal studies have shown that there may be inhibition of the cellular response to PTH. Hypocalcemia has been frequently seen due to inhibition of the bone resorptive response to PTH. Hyperparathyroidism is another suggested possible mechanism. This can be

associated with normal vitamin D status²¹ or hypovitaminosis.²⁰ Hyperparathyroidism activates bone resorption as a primary phenomenon and secondarily activate bone formation through a coupling phenomenon.

Two mechanisms are proposed for vitamin D inactivation by AEDs – hepatic enzyme induction and pregnane X receptor (PXR) and SXR activation.^{21,47,48} Vitamin D (D2 and D3) are normally taken up by the liver and transformed into 25(OH) D by the mitochondrial vitamin D hydroxylase CYP27A. The AED binds to the SXR and activates it. The complex binds to RXR, which then interacts with the vitamin D responsive element for the 24-OHase.^{21,48,49,50} This accelerates the destructive process of 25(OH) D and 1, 25(OH) 2D. This accelerated clearance will enhance the routine physiological adaptive mechanisms in response to progressive hypovitaminosis leading to secondary hyperparathyroidism.

Hypovitaminosis D also causes decreased calcium absorption in the intestine. VPA is a non-enzyme inducing AED and the reason for decreased BMD with VPA treatment is not well known.¹⁹ Both the EIAED and the NEIAED directly affects osteoblast and osteoclast activity maintaining a balance between them.¹⁹ Valproate association with BMD is probably by hormonal changes as suggested by the development of a polycystic ovary syndrome. EIAEDs apart from decreased calcium absorption also induce increased catabolism of sex steroids osteoporosis.³² Furthermore, A direct toxic effect of phenytoin on bone cells have been reported.⁵¹ Calcitonin deficiency is another postulated mechanism. Calcitonin is a hormone produced by the thyroid gland that inhibits osteoclast-mediated bone resorption. Calcitonin deficiency has been demonstrated both in vitro and in vivo may therefore accelerate bone turnover.^{52,53}

7. AED and bone metabolism

Phenytoin affects bone metabolism by increasing vitamin D metabolism or directly inhibiting intestinal calcium absorption.^{1,20} A study suggested that patients on phenytoin treatment may develop reduced BMD bone within 1 year.⁵⁴ The effect of VPA on bone health is controversial. Initial reports did not find any significant abnormality on the effect of VPA on BMD.^{12,55} But later studies have found that adults taking long-term VPA have increased serum concentrations of calcium, low serum 1,25 [OH]₂D concentration, and increased markers of bone resorption and formation.¹⁹ A metaanalysis of 11 studies which included 645 subjects evaluating effects of AED on lumbar spine found VPA found significantly decrease BMD of lumbar spine in epileptic children, while carbamazepine had no significant effect.^{56,57} The effect of the newer AED on bone mineral metabolism and BMD has been studied in few studies. A study in adult patients on lamotrigine (LTG), topiramate, vigabatrin, gabapentin did not find any significant abnormality on bone mineral metabolism and BMD.⁵⁸ Children treated with VPA and LTG especially in combination developed short stature, low bone mass, and reduced bone formation.⁵⁹ Polypharmacy further increases the risk of inducing low bone mass in adult patients.³⁵ A study measuring BMD on children with epilepsy showed that lamotrigine might not interfere with bone accrual.⁶⁰ A study done to access the rate of hip bone loss in older community dwelling men concluded that NEIAED was an independent predictor of increased rates of hip bone loss.⁶¹ A prospective study from south India showed that patients on AED with normal 25(OH) D levels at recruitment, irrespective of the type of antiepileptic medications even at subtherapeutic serum levels of the drug, developed 25(OH) D deficiency and insufficiency states at one year.⁶² NEIAED's can also affect bone health. A study comparing effect of levetiracetam and older AEDs on bone health concluded that both groups were

Table 2

Suggested mechanisms for AED induced bone disease.

-
- a Vitamin D metabolism
 - a) Vitamin D inactivation by hepatic induction of the cytochrome P450 enzyme.
 - b Increased conversion of vitamin D to polar inactive metabolites in the liver microsomes, reducing bioavailable vitamin D.
 - c PXR activators increasing expression of the CYP24 resulting in lower cellular concentration of active vitamin D
 - Hyperparathyroidism.
 - a) Inhibition of the cellular response to PTH.
 - Vitamin D insufficiency.
 - Calcium metabolism.
 - a) Interfere with intestinal absorption of calcium.
 - Decreased vitamin D mediated absorption.
 - Calcitonin deficiency
 - Interference with vitamin K metabolism.
 - Direct drug effect on bone cell functions- osteoblast inhibition.
-

associated with reduced bone turnover and bone loss at fracture risk sites over 1 year.⁶³

Yet another study analyzing effect of levetiracetam therapy on bone mineral density showed adverse effects on BMD though not significant and also noted a differential effect of AED between genders.⁶⁴ A meta-analysis done to characterize bone health in children receiving AED's concluded that hypovitaminosis with reduced bone density and impaired bone growth may be seen in children. However the study was cross sectional, included CBZ and VPA as primary study drugs and differed in skeletal sites. The study also concluded that Polytherapy was associated with a larger decrease in bone density than monotherapy.⁶⁵

8. Measuring bone strength

Screening for bone health with direct measures can be done by direct measurement of bone densitometry by dual-energy x-ray absorptiometry (DEXA). The procedure is performed like a digital X ray. Bone density measurement is done at wrist, hip, and lower spine and then it is scored. If the score is less than –1.0, the term “osteopenia” is applied. For a score less than –2.5, it is called “osteoporosis.” Adult patients receiving AEDs have shown significantly reduced BMD by using DEXA at the ribs and spine,³⁷ femoral neck;^{37,38,57} and total hip.³⁷ DEXA of the hip helps in identifying patients on AED's at risk for fractures. DEXA will be useful in situations where vitamin D is normal which was seen in a study where young male patients on chronic AED had significant bone loss at the hip in the absence of vitamin D deficiency.³⁸ A study showed that BMD for both the T- and Z-score of the lumbar spine, femur head, femoral neck and trochanter was significantly decreased in adults treated with AED and 59% had osteopenia at either the spine or the hip.³⁷

Both males and females with epilepsy on AED can have reduced BMD. Determining factors for the gender differences are age of onset of epilepsy, growth trends, and hormonal differences. Lower bone accrual in adolescence may contribute to increased fracture risk for both genders with epilepsy.⁶⁶

9. Bone health in women with epilepsy

Epilepsy in women plays a different role as concerned to bone health. Several factors modulate the disease like sex hormones, menopause, which have gender specific implications on bone health. AEDs place women with epilepsy at increased risk for bone disorders and fractures, which is particularly for menopausal women.

In a study done on premenopausal women, phenytoin was seen to cause significant bone loss at femur over 1 year. However the

study did not show any major adverse effects on bone turnover or bone mineral density with carbamazepine, lamotrigine and VPA.⁵⁴ Women over 65 years on AED for more than 5 years are at risk of hip fracture by 29%. Continuous AED use in elderly women is associated with increased rates of bone loss at the calcaneus and hip.³⁹ A recent study showed that levetiracetam therapy for one year affected the lumbar spine BMD in females than males however the study had small size.⁶⁴

9.1. Children

Chronic AED use in children also has shown to produce low bone mineral density and an increased risk of fracture. A study on 73 ambulatory children on VPA and oxcarbazepine showed significant decrease in growth velocity after 1 year of treatment.⁶⁷ However a previous study with a follow up of 2 years did not find any bone loss in children receiving long-term AED medication.⁶⁸

A study from a tropical country found that long term AED use puts children with epilepsy at risk for vitamin D deficiency.⁶⁹ A recent analysis of 11 studies also concluded that reduced bone density, impaired bone growth, and vitamin D deficiency may be seen in children on AED.⁶⁵

9.2. Recommendations for maintaining bone health in patients on AED's

9.2.1. Measures at initiation of therapy

1. Identify high-risk patients. (Postmenopausal, institutionalized, elderly, enzyme inducing AED, polytherapy)
2. Ensure patients undertake weight-bearing exercises to the comfort of the patient.
3. Maintain balanced diet with adequate calcium and sunlight exposure for vitamin D.
4. Advise to stop smoking, alcohol and avoid heavy caffeine drinks.
5. Prescribe 1000–1500 mg of calcium and 400 IU of vitamin D daily.

9.3. Measures after initiation of AED therapy

1. Measure calcium and 25- hydroxyvitamin D levels after 6–12 months of AED therapy
2. Yearly assessment of parameters if normal
3. If hypovitaminosis, initiate treatment after obtaining baseline BMD assessment by DEXA scan
4. Treatment includes vitamin D supplementation and biphosphonates in consultation with endocrinologist.

10. Treatment

There is insufficient data to prove the efficacy of prophylactic supplementation with calcium and vitamin D for patients at risk of reduced bone density from antiepileptic drugs. But studies have demonstrated that supplementation with vitamin D for ambulatory patients on AED increased bone density after 1 year of treatment.⁷⁰

There are several interventions available for bone disease, including calcium and vitamin D supplementation, bisphosphonates, hormone replacement, selective estrogen modulators (SERMs) and calcitonin, although few studies have addressed its efficacy in bone disease associated with AEDs. The two approved formulations of bisphosphonates include alendronate and risendronate. Bisphosphonates are potent inhibitors of bone resorption and with the information of AED associated increased bone resorption may be an effective treatment for bone disease in patients receiving AEDs. Role of hormone replacement in stopping bone loss is controversial. Moreover hormone replacement therapy may increase seizure activity.⁷¹

Bone health is an important long-term health concern for patients with epilepsy. There are certain recommendations for maintenance of optimal bone health in patients taking AED. As epilepsy requires long-term treatment, judicious choice and use of an AED is warranted while initiation keeping bone health in mind.^{72,73} PWE have an increased incidence of falls, injuries during seizures and fractures. Vitamin D deficiency may also lead to proximal weakness of muscles and falls. The presentation of epilepsy is diverse from mild to severe with some patients requiring institutionalization for their motor and mental handicap apart from their seizures. The role of regular exercise healthy diet, and nutritional supplementation cannot be overemphasized for maintenance of a healthy bone in persons with epilepsy.

Conflict of interest

The authors have none to declare.

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The authors report no disclosures relevant to the manuscript.

Author contributions

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